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Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Scope

The **Atlas of Genetics and Cytogenetics in Oncology and Haematology** is made for and by: clinicians and researchers in cytogenetics, molecular biology, oncology, haematology, and pathology.
One main scope of the Atlas is to conjugate the scientific information provided by cytogenetics / molecular genetics to the clinical setting (diagnostics, prognostics and therapeutic design), another is to provide an encyclopedic knowledge in cancer genetics. The Atlas deals with cancer research and genomics. It is at the crossroads of research, virtual medical university (university and post-university e-learning), and telemedicine. It contributes to "meta -medicine", this mediation, using information technology, between the increasing amount of knowledge and the individual, having to use the information.Towards a personalized medicine of cancer.

It presents structured review articles ("cards") on:
1- Genes,
2- Leukemias,
3- Solid tumors,
4- Cancer-prone diseases, and also
5- "Deep insights": more traditional review articles on the above subjects and on surrounding topics.
It also present
6- Case reports in hematology and
7- Educational items in the various related topics for students in Medicine and in Sciences.
The Atlas of Genetics and Cytogenetics in Oncology and Haematology **does not publish** research articles.

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Gene Section

Review

FZD4 (frizzled class receptor 4)

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Abstract

Fzd4 is a receptor for Wnt proteins, belonging to the frizzled receptors family. Its stimulation can activate both Wnt/β-catenin canonical and Wnt/Ca^{2+} non canonical pathways. This receptor plays an important role in the development processes, in particular in the retinal vascularization: it binds the Norrin ligand, a Wnt-unrelated growth factor, and activates β-catenin signalling pathway. Mutations of FZD4 gene are associated with Familial Exudative Vitreoretinopathy (FEVR). Recently dysregulation of FZD4 expression has been reported in different type of cancers, but FZD4 contribution in tumor pathogenesis and progression is still not entirely elucidated.

Keywords
Frizzled 4, WNT, Wnt/β-catenin signaling

Identity

Other names
Frizzled 4, Seven Transmembrane Spanning Receptor, Frizzled (Drosophila) homology 4, Frizzled homolog 4 (Drosophila), CD344 Antigen, FEVR, Fz-4, FZD4, Wnt receptor Frizzled -4, hFz4

HGNC (Hugo)
FZD4

Location
11q14.2

Location (base pair)
Starts at 86945675 and ends at 86955398 bp from pter (according to hg38-Dec_2013)

DNA/RNA

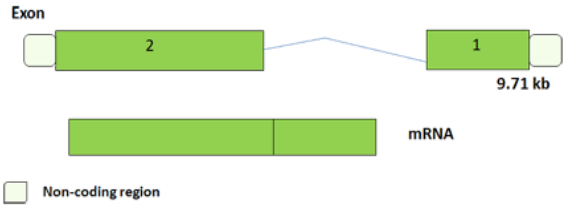


Figure 1: Schematic representation of FZD4 gene that contains a total of two exons and FZD4 transcript.

Description

DNA size: 9.71kb encoding two exons. This gene has one transcript (splice variant), 82 orthologues, 12 paralogues (www.emsable.org). Sagara et al., reported a splice variant of FZD4 gene which they called FZD4SA, it retains intronic sequence and encodes shorter isoform of only 125 aa. However, its expression is not supported by other experimental evidences.

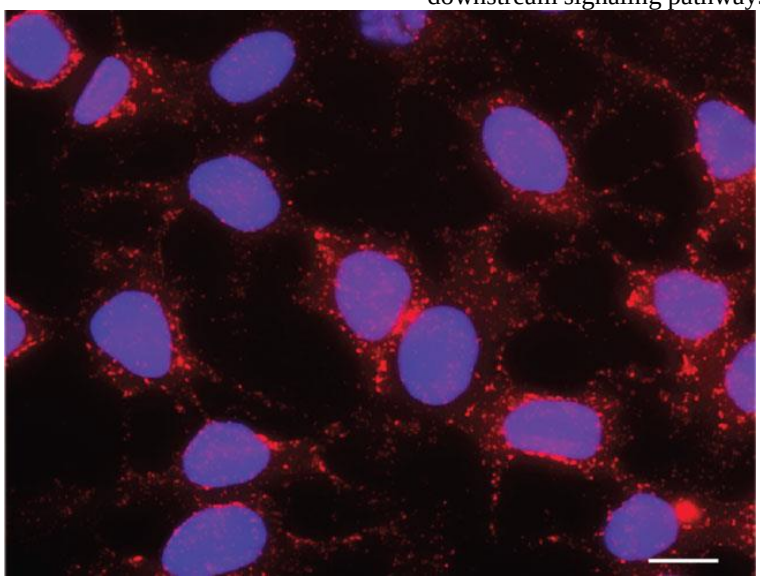
Transcription

The FZD4 mRNA transcript is 7383 bp. FZD4-001 ENST00000531380.1: mRNA7383 bp, protein 537 aa.

Protein

Description

The gene FZD4 encodes a 537 aa protein with a molecular weight of 59 kDa. FZD4 is a member of the seven transmembrane receptor family consist of 10 receptors that are activated by Wnt family of lipo-glycoproteins. The Wnt/ FZD signaling is involved in a variety of biological processes and its dysregulation have been implicated in cancer development. FZD4 protein contains the N-terminal signal peptide (aa 1-36) that assurances proper membrane insertion of the protein, an extracellular cysteine rich domain (CRD; aa 40-161), which creates the binding site for WNT ligands, a seven-pass transmembrane domain (aa 161-221) that gives rise to three intracellular loops, three extracellular loops and a C- terminal domain (aa 221-537). The CRD domain is necessary to bind WNT ligands or Norrin ligand leading to initiation of distinct downstream signaling pathways. (Schulte G., 2010).



Expression

In human, FZD4 is a ubiquitous protein. It is expressed in brain, ovary, liver, pancreas, brain, colon, heart, skeletal muscle, endothelial cells, endometrium, bone marrow, prostate, spleen, breast (www.ncbi.nlm.nih.gov).

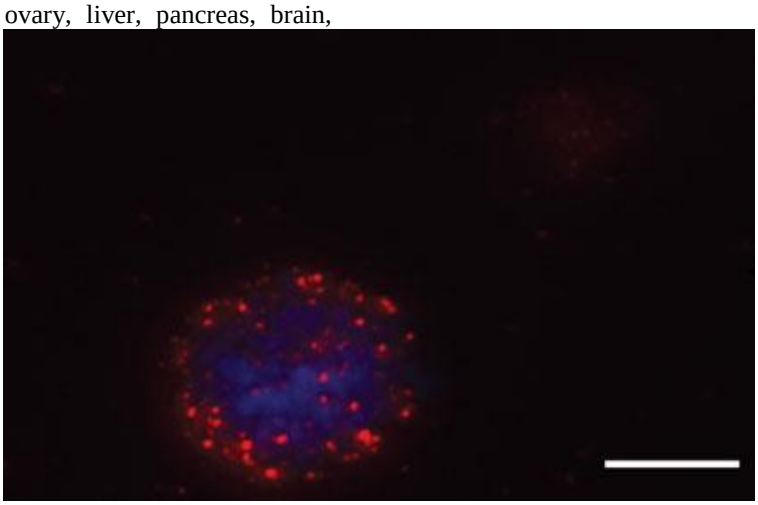
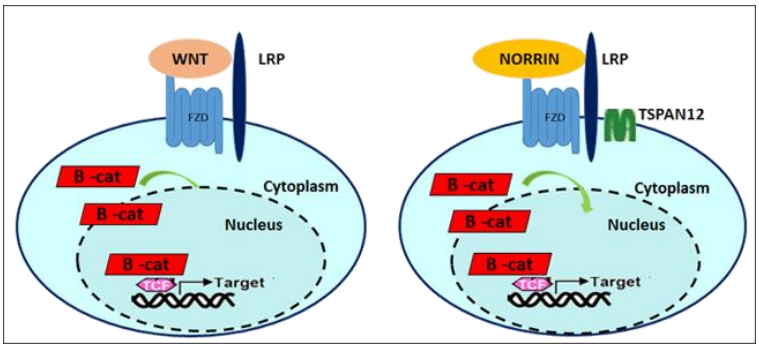


Figure 3: Visualization of FZD4/WNT10B interaction in MCF7 adherent (top) and tumorsphere (bottom) by proximity ligation assay (Lazzaroni et al.,2016).

Localisation

FZD4 is localized on the plasma membrane surface. It can be internalized through both constitutive and agonist dependent endocytosis in response to Wnt5a stimulation (Chen W. et al., 2003).



Function

FZD4 is a member of Frizzled gene family involved in neuronal, follicle, cardiomyocyte and retinal vascular development, likewise its dysregulated expression lead to cancer and other diseases. Depending on the cellular contest, FZD4 interacts with different WNT ligands, leading to the activation of Wnt/β catenin signaling and sometimes non canonical Wnt/Ca^{2+} signaling. Wnt/β catenin signaling is activated when WNT ligands bind CDR FZD/Low-density lipoprotein receptor-related protein5/6 (LRP5/ LRP6) complex, in this case CTNNB1 (β-catenin) degradation complex becomes inactivated, resulting in stabilization of β-catenin that can translocate in the nucleus, where it interacts with LEF1 (TCF/LEF) transcription factor, inducing the transcription of target genes (Clevers H., 2006). Recently, WNT10B/FZD4 interaction in the MCF7 breast cancer cell line suggests an autocrine activation of Wnt signalling in this cell line model (Lazzaroni F. et al, 2016). In melanoma FZD4 binds WNT5A and stimulates tumor invasion through activation of βcatenin signaling (Grossman A. et al., 2013), while in acute myeloid leukemia the interaction between WNT3A and FZD4 induce higher resistance against apoptosis (Tickenbrock L. et al., 2008). WNT2, WNT5A/ WNT5B and WNT11 via FZD4 and FZD6 induced non canonical Wnt signaling activation that regulates cardiomyocite differentiation (Mazzotta S. et al., 2016)
FZD4 is also the only FZD family member that binds selectively a growth factor called NDP (Norrin) and regulates endothelial cells growth during retinal vascular development. In retina, the binding of Norrin with FZD4 conjugated with LRP5 co-receptor and protein TSPAN12 (Tetraspanin-12), results in activation of βcatenin signalling (Schulte G., 2010), alteration in one of this gene is associated with Familial Exudative Vitreoretinopathy.

Homology

The FZD4 gene is conserved in chimpanzee, mouse, Rhesus monkey, dog, cow, rat, chicken, zebrafish and frog.

Mutations

Germinal

Several types of mutations (missense, nonsense, small deletions) have been reported for the human FZD4 gene and are related to the familial exudative vitreoretinopathy (FEVR). Among these mutations, different heterozygous substitutions have been reported: M342V, W335C, R417, I256V, P33S, G36N, H69Y, M105T, M105V, C181R, C204R, C204Y, C45Y, Y58C, W226X, and G488D (Zhang K. et al., 2011; Kondo H. et al. 2003; Quin et al., 2005) It has also been described a loss of function mutation of FZD4 with nucleotides 1479-1484 deletion in two cases of FEVR, resulting in the lacking of met493 and trp494 that leads to a frameshift and creates a stop codon at residue 533 (Robitaille J. et al.,2002).

Implicated in

Familial Exudative Vitreoretinopathy (FEVR)

Familial Exudative Vitreoretinopathy (FEVR) is a hereditary ocular disorder characterized by incomplete development of the retinal vasculature.

It is possible to distinguish two forms of FEVR: one with dominant autosomal inheritance and one with X-linked recessive inheritance (Gilmour DF., 2015).

Autosomal inheritance has been associated with mutation of FZD4, LRP5 or Tetraspanin 12 (TSPAN12) genes, while X-linked recessive inheritance is due to mutation of Norrin gene (NPD) that it is also involved in other ocular disease.

Several FZD4 mutations were connected with FEVR, many of which were found in the extracellular portion of the protein. Kaykas et al., have shown how some FZD4 mutations in FEVR lead to the retention of mutated protein within the endoplasmic reticulum (ER), where it is recognized by endoplasmic-reticulum-associated protein degradation (ERAD) and degraded, not allowing its exposure on the plasma membrane. They also demonstrated that oligomerization of mutants and wild-type FZD4 in the ER reduces the FZD4 function by preventing a sufficient amount of FZD4 from reaching the cell membrane and inhibits its

signaling. This dominant-negative effect can partly explain the pathological mechanism that causes the disease phenotype, in patients with heterozygous FZD4 mutations. Mutations that do not cause retention in ER of mutated protein, induce a conformational modification of the CRD FZD4 that doesn't permit the biding to its ligands or downstream targets.

Acute myeloid leukemia (AML)

It was demonstrated that FZD4 represents one of the mechanism of canonical or non canonical Wnt signaling activation in the pathogenesis of AML. Recently microarray analysis confirmed a higher expression of FZD4 in primary AML blast cells. (Beghini A. et al., 2012).

Tickenbrock, A. et al, also showed FZD4 overexpression in primary AML blasts, both in the presence or absence of FLT3 mutations. They also showed a canonical Wnt pathway activation due at specific WNT3A/FZD4 interaction, that leads to the stabilization of β-catenin and induces higher resistance against apoptosis. It was observed an involvement of FZD4 in differentiation of AML cell line mediated by 6-benzylthioinosine (6-BT) treatment. 6-BT treatment results in downregulation of canonical Wnt molecules and up-regulation of transcriptional level of the non canonical Wnt ligand Wnt5a and receptors FZD2, FZD4, FZD5, resulting in activation of Wnt/Ca^{2+} pathway (Zang S. et al., 2014).

Non small cell lung cancer (NSCLC)

Recently several studies have reported that single nucleotide polymorphisms (SNPs) of FZD4 gene can influence recurrence and survival of early stage NSCLC patients treated with only surgery or in combination with chemotherapy.

miR-related SNP (rs713065) in the 3?UTR region of FZD4 gene is associated with decreased risk of death in early stage NSCLC patients treated with only surgery, while it is related to increased risk of death in patients treated with surgery plus chemotherapy (Pu X. et al., 2013). This FZD4-miR-SNP specifically interacts with MIR204 which acts as a tumor suppressor and inhibits the expression of FZD4 and transduction of Wnt/βcatenin signalling (Lin J. et al, 2017).) This FZD4-miR-SNP specifically interacts with miR-204 which acts as a tumor suppressor and inhibits the expression of FZD4 and transduction of Wnt/βcatenin signalling (Lin J. et al, 2017).

Coscio A. et al, demonstrated that miR-SNP (rs10898564) of FZD4 is most significantly associated with increased recurrence and death risk in NSCLC patients treated with only surgery but not in patients treated with surgery and chemotherapy. These reports suggest a potential role of FZD4-SNPs as predictive biomarkers for both recurrence and survival in early stage NSCLC patients.

Prostate cancer

In prostate cancer cells have been shown activation of Wnt signalling through FZD4 leading to epithelial-to-mesenchymal transition (EMT) and loss of cell adhesion (Gupta S. et al., 2010; Acevedo VD et al., 2007).

Breast cancer

Recently Lazzaroni F. et al. evidenced an autocrine activation of Wnt signalling in breast cancer cell line model. In MCF7 cell line model they identified the WNT10B/FZD4 interacting complex using the in situ proximity ligation assay and a dose dependent reduction of WNT10B/FZD4 complex after the treatment with pharmacological inhibitor of porcupine, a membrane-bound acyltransferase that is essential to the production of Wnt proteins.

Liver cancer

It was revealed that Let7b microRNA inhibit Wnt/β-catenin signaling pathway via downregulation of FZD4 in liver cancer cell, resulting in a reduction of proliferation, invasion, migration of liver cancer cells and reduction in the amount of cancer stem cells in liver (Cai H.et al 2017).

Glioblastoma

Microarray analysis in U87R4 invasive glioblastoma cell line reported an overexpression of FZD4, which actives Wnt/β catenin signalling pathway and promotes stemness and invasiveness of glioblastoma cells. (Jin X. et al. 2011).

Medulloblastoma

Recently evidences showed an involvement of Norrin/FZD4 signaling pathway in the cerebellar tumor medulloblastoma (MB) initiation. In this tumor, Norrin/FZD4 pathway acts as anti-tumor signal in the preneoplastic niche, in fact loss of function of Norrin/FZD4 signaling in the endothelian cells promotes the formation of preneoplastic lesion of MB and their progression to malignancies (Bassett E. et al., 2016).

Bladder cancer

FZD4 is a target of miR-493 in the bladder cancer. It was observed a down-regulated expression of miR-493 in the bladder cancer tissue in comparison with normal bladder tissue. MIR493 transfection in the T24 or J82 bladder cancer cell line inhibits FZD4 and Rho4 expression, resulting in the inhibition of cell motility and migration

These results, suggested that miR-493 represent a new tumor suppressor in the bladder cancer (Ueno K. et al., 2012).

Melanoma

It was reported that in melanoma cells Wnt signalling activation through FZD4 promotes tumor cell invasion and metastasis. WNT5a binds FZD4/LRP6 receptor complex and actives the guanosine triphosphatase adenosine diphosphate ribosylation factor 6 (ARF6), leading to the disruption of N-cadherin-βcatenin complex and accumulation of nuclear βcatenin, which increases the transcription of its target genes and stimulates melanoma invasion (Grossman A. et al., 2013)

Chronic Myeloid Leukemia

Agarwal P. et al., revealed a role of FZD4 in Wnt-mediated regulation of CML progenitor growth and their resistance to tyrosine kinase inhibitor (TKI) treatment. Silencing of FZD4 expression in combination with Nilotinib (NIL) treatment reduces Wnt signalling activation and the colony forming capacity of CML cells.

Colorectal cancer

Expression of FZD4 in colorectal cancer and its binding with the Norrin ligand, produced by the same cells and endothelial tumor cells, activates β-catenin signalling and regulates angiogenesis in the colorectal cancer microenvironment (K. Platinus et al. 2014).

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Zhang K, Harada Y, Wei X, Shukla D, Rajendran A, Tawansy K, Bedell M, Lim S, Shaw PX, He X, Yang Z. An essential role of the cysteine-rich domain of FZD4 in Norrin/Wnt signaling and familial exudative vitreoretinopathy. J Biol Chem. 2011 Mar 25;286(12):10210-5

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Gene Section

Review

MAZ (MYC Associated Zinc Finger Protein)

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DOI: 10.4267/2042/68930

Abstract

Myc-associated zinc finger protein (MAZ), also known as serum amyloid A-activating factor 1 (SAF1), Pur-1 or Zif87, is ubiquitously expressed in various tissues. MAZ is a transcription factor with six Cys2His2-type zinc finger motifs at the carboxyl-terminus that interact with a permutation of the GGGAGGG sequence motif present in GC-rich promoter regions of target genes, likely through DNA unfolding of G-quadruplex structures to modulate gene expressions. MAZ is also suggested to participate in transcription termination and polyadenylation. Deregulated expression of MAZ is reported to correlate with various tissue malignancies that include the breast, thyroid, hepatocellular and urothelial cancers.

Keywords

MAZ; transcription factor; Zinc finger; DNA binding; Purine binding; breast cancer; thyroid cancer; hepatocellular cancer; urothelial cancer.

Identity

Other names

PUR1 (Purine-Binding Transcription Factor), SAF-1 (Serum Amyloid A Activating Factor 1), SAF-2 (Serum Amyloid A Activating Factor 2), SAF-3 (Serum Amyloid A Activating Factor 3), ZF87 (Transcription Factor Zif87), ZNF801 (Zinc Finger Protein 801)

HGNC (Hugo)

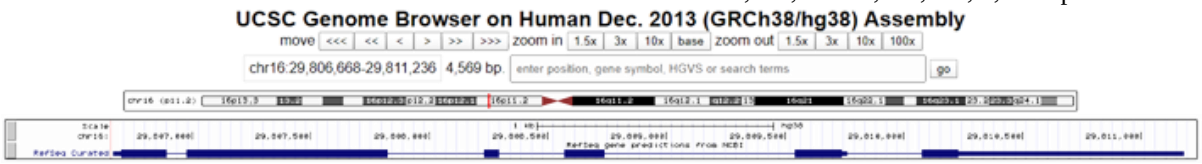
MAZ

Location

16p11.2

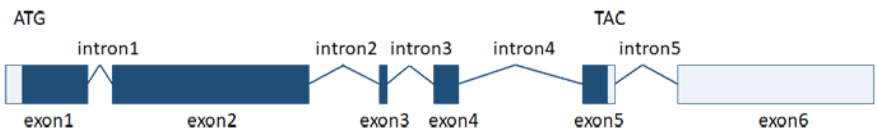
Location (base pair)

chr16:29,817,858-29,822,504; 4,647 bp.



UCSC representation of the gene on chromosome 16. RefSeq sequence shows introns as lines, exons as boxes and encoding exons as thicker boxes. Retrieved from: http://genome.ucsc.edu on November 6, 2017.

DNA/RNA



The human MAZ consists of six exons, the first five of which are encoding exons; total exon length is 4.57 kb (Song et al., 1998).

Description

The human MAZ contains six exons; the encoding sequence consists of 1431 bases (Song et al., 1998).

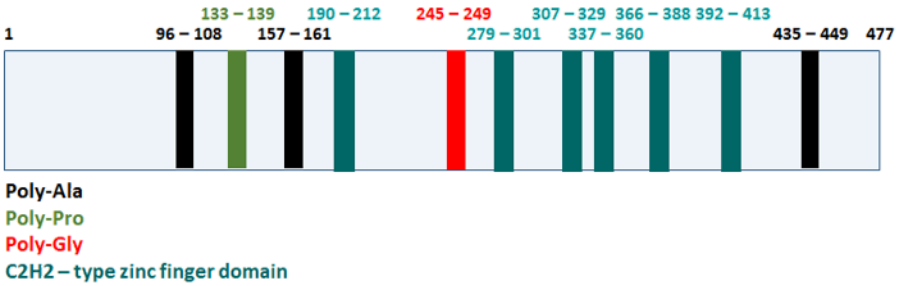
Transcription

The human gene encoding for MAZ is located on chromosome 16p11.2 and is transcribed as an mRNA of 2.7 kilobases (kb). The primary transcript encodes a 477 amino-acid long MAZ-1 protein with a 60-kDa molecular mass that contains six C2H2-type zinc-finger domains responsible for DNA binding. MAZ protein has two additional isoforms: MAZ-2 and MAZ-3. The MAZ-2 transcript is generated by an alternative splicing that results in the insertion of a new exon originating from the non-coding sequences of the intron 4. This transcript gives rise to the MAZ-2 isoform, which is a 493 amino-acids long protein with distinct carboxyl-terminus which contains two additional zinc-finger domains (Ray et al., 2002). The MAZ-2 isoform is reported to have a higher DNA-binding activity and to act as a negative regulator of MAZ-1 function (Ray et al., 2002). The MAZ-3 transcript is expressed at very low levels under normal physiological condition in various tissues, but is highly expressed during inflammation. The MAZ-3 transcript is transcribed from a distinct upstream promoter and is processed with alternative splicing. The MAZ-3 transcript is translated from a different starting codon that gives rise to the MAZ-3 isoform of 455 amino-acids (Ray et al., 2009).

Pseudogene

No reported pseudogenes are found.

Protein

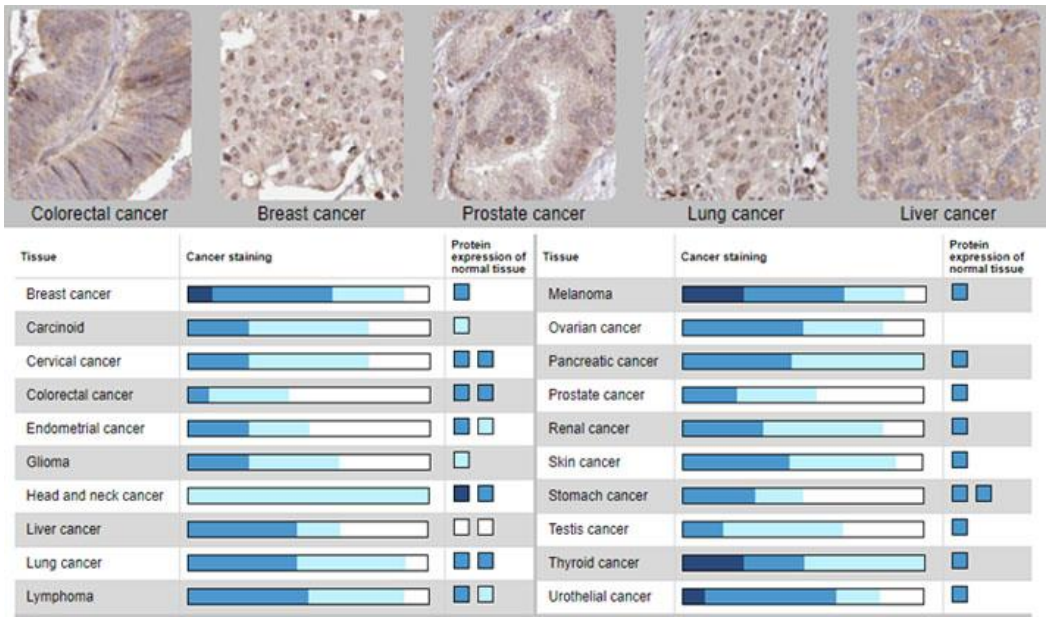


Domains of MAZ are depicted with vertical colored lines; Blacks are Poly-Alanine repeats; Green is Poly-Proline tract; Red column is Poly-Glycine repeat. C2H2-type zinc finger domains of MAZ-1 are represented in dark blue-green vertical lines

.

Description

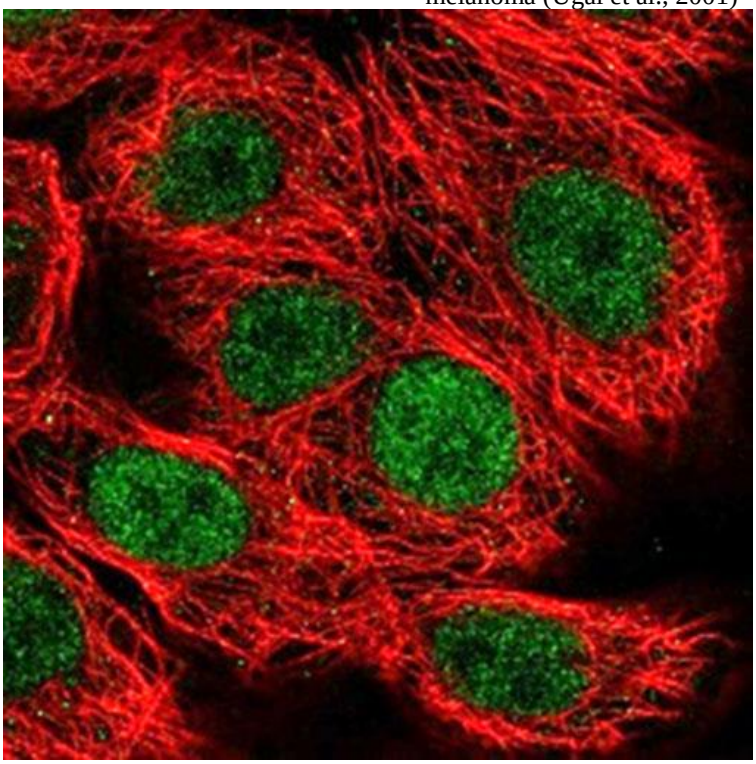
The human MAZ protein contains three Poly alanine, one poly-proline and one poly-glycine domains (Song et al., 1998). Poly-alanine repeats considered to have role in cellular localization of the protein; the alteration in the intracellular distribution may contribute to diseases, including muscular dystrophy (OPMD) (Oma et al., 2004). Similarly, poly-glycine repeats are responsible in protein targeting (Uthayakumar et al., 2012). Poly-proline tracks, on the other hand, generates structures that are predicted to have important roles in protein-protein interactions (Williamson, 1994). The human MAZ-1 contains six C2H2-type zinc finger domains (Song et al., 1998), which are frequently occurring in proteins involved in transcriptional regulation.



Expression and synthesis of MAZ in various cancerous tissues. Retrieved from: http://www.proteinatlas.org/ENSG00000103495-MAZ/cancer on November 2, 2017.

Expression

MAZ is expressed in the human heart, brain, lungs, liver, skeletal muscle, pancreas, and prostate (Jiao et al., 2013; Dudas et al., 2008). The synthesis of MAZ protein is observed to occur at high levels in breast, thyroid and urothelial cancers as well as in melanoma (Ugai et al., 2001)



Immunofluorescent staining of human cell line MCF7. Retrieved from: http://www.proteinatlas.org/ENSG00000103495-MAZ/cell on November 2, 2017. Immunofluorescent staining of MCF7 cells derived from breast adenocarcinoma shows that MAZ localizes to the nucleus.

Localisation

MAZ is located in the nucleus (Jordan-Sciutto et al, 2000).

Function

MAZ as a transcription factor interacts with a permutation of the GGGAGGG sequence motif

present in GC-rich promoter regions of target genes by unfolding of G-quadruplex structures of DNA (Cogoi et al., 2014) to activate or repress transcription. MAZ is also suggested to participate in transcription termination and polyadenylation. Several oncogenes, including MYC, HRAS, PPARG, TSG101, VEGFA, CAV1, PTHR1, NOS3, MYB, and hTER, are transcriptionally regulated by MAZ (Jun Song et al., 2001; Lee et al., 2016; Ray et al., 2002). Deregulated expression of MAZ appears to participate in the development and/or progress various tissue malignancies including the breast, thyroid, hepatocellular and urothelial cancers (Jiao et al., 2013; Dudas et al., 2008; Yu et al., 2017; Ray, 2011; Zhu et al., 2016)

Homology

The human MAZ protein is conserved 100% in chimpanzee (P.troglodytes), 98.4% in mouse (M.musculus), and 98.4% in rat (R.norvegicus); with conserved DNA of 99.8%, 93.2%, and 92.7%, respectively (Retrieved from: https://blast.ncbi.nlm.nih.gov/Blast.cgi. November 2, 2017).

Mutations

Note

Genetic mutations are not described for MAZ.

Implicated in

Prostate cancer

It was reported that the MAZ expression is higher in clinical prostate cancer (PCa) specimens than in benign prostatic hyperplasia (BPH) and adjacent normal tissues (Jiao et al., 2013). Moreover, the MAZ expression appears to be positively correlated with the expression of androgen receptor (AR), which is critical for the initiation and development of androgen-dependent PCa (Jiao et al., 2013). Extending these findings, experimental studies in cell models derived from PCa indicated that MAZ is involved in the phenotypic manifestation of PCa cell models as siRNA knockdown of MAZ levels reduces cell proliferation, migration, and invasion through mechanisms involve the expression of AR (Jiao et al., 2013).

Hepatocellular carcinoma

The expression of MAZ was reported to be upregulated in the majority (78.94%) of hepatocellular carcinoma (HCC) samples compared to normal liver samples (Dudas et al., 2008). Experimental studies using cell lines derived from HCC further suggest that MAZ-mediated regulation of PROX1, which is a transcription factor critical for the expression of a number of genes involved in hepatic metabolic functions, contributes to the progression of HCC (Dudas et al., 2008).

Breast cancer

Based on data sets in Gene expression-based Outcome for Breast Cancer Online (GOBO, http://co.bmc.lu.se/gobo/), the expression of MAZ is found to be correlated with distant metastasis-free survival (DMFS) in basal-like breast cancer (BLBC) patients and that the under-expression of MAZ is involved in the metastatic spread of BLBC (Yu et al., 2017). Based on these finding, it was suggested that MAZ plays dual roles in basal-like breast cancer (BLBC): it suppresses cancer progression but promotes cellular proliferation (Yu et al., 2017). Experimental studies using model cell lines derived from breast cancer indeed suggest that MAZ promotes cell proliferation yet it suppresses the aggressiveness of BLBC by controlling the transition toward a more mesenchymal phenotype (Yu et al., 2017; Ray, 2011).

Pancreatic carcinoma

Based on samples from pancreatic carcinoma patients, it was reported that the expression of MAZ is significantly higher in PC tissue compared to the adjacent non-tumor tissues (Zhu et al., 2016). Moreover, it appears that the over-expression of MAZ is associated with poor prognosis of PC patients (Zhu et al., 2016).

Hodgkin's Disease and Paraneoplastic Cerebellar Dysfunction

In neuronal cells, MAZ interacts with the Deleted in Colorectal Cancer product (DCC), the receptor for NTN1 netrin-1 which plays a central role in axonal guidance and neuronal migration as well as survival during development. Analyses of sera from patients with HD and PCD Hodgkin's disease and paraneoplastic cerebellar degeneration indicated that patient sera contain auto-antigens directed against the MAZ-DCC complex. Based on these observations, it was speculated that auto-antigens could interfere with neuronal function resulting in neuronal degeneration (Bataller and Wade, 2002).

To be noted

Expression of the MAZ gene is found to be regulated by MIR-125B, which is suggested to affect VEGF-induced angiogenesis in glioblastoma (Vandertop et al., 2017).

MIR449A targets MAZ transcripts, the down-regulation of which is reported to contribute to glioblastoma (Chen et al., 2015; Zhao et al., 2014; Yao et al., 2015).

MIR34C is also reported to target MAZ. Decrease levels of MAZ by miR-34c are suggested to impair the integrity and increased the permeability of blood-tumor barrier (Zhao et al., 2014).

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Gene Section

Review

UHMK1 (U2AF homology motif kinase 1)

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DOI: 10.4267/2042/68931

Abstract

UHMK1 (also known as KIS) is a serine/threonine kinase initially identified as a Stathmin interacting protein. UHMK1 is characterized by an N-terminal kinase domain and a C-terminal UHM motif. Through the UHM motif, the protein is capable of interacting with splicing factors, such as SF1 and SF3B1, involved in early steps of spliceosome assembly. UHMK1 is ubiquitously but preferentially expressed in the developing nervous system, where it plays a role in mRNA processing, translational enhancing, neurite outgrowth and postsynaptic plasticity. Protein interactions between UHMK1 and a range of proteins pointed to its function in different cellular processes, such as RNA metabolism, cell cycle progression, cell migration and membrane trafficking. More recently, a role of UHMK1 in cell differentiation has also been proposed.

Keywords
phosphorylation; splicing; cell-cycle control; nervous system

Identity

Other names
KIS, KIST, P-CIP2

HGNC (Hugo)
UHMK1

Location
1q23.3

Location (base pair)
Starts at 162497174 and ends at 162529629 bp from pter (according to GRCh38.p7, 2016)

DNA/RNA

Description

The UHMK1 gene is located on the chromosome 1, band q23, orientated in the plus (+) strand. The genomic locus spans 32456 base pairs (NC_000001.11), contains 8 exons and two alternative first exons.

Transcription

Three alternatively spliced transcripts of 8535, 8194 and 8446 base pairs are formed (NM_175866, NM_001184763 and NM_144624, respectively). The transcript variant 1 (NM_175866) codes for the longest protein isoform, which has 419 amino acids in length (isoform 1; NP_787062). The transcript variant 2 (NM_001184763) differs in the 5' UTR and initiates translation at the alternative start codon. The resulting protein (isoform 2; NP_0011716921) of 345 amino acids has a distinct 15 amino acids N-terminal, encoded by the alternative exon 1, and the remaining 330 amino acids encoded by exons 2-8. The transcript variant 3 (NM_144624) lacks exon 7, which results in a frame shift and early stop codon within exon 8. The encoded protein (isoform 3; NP_653225) of 344 residues, shares the first 341 amino acids (exons 1-6) with isoform 1, differing only in the last 3 amino acids at the C-terminal

(Figure 1). An additional processed transcript of 3345 bp (ENST00000282169.8) retaining intron 2 (between exons 2 and 3), which does not contain an open reading frame (ORF) has been annotated for this gene. Moreover, the first 540 nucleotides of UHMK1 locus (NC_000001.11) are shared with the LOC105371497 gene, which produces a 708 bp long non-coding RNA (XR_922225.1), transcribed in the opposite direction of UHMK1 (https://www.ncbi.nlm.nih.gov/gene/127933).

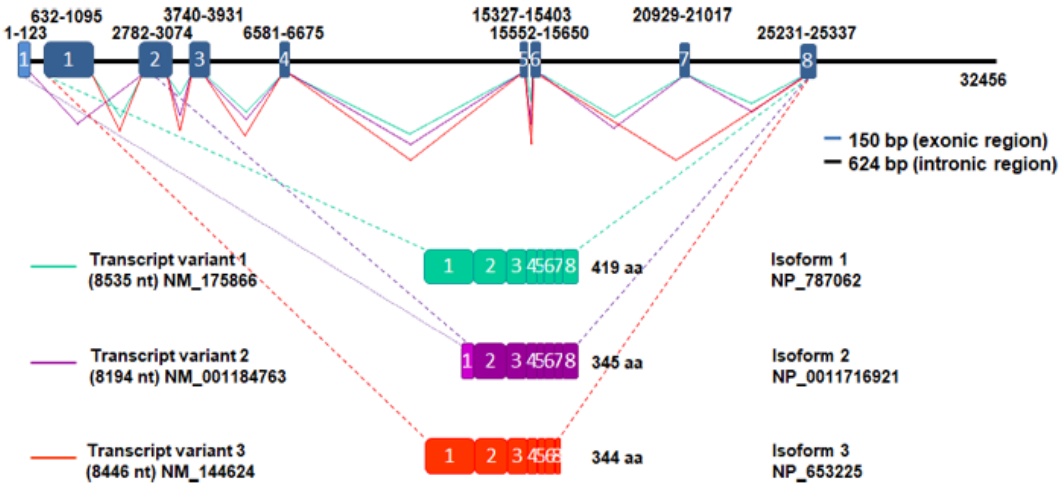

Figure 1. Genomic organization, alternative splicing and protein isoforms of UHMK1. Exons are represented by numbered blue boxes and introns by the black line. The positions of the exons within the genome (NC_000001.11) are numbered. Exon joining is represented for each transcript by light green, purple and orange continuous lines; dashed lines indicate the respective protein isoform; dotted lines indicate the alternatively first exon usage. Size of the transcript variants are shown in parentheses. The transcript variant 1 codes for the longer protein (UHMK1 isoform 1, light green). The transcript variant 2 comprises an alternative first exon (light purple box), which encodes the distinct 15 amino acids N-terminal of the protein (UHMK1 isoform 2, purple). The transcript variant 3 lacks exon 7, whose excision results in a frameshift and early stop codon in exon 8. The resulting UHMK1 isoform 3 (orange), exhibits a distinct C-terminal formed by 3 aminoacids encoded by the beginning of exon 8. Sizes were scaled up, where 0.5 cm symbolizes 150 bp of exonic region (blue boxes) and 624 bp of intronic regions (black line). Number and position of aminoacids are depicted for each isoform.

Protein

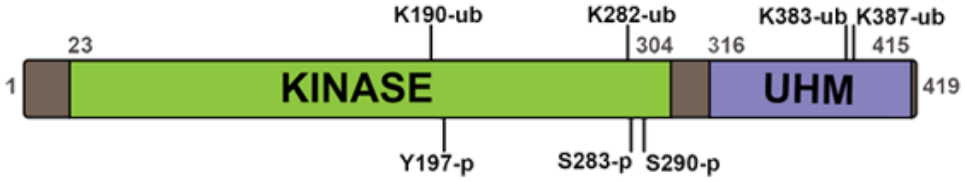

Figure 2. Diagram representing UHMK1 protein and the posttranslational modifications. UHMK1 is characterized by an N-terminal kinase core of 282 aminoacids, represented in green and a C-terminal UHM of 100 aminoacids, represented in violet. All residues described to be phosphorylated or ubiquitinated in large scale proteomic studies are depicted. Source: Phosphoproteomic databases PhosphoSitePlus (http://www.phosphosite.org) UHM: U2AF homology motif (modified from Archangelo, et al. 2013).

Description

UHMK1 is a serine/threonine kinase with calculated molecular weight of 46.5 kDa and a theoretical pI of 5.59 (PhosphoSite Plus). The primary sequence of the protein is characterized by an N-terminal kinase core (282 aminoacids) and the C-terminal U2AF homology motif (UHM), responsible for establishing protein interactions with UHM-ligand motifs (ULM), particularly present among splicing factors (Kielkopf et al., 2004; Manceau et al., 2006). UHMK1 phosphorylates preferentially proline directed serine residues on its target proteins (Maucuer et al., 2000). The lysine 54 within the N-terminal region is essential for its kinase activity and autophosphorylation activity has been observed (Boehm et al., 2002; Maucuer et al., 1997). A variety of large scale proteomic studies identified two types of posttranslational modifications within UHMK1,

namely lysine-ubiquitination (K190-ub, K282-ub, K383-ub and K387-ub) and phosphorylation (Y197-p, S283-p and S290-p) as indicated at the phosphoproteomic database PhosphoSitePlus (http://www.phosphosite.org) (Figure 2).

Expression

UHMK1 is ubiquitously expressed throughout rat and human tissues, with enriched expression in the nervous system (Bieche et al., 2003; Caldwell et al., 1999; Maucuer et al., 1997). Uhmk1 mRNA is expressed during rat embryonic development and increases after birth and during the first month of brain development (Bieche et al., 2003). In the adult brain, in situ hybridization revealed remarkable expression in the substantia nigra and some sensorial and motor nuclei in the brain stem (Bieche et al., 2003). In the human brain, UHMK1 expression was detected in all regions examined, with highest levels in the deeper cortical layers. Strong expression was observed in dentate gyrus, CA1, CA3 and CA4 regions of the hippocampus, in Purkinje cells and granule cell layer of the cerebellum. No expression was detected in the white matter (Bristow et al., 2009).

In the hematopoietic compartment, high levels of UHMK1 transcripts were observed in differentiated lymphocytes (CD4+, CD8+ and CD19+) compared to the progenitor enriched subpopulation (CD34+) or leukemia cell lines. UHMK1 expression was upregulated in megakaryocytic-, monocytic- and granulocytic-induced differentiation of leukemia cell lines and in erythrocytic-induced differentiation of primary CD34+ cells (Barbutti et al., 2017).

Levels of UHMK1 protein are induced by mitogens. In serum starved cells, UHMK1 expression was reduced in contrast to serum stimulated cells (Boehm et al., 2002; Crook et al., 2008; Petrovic et al., 2008). UHMK1 expression increased after quiescent peripheral blood lymphocytes (PBLs) were induced to proliferate upon mitogen activation (Barbutti et al., 2017). Moreover, the amount of UHMK1 protein varies throughout the cell cycle. In synchronized cells, UHMK1 accumulates in G_1 phase and decreases during S phase of the cell cycle (Archangelo et al., 2013).

Little is known about the transcriptional regulation of UHMK1, which was described as direct target of the transcription factors GABP (Crook et al., 2008) and FOXM1 (Petrovic et al., 2008). The core promoter region of UHMK1 was described within -141 to -41 base pairs upstream of the transcription start site and has no consensus sequences for TATA or CCAAT boxes. Instead, it has GC-box and 3 Ets-binding sites (EBS-1, EBS-2 and EBS-3), which are essential for the promoter activity, in vitro. The regions spanning EBS-1 and EBS-2 (-103/-73 bp), and EBS-3 (-52/-42 bp) bind GABP in response to serum, leading to UHMK1 expression, cell migration and cell cycle progression of VSCM cells (Crook et al., 2008).

FoxM1 binds an internal regulatory region within UHMK1 and transactivates its expression in vitro. FoxM1 appears to be essential for serum-dependent activation of UHMK1 mRNA expression, as assessed in FoxM1-/- MEF cells. It was suggested that FoxM1-induced UHMK1 expression is required for UHMK1-mediated phosphorylation and consequently degradation of CDKN1B ($p27^{Kip1}$) (Petrovic et al., 2008).

Furthermore, UHMK1 was described as transcriptional target of the WD repeat domain 5 (WDR5), a core component of the KMT2A (MLL) / SETD1A complex, known for its methyltransferase activity on H3 lysine 4 (H3K4). The H3K4me3 epigenetic modification correlates with gene activation, thus it is suggested that WDR5-mediated H3K4me3 at UHMK1 locus promotes its expression (Chen et al., 2015).

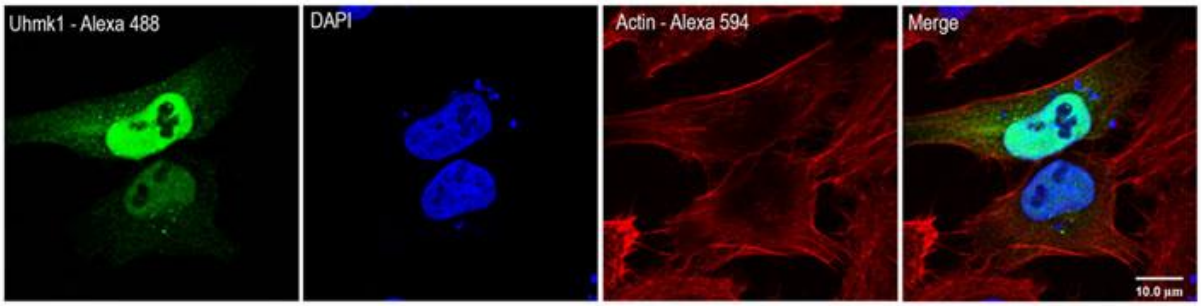

Figure 3. Subcellular localization of Uhmk1. Confocal image of HeLa cells transiently transfected with plasmid expressing ha-tagged Uhmk1 (pECE-HA-Kis; Manceau et al, 2008). Ectopic Uhmk1 localizes mainly to the nucleus and to a lesser extent to the cytoplasm. The anti-Kis 3B12 antibody (Manceau et al, 2012) and Phalloidin (Invitrogen A1238) were used to detected Uhmk1 and Actin, respectively. 63x objective, zoom 2,5 x. Personal data.

Localisation

The UHMK1 protein localizes mainly to the nucleus and to a lesser extent to the cytoplasm (Boehm et al., 2002; Maucuer et al., 1997) (Figure 3). Shuttling between nucleus and cytoplasm has been described for the GFP-fused protein by fluorescence recovery after photobleaching (FRAP) (Francone et al., 2010).

The kinase domain is essential for the protein nuclear localization, since deletion mutants of this domain, particularly the residues 1-211, extinguished Uhmk1 signal in immunofluorescence analysis (Manceau et al., 2008). Overexpressed ha-tagged Uhmk1 localized to the RNA granules of axon and dendrites of cortical neurons (Cambray et al., 2009). Also, a nucleolar enriched localization was observed when ha-tagged Uhmk1 was co-expressed with its GFP-fused interacting partner PIMREG (Archangelo et al., 2013).

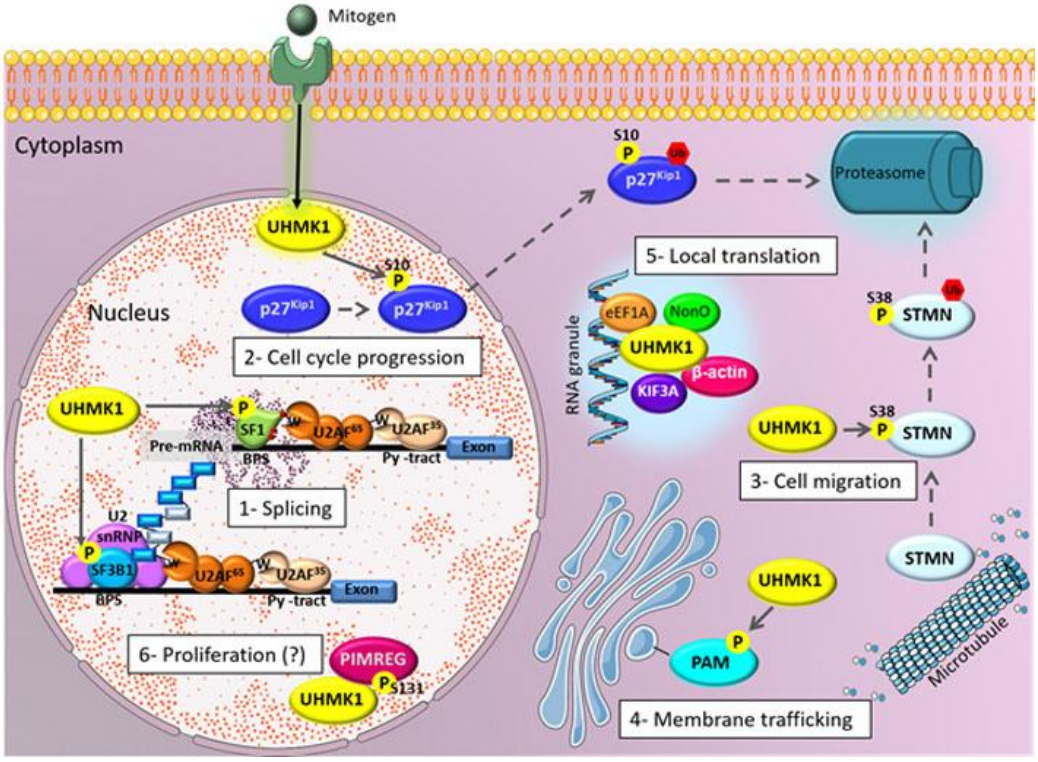

Figure 4. Potential functions of UHMK1. 1- UHMK1 interacts with and phosphorylates the splicing factors SF1 and SF3B1. 2- UHMK1 counteracts the inhibitory effect of $p27^{Kip1}$ on cell cycle. Upon mitogenic activation, UHMK1 is upregulated and phosphorylates $p27^{Kip1}$, which is exported from the nucleus and targeted for degradation by the proteasome. 3- UHMK1 impairs cell migration through negatively regulating the microtubule destabilizing protein Stathmin (STMN). UHMK1-mediated phosphorylation of STMN on S38 targets the protein for degradation. 4- UHMK1 regulates the secretory pathway in neurons and endocrine cells through its interaction with the peptidylglycine α-amidating mono-oxigenase (PAM). 5- UHMK1 interacts with components of neuronal RNA granules, such as KIF3A, NonO and eEF1A. It also associates with RNP-transported mRNAs and stimulates translation driven by the β-actin 3' UTR. 6- UHMK1 interacts with and phosphorylates the proliferation marker PIMREG, suggesting a potential role in regulating proliferation. Black arrow: represents the mitogen-dependent activation of UHMK1. Grey arrows: indicate the UHMK1-mediated phosphorylation of target proteins. Grey dotted arrows: represent the fate of the UHMK1 phosphorylated proteins targeted for degradation. P: phosphorylation; Ub: ubiquitination. Illustration was drawn using Servier Medical Art.

Function

UHMK1 was described to interact with a range of proteins, shedding light on different functions of this protein in diverse cellular processes (Figure 4).

UHMK1 is the only kinase that possesses the N-terminal kinase core juxtaposed to a C-terminal U2AF homology motif (UHM) (Maucuer et al., 1997). Through the UHM motif, UHMK1 interacts with the splicing factors SF1 and SF3B1 (Manceau et al., 2008). Upon interaction, UHMK1 phosphorylates SF1, which enhances SF1 specific binding to $U2AF^{65}$ and reduces the SF1-$U2AF^{65}$ binding to the 3' splice site RNA (Chatrikhi et al., 2016; Manceau et al., 2006). In addition, UHMK1 expression is necessary for normal phosphorylation of SF1 in vivo (Manceau et al., 2012). The fact that UHMK1 interacts with and regulates splicing factors suggests that UHMK1 might be involved in RNA metabolism.

Since UHMK1 is highly expressed in neurons, it is expected to exerts important functions in the nervous system. It was demonstrated an abnormal phosphorylation of SF1 in brain extracts of neonate $Uhmk1^{-/-}$ mice. Also, Uhmk1 deletion resulted in increased ratio of pre-mRNA relative to mRNA, and consequently down-regulation of brain specific genes, like cys-loop ligand-gated ion channels and metabolic enzymes. Although adult $Uhmk1^{-/-}$ mice did not present an obvious phenotype, animal

behavior was affected. The Uhmk1$^{-/-}$ mice displayed locomotor hyperactivity, reduced fear conditioning and learning capacities from aversive stimuli (Manceau et al., 2012).

The murine Uhmk1 was described to interact with known components of neuronal RNA granules, such as KIF3A, NONO and EEF1A1. The protein colocalizes with KIF3A kinesin in neurites and is required for neuritic outgrowth in cortical mouse neurons. Furthermore, Uhmk1 associates with RNP-transported mRNAs and stimulate translation driven by the β-actin 3' UTR, suggesting that Uhmk1 contributes to modulate translation in RNA-transporting granules as a result of local signals (Cambray et al., 2009). Still, comparison of primary cultures derived from Uhmk1$^{-/-}$ mice did not reveal a significant difference in neuritic arborization of cortical neurons (Manceau et al., 2012).

Furthermore, a study investigating Uhmk1 action on hippocampal synaptic plasticity in mice, showed that Uhmk1 knockdown impaired spine development, altered actin dynamics, and reduced postsynaptic responsiveness. Moreover, Uhmk1 depletion resulted in decrease of the postsynaptic scaffolding protein PSD-95 and of AMPA receptor subunits. Thus Uhmk1 enhances translation of AMPA receptors and stimulates dendritic spine remodeling (Pedraza et al., 2014).

Another described function of UHMK1 involves the regulation of secretory pathway in neurons and endocrine cells through its interaction with peptidylglycine α-amidating mono-oxigenase (PAM) (Alam et al., 1996). PAM cytosolic domain (CD) phosphorylation by UHMK1 (Ser-949) is required for the correct routing of this protein and consequently for its ability to affect trafficking in the regulated secretion pathway (Alam et al., 2001; Caldwell et al., 1999). Lately, it was described an intramembrane proteolysis pathway for PAM, generating a soluble fragment of the cytosolic domain (sf-CD), which accumulates in the nucleus in a phosphorylation-dependent manner, modulating the expression of genes involved in the secretory pathway. UHMK1 phosphorylates sf-CD, diminishing its localization in the nucleus and negatively regulating the expression of a subset of genes (Francone et al., 2010; Rajagopal et al., 2010).

An extensively documented function of UHMK1 is its ability to positively regulate cell cycle progression through phosphorylation and inhibition of the cyclin dependent kinase inhibitor (CDKI) p27^{Kip1}. Upon mitogenic activation, UHMK1 expression is upregulated and phosphorylates p27^{Kip1} on serine 10 (Ser10). As a consequence, p27^{Kip1} is exported from nucleus to cytoplasm, where it is targeted to the proteasome and degraded, and has no longer inhibitory effect on cell cycle. Thus, UHMK1 promotes cell cycle re-entry by inactivating p27^{Kip1} following growth factor stimulation (Boehm et al., 2002).

Another important target of UHMK1 is the microtubule-destabilizing protein, Stathmin (Maucuer et al., 1995). UHMK1 interacts with and phosphorylates Stathmin on serine 38 (Ser38), targeting this protein to proteasome. Through negative regulation of Stathmin, UHMK1 alter microtubule dynamics and consequently impairs cell migration (Langenickel et al., 2008).

UHMK1 expression is upregulated upon hematopoietic cell differentiation, thus a possible role of UHMK1 in cell differentiation was proposed (Barbutti et al., 2017). This idea was supported by the fact that UHMK1 mRNA is highly expressed in the mature brain and in terminally differentiated neural cells (Bieche et al., 2003) as well as during osteoclasts differentiation (Choi et al., 2016). The human UHMK1 shares high homology with a number of species as depicted in Table 1.

PIMREG (previously known as FAM64A; CATS) is a proliferation marker shown to interact with UHMK1. The fact that UHMK1 interacts with and phosphorylates PIMREG suggests that UHMK1 regulates PIMREG function and/or localization. Nevertheless, the functional implication of this interaction remains elusive (Archangelo et al., 2013).

Homology

The human UHMK1 shares high homology with a number of species as depicted in Table 1. The human UHMK1 shares high homology with a number of species as depicted in Table 1.

Table 1. Homology between the human UHMK1 and other species

***Homo sapiens* UHMK1**	**Symbol**	**Protein** (% Identity)	**DNA**(% Identity)
vs. ***P. troglodytes*** *vs.* ***M. mulatta***	UHMK1 UHMK1	99.8 (XP_001174268) 99.8 (NP_001253697)	99.7 (XM_001174268) 99.0 (NM_001266768)
vs. ***C. lupus***	UHMK1	99.8 (XP_536143)	95.8 (XM_536143)
vs. ***B. taurus***	UHMK1	99.8 (NP_001192514)	95.9 (NM_001205585)

vs. ***M. musculus***	Uhmk1	99.3 (NP_034763)	93.0 (NM_010633)
vs. ***R. norvegicus***	Uhmk1	99.3 (NP_058989)	92.6 (NM_017293)
vs. ***G. gallus***	UHMK1	88.2 (XP_015145890)	81.6 (XM_015290404)
vs. ***D. rerio***	uhmk1	73.6 (NP_001070127)	69.4 (NM_001076659)

(Source: http://www.ncbi.nlm.nih.gov/homologene/)

Mutations

Somatic

Recurrent mutations have not been identified for the UHMK1 gene. Nonetheless, more than 160 unique mutations were reported in this gene in the catalogue of somatic mutations in cancer database (COSMIC), mainly in lung, gastric, esophageal, colon, rectal and hepatocellular/liver cancer (http://cancer.sanger.ac.uk/cancergenome/projects/cosmic).

Implicated in

Breast cancer

Erlotinib resistence in breast cancer treatment was attributed to $p27^{Kip1}$ cytoplasmic localization. UHMK1 depletion by siRNA enhanced erlotinib cytotoxicity in EGFR-expressing breast cancer cells, due to its accumulation in the nucleus and reduced $p27^{Kip1}$ cytoplasmic localization (Zhang et al., 2010). Besides, UHMK1 expression was reported to be inhibited in a dose-dependent manner by the anti-HER2 antibody trastuzumab, used for treatment of human metastatic breast cancer with HER2 overexpression (Le et al., 2005).

Neurological tumors

Higher levels of UHMK1 transcripts were observed in small cohort of neurological tumors associated with neurofibromatosis type 1 (NF1). Among the NF1-associated tumors analyzed, plexiform neurofibroma and malignant peripheral nerve sheath tumors (MPNSTs) presented higher UHMK1 mRNA levels compared to dermal neurofibroma (Bieche et al., 2003).

Bladder cancer

Silencing of WDR5, a protein shown to be upregulated in bladder cancer, reduced the H3K4me3 epigenetic marker on its target genes, such as UHMK1 and consequently downregulated UHMK1 expression in bladder cancer cells (Chen et al., 2015).

Hematological malignancies

No aberrant expression was observed in patient samples with myelodysplastic syndrome (MDS), acute myeloid (AML) or lymphoblastic (ALL) leukemia. Nonetheless, in MDS patients, increased levels of UHMK1 expression positively impacted event free and overall survival (Barbutti et al., 2017).

Schizophrenia

Puri and colleagues performed a fine mapping by genetic association and identified two SNPs within the UHMK1 gene (rs10494370, p =.004, and rs7513662, p = .043), which showed significant association with schizophrenia (Puri et al., 2007). The genetic association of these markers was confirmed in a second case-control (Puri et al., 2008). Nevertheless, the association of UHMK1 with schizophrenia is controversial since the data from different cohorts did not support the findings (Betcheva et al., 2009; Dumaine et al., 2011).

Osteoporosis

The SNP rs16863247 was identified within the UHMK1 locus in a genome-wide association study (GWAS) carried out to identify genetic variants that influence bone mineral density (BMD) in east Asians. Thus, UHMK1 was described as a bone mineral density susceptibility gene for this ethnical group. The authors also showed opposed expression levels of UHMK1 during osteoblast and osteoclast differentiation and proposed that UHMK1 may play a role in bone metabolism by controlling osteoclast and osteoblast differentiation (Choi et al., 2016).

Vascular remodeling and wound repair

Langenickel and coworkers demonstrated the importance of UHMK1 expression in controlling vascular remodeling and wound repair. These processes are characterized by vascular smooth muscle cell (VSCM) proliferation and cell migration, which can be achieved by inhibiting $p27^{Kip1}$ and Stathmin, two known substrates of UHMK1. In a mouse model, deletion of Uhmk1 led to accelerated neointima formation and vessel occlusion, caused by increased migratory activity of VSMCs, as a consequence of diminished degradation of Stathmin (Langenickel et al., 2008).

Corneal fibrosis

It was shown that FGF2-mediated proliferation of corneal endothelial cells (CECs) is partially dependent on UHMK1 upregulation and its inhibitory effects on CDK inhibitor $p27^{Kip1}$ (Lee and Kay, 2011; Lee et al., 2011).

Cerebral visual impairment

UHMK1 was recently reported among candidate genes for cerebral visual impairment (CVI), a major cause of low vision in childhood (Bosch et al., 2016).

To be noted

It is well accepted that UHMK1 promotes cell cycle re-entry by inactivating $p27^{Kip1}$ following growth factor stimulation. Thus it is expected that abnormally elevated UHMK1 activity, which is supposed to relieve cells from p27Kip-dependent growth inhibition, could be involved in some aspects of tumor development. Nonetheless, no aberrant expression of UHMK1 has been reported amongst different cancer samples (Barbutti et al., 2017; Bieche et al., 2003), except in a few cases of neurological tumors associated with NF1 (Bieche et al., 2003). Hence, whether it plays a role in tumorigenesis or not remains largely elusive and must be further investigated.

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Leukaemia Section

Review

i(8)(q10) in ALL

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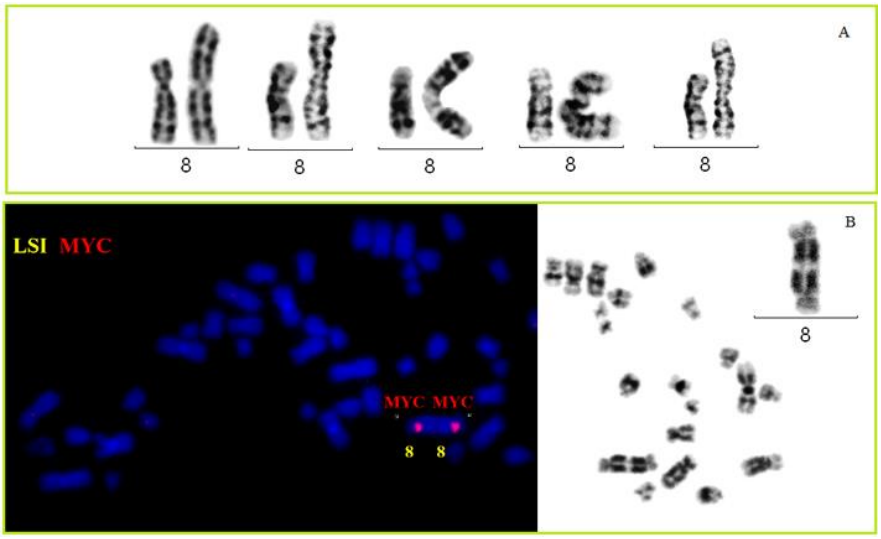
Abstract

Isochromosomes are nonrandom chromosomal anomalies in acute lymphoblastic leukemia (ALL), but relatively few patients ALL and i(8)(q10) have been reported. In the majority of cases, i(8)(q10) was part of complex karyotypes, suggesting that it is a secondary chromosomal abnormality in ALL associated with clonal evolution.

KEYWORDS
Isochromosome; Acute lymphoblastic leukemia; Chromosome gain; Clonal evolution.

Identity



Partial karyotypes with isochchromosome i(8)(q10) (A). Fluorescence in situ hybridization with LSI MYC probe hybridizing to 8q24 (Vysis/Abott Molecular, US) showing end-to-end joining of homologous chromosomes 8 at the telomeres (B). It can be hypothesized that telomeric fusion of homologous chromosomes can promote creation of an unstable dicentric chromosome potentially causing an unbalanced translocation product. However, the precise consequences of telomere fusion events and their role in formation of isochromosomes remain unclear.

Clinics and pathology

Disease

Acute lymphoblastic leukemia

Phenotype/cell stem origin

Associated with B-lineage immunophenotype with exception of 1 chronic myeloid leukaemia (CML) with lymphoid blast crisis of B-cell type who developed a secondary T-cell ALL (Dawson et al., 1999) case and 2 biphenotypic leukemia (Sulak et al.,1990; Saikevich et al., 1991) patients.

Epidemiology

At least 40 reported cases (21 males, 19 females aged 0 to 85 years; median age 17 years) were described. Nearly half the cases were children: 2 female infants (O'Malley et al., 1988; Pui et al., 1991) and 12 pediatric cases aged 0 to 15 years (Pollak & Hagemeijer 1987; Krance et al., 1992; Pui et al., 1992; Rafi et al., 2000; An et al., 2008; Suenobu et al., 2010; Chapiro et al., 2011; Harrison et al., 2014; Olsson et al., 2015; Yasuda et al., 2016; Zhang et al., 2016) or young adults aged 17 to 24 years old (Mossafa et al., 1994; Tang et al., 1998; Jarosova et al., 2000; Soriani et al., 2011; Harrison et al., 2014; Safavi et al., 2015) (Table 1).

	Sex/Age	Karyotype
1	F/7	47,XX,del(7)(p?),i(8)(q10),add(9)(p21),ins(9;9)(p21;q12q22),add(14)(q?)
2	F/0	46,XX,ins(11;4)/46,idem,del(5)(q15q33)/46,idem,del(5),i(8)(q10)/46,idem,t(2;4)(q33;p16),del(5)/47,idem,+8/
3	M/85	77-87,XY,-X,-Y,del(5)(q23)x2,i(8)(q10)x2,add(22)(q13),inc **Bilineage or biphenotypic leukemia**
4	M/53	46,XY,+1,der(1;16)(q10;p10),i(8)(q10),t(9;22),-12,der(15)t(12;15)(q12;p11),i(17)(q10),+21
5	F/0	50,XX,+X,+X,i(8)(q10),+10,-20,+21,i(21)(q10)x2,+mar
6	M/63	43,XY,t(1;9)(q?32;p?24),-2,der(3)t(3;12;17)(p?14;p?11;q?25),-5,i(8)(q10),-12,der(17)t(3;12;17) **Bilineage or biphenotypic leukemia**
7	M/13	46,XY,i(8)(q10),t(12;17)(p13;q21)
8	M/10	46,XY,i(7)(q10),t(9;22)(q34;q11)/48,idem,i(8)(q10),+i(8)(q10)x2
9	M	49,XY,+4,+8,i(8)(q10)x2,t(9;22)(q34;q11),+der(22)t(9;22)
10	F	46,XX,t(9;22)(q34;q11)/47,idem,+i(8)(q10)/47,idem,+8,i(8)(q10)x2
11	F/60	46,XX,t(9;22)(q34;q11)/46,idem,i(8)(q10)
12	M/44	46,XY,i(8)(q10),t(9;22)(q34;q11)
13	F/24	46,XX,del(6)(q21q24),i(8)(q10)
14	M	46,XY,t(14;18)(q32;q21)/46,XY,del(3)(p24),i(8)(q10),del(12)(p12)
15	F/42	47,XX,dup(1)(q21q32),add(2)(p11),+7,i(8)(q10),t(8;22)(q24;q11)/47,idem,-dup(1),+trp(1)(q21q32)
16	F/36	53,XX,+4,t(9;22)(q34;q11),i(8)(q10),+18,+19,+der(22)t(9;22)x2
17	M/53	46,XY,t(9;22)(q34;q11)/45,XY,-7,i(8)(q10),ider(9)(q10)t(9;22),der(22)t(9;22)

18	M	48,XY,i(8)(q10),t(9;22)(q34;q11),+2mar
19	F/21	46,XX,i(7)(q10),i(8)(q10),t(9;22)
20	M	47,Y,-X,-5,-7,+13,-14,-15,+5-6mar/84-91,YY,-X,-X,-4,-4,-5,-5,-7,-7,i(8)(q10),-14,-14,-15,del(22)(q13),+8-10mar
21	M/39	46,Y,t(X;11),i(7)(q10),dup(8)(q21q22)/46,idem,i(8)(q10)/45,idem,-Y **T-cell ALL after chemotherapy for CML**
22	M/17	45,XY,i(8)(p?),?add(12),-21/45,XY,i(8)(q10),der(12)del(12)(p13)dic(12;21)(p13;p11)
23	F/15	45,X,-X,-6,del(7)(q21),i(8)(q10),-9,add(9),add(12)(q24),t(12;21)(p13;q22),der(13)t(?6;13)(q12;q32),der(22)t(9;22),+1-2mar
24	M/62	46,XY,del(1)(q32),i(8)(q10),-9,-10,der(22)t(9;22)(q34;q11),+2mar
25	F/48	45,X,-X,add(1)(p36),-5,add(6)(q15),i(8)(q10),add(18)(p11)
26	F/14	45,XX,i(8)(q10),dic(9;12)(p11;p11),der(17)t(?X;17)(?q12;?p11)
27	F/13	46,XX,dic(9;20)(p11;q11),+21/46,idem,i(8)(q10)/46,idem,add(15)(p10)
28	M/51	46,XY,i(8)(q10),t(9;22)(q34;q11),der(9)t(8;9)(q1?;p12)
29	M	47,XY,i(8)(q10),+21c
30	F/13	45,XX,t(9;22)(q34;q11),add(10)(q22),-12,der(12)t(12;12)(p13;q13),i(17)(q10)/45,idem,i(8)(q10) 46,X,-X,+1,t(2;16)(p10;q10),+8,-9,t(9;22),add(10),-12,der(12),-13,i(17)(q10),+18,add(19)(p13),del(19)(q?),+21,-22,+mar/47,idem,+8 **therapy for neuroblastoma**
31	M/17	48,XY,i(8)(q10),+i(8)(q10)x2,t(9;22)(q34;q11)/49,idem,+der(22)t(9;22)
32	M/7	46,XY,t(14;20)(q32;q12)/46,idem,i(8)(q10)
33	F/7	45,XX,dup(1)(q21q32),i(8)(q10),t(9;14)(p22;q11),der(11)t(11;21)(q13;q11)t(21;22)(q22;q11)t(22;22)(q11;q22)
34	M	46,XY,-21,+r/46,idem,inv(11)(p15q13)/46,idem,i(8)(q10)
35	F/19	44,XX,i(8)(q10),-10,add(11)(q23),add(12)(p13),-14,add(14)(q32),add(15)(q25), +16,add(21)(q22),-22,+mar

1.Pollak & Hagemeijer 1987; 2.O'Malley et al., 1988; 3.Sulak et al.,1990; 4.Kageyama et al., 1991; 5.Pui et al., 1991; 6.Saikevich et al., 1991; 7.Krance et al., 1992; 8.Pui et al., 1992; 9.Dewald et al., 1993; 10.Tuszynski et al., 1993; 11-13.Mossafa et al., 1994; 14.Pirc-Danoewinata et al., 1995; 15.Martineau et al., 1996; 16-17.Rieder et al., 1996; 18.Pabst et al., 1996; 19.Tang et al., 1998; 20.Dabaja et al., 1999; 21.Dawson et al., 1999; 22.Jarosova et al., 2000; 23.Rafi et al., 2000; 24.Rieder et al., 2003; 25.Strefford et al., 2007; 26-27.An et al., 2008; 28.Coyaud et al., 2010; 29.Kowalczyk et al., 2010; 30.Suenobu et al., 2010; 31.Soriani et al., 2011; 32.Chapiro et al., 2013; 33-36.Harrison et al., 2014; 37.Olsson et al., 2015; 38.Safavi et al., 2015; 39.Yasuda et al., 2016; 40.Zhang et al., 2016.

Abbreviations: M, male; F, female.

Prognosis

As it occurs rarely as a sole anomaly only in sporadic cases in ALL, thus the prognosis is uncertain; patients with favorable primary aberrations and i(8)(q10) may maintain favorable clinical outcome similar to patients with +8; its combination with unfavorable primary anomaly or complex anomalies may lead to the worst prognosis.

Cytogenetics

Cytogenetics morphological

Sole abnormality in 3 (Kowalczyk et al., 2010; Olsson et al., 2015; Yasuda et al., 2016) and in the stemline, but with other chromosomal changes in 4 patients (Pirc-Danoewinata et al., 1995; Dabaja et al., 1999; Jarosova et al., 2000; Zhang et al., 2016). Double i(8)(q10) was detected in 5 cases (Sulak et al.,1990; Pui et al., 1992; Dewald et al., 1993; Tuszynski et al 1993; Soriani et al., 2011). Complex karyotypes, mainly with occurrence of primary anomalies in the remaining cases. Among them, the most common structural anomaly was t(9;22)(q34;q11) , found in 16 patients (Kageyama et al., 1991; Pui et al., 1992; Dewald et al., 1993; Tuszynski et al., 1993; Mossafa et al., 1994; Rieder et al., 1996; Pabst et al., 1996; Tang et al., 1998; Rafi et al., 2000; Rieder et al., 2003; Coyaud et al., 2010; Suenobu et al., 2010; Soriani et al., 2011; Safavi et al., 2015).

Result of the chromosomal anomaly

Fusion protein

Oncogenesis

Partial chromosome 8q gain resulting from an isochromosome i(8)(q10) is a nonrandom chromosomal anomaly in ALL. It occurs rarely as a sole anomaly and is mainly observed together with primary chromosome aberrations, most frequently with t(9;22)(q34;q11). Therefore, the occurrence of i(8)(q10) in ALL may signal clonal evolution, often associated with disease progression. The consequence of the formation of i(8)(q10) is gain of 8q and loss of 8p, leading to imbalances in gene dosage. As trisomy 8 is among the most common secondary chromosome changes in hematological malignancies, it is likely that gain of 8q, but not the loss of 8p is important in leukemogenesis. In this regard it is interesting to note, that while extra chromosome 8 is a common clonal evolution marker for progression in CML, the occurrence of i(8)(q10) has been only rarely described during CML transformation. While differential diagnosis between blast transformation of CML and Ph1(+) ALL may be difficult, particularly in cases identified initially in blastic crisis, it is possible that i(8)(q10) is a specific secondary anomaly to t(9;22)(q34;q11) in a pre-B immunophenotype ALL.

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Leukaemia Section

Review

Acute lymphoblastic leukemia in Down syndrome

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Abstract

Review on acute lymphoblastic leukemia in Down syndrome, with data on clinics, pathology, and involved genes.

KEYWORDS
Down syndrome; leukemia; lymphoblastic leukemia.

Clinics and pathology

Disease

Acute lymphoblastic leukemia (ALL) associated with Down syndrome (ALL-DS), is predominantly a B lymphoblastic leukemia, with only very rare cases of mature B cell ALL (Burkitt leukemia) and T-cell ALL.

Epidemiology

Trisomy 21 has an incidence of approximately 1 in 700 live births. The frequency of acute lymphoblastic leukemia in Down syndrome (ALL-DS) is estimated at 1 in 300 (Lange, 2000). The incidence of ALL-DS <5 years of age is 40.7 times greater than that in individuals without Down syndrome of the same age; in addition, there remains an increased risk of ALL-DS compared to those without Down syndrome up to the age of 30 years (Hasle et al., 2000). However, unlike those without Down syndrome, ALL -DS usually does not present in patients <1 year of age.

Clinics

Other than the lack of presentation in children <1 year of age, ALL-DS has similar clinical features to ALL in children without Down syndrome, including age, sex, presenting white blood cell count, and NCI risk group (Maloney et al., 2010). Some studies identify similar rates of mediastinal masses and central nervous system involvement at diagnosis in those with ALL-DS and those with ALL without Down syndrome, but other studies identified decreased CNS disease and mediastinal masses in those with ALL-DS (Maloney, 2011).

Cytology

Blasts are characterized as small to medium in size with high nuclear-to-cytoplasmic ratios, round to irregular nuclei, smooth chromatin, and scant deeply basophilic agranular cytoplasm.

Pathology

The blasts of ALL-DS usually have an immature B cell phenotype, expressing CD19, CD10, and CD79a.

Cytogenetics

The cytogenetics of ALL-DS differs from the cytogenetics in those with ALL not associated with Down syndrome. The children with ALL-DS have a

decreased frequency of favorable cytogenetics including high hyperdiploidy, trisomies of chromosomes 4, 10, and 17, and the t(12;21) translocation compared to children without Down syndrome (Maloney et al., 2010; Bruwier and Chantrain, 2012); these ALL-DS children also have a decreased frequency of unfavorable translocations such as t(9;22) and 11q23 (MLL) rearrangements. Approximately 50-60% of ALL-DS have been found to have CRLF2 gene rearrangements by FISH or RT-PCR (Mullighan et al., 2009; Hertzberg et al., 2010). The most common rearrangement is a deletion in the pseudoautosomal region 1 (PAR1) of Xp22.33/Yp11 resulting in a fusion between the first noncoding exon on P2RY8 with the entire coding region of CRLF2 (del(X)(p22.33p22.33)/del(Y)(p11p11)) (Mullighan et al., 2009). Less commonly, CRLF2 rearrangements with IGH (immunoglobulin heavy chain locus) are identified (t(X;14)(p22;q32)/t(Y;14)(p11;q32)). These fusions result in overexpression of CRLF2. Overexpression of CRFL2 has not been found to be correlated with outcome.

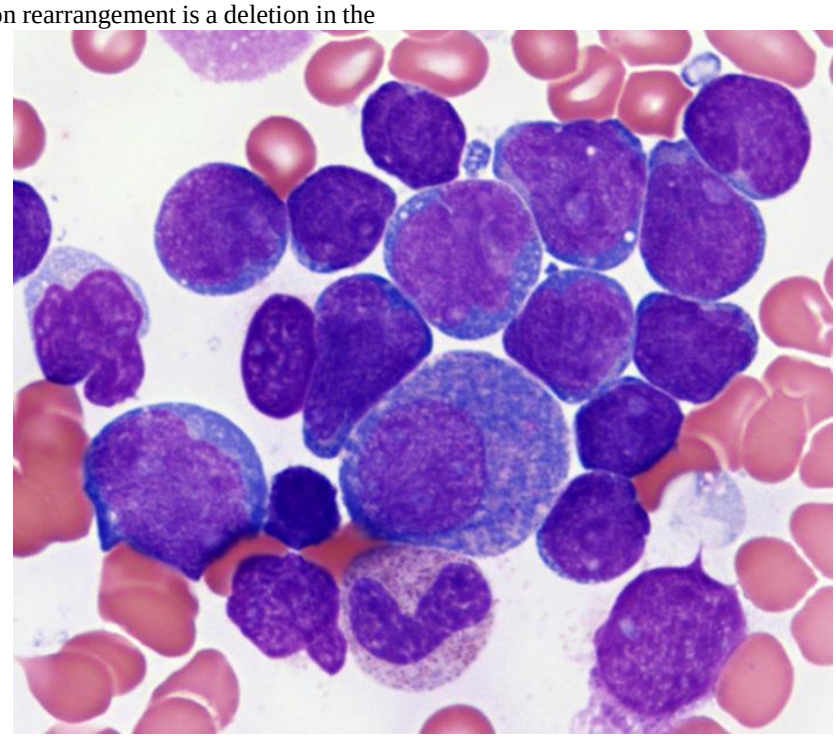

Figure 1: Bone marrow aspirate smears reveal increased blasts which are small to medium in size with high nuclear-to-cytoplasmic ratios, round to irregular nuclei, smooth chromatin, and scant basophilic agranular cytoplasm. Some background maturing myeloid cells are also present in this case.

Overall, these common B-ALL gene rearrangements, which occur at a rate of approximately 60% in non-Down syndrome patients, only occur at a rate of approximately 20% in ALL-DS. Instead, ALL-DS is more likely to have a normal karyotype (with the exception of the constitutional trisomy 21). In those without normal karyotypes, DS-ALL are more likely to be low hyperdiploid, with common acquired changes including +X and/or del(9p) (Forestier et al., 2008; Lundin et al., 2014).

Genes

JAK2 activating mutations have been found in approximately 20% of ALL-DS, with the most common mutations occurring at or around amino acid R683 in the pseudokinase domain (Bercovich et al., 2008; Kearney et al., 2009; Gaikwad et al., 2009); however, other JAK2 mutations have been identified in ALL-DS, as have mutation in other JAK genes including JAK1 (Mullighan et al., 2009). These JAK2 mutations are found predominantly in those with CRLF2 gene rearrangements. JAK2 mutation status has not been found to correlate with outcome. The JAK2 mutations are thought to act in concert with the CRFL2 gene rearrangements, resulting in cytokine-independent growth and leukemogenesis (Mullighan et al., 2009).

In addition to mutations in the JAK-STAT pathway, mutations in the RAS/receptor tyrosine kinase (RTK) pathway genes such as KRAS and NRAS have been identified at a rate of approximately 35%; these mutations are mutually exclusive of the JAK2 mutations (Nikolaev et al., 2014). However, similar to the JAK2 mutations, the RAS pathway mutations often occur in the setting of CRLF2 rearrangements. Nikolaev et al. (2014) also identified mutations in cohesion complex genes, epigenetic modifiers/remodellers of DNA or chromatin, classical tumor suppressor genes, and lymphoid

differentiation factors/markers.

Activating mutations in CRLF2 can also occur, again usually in the setting of CRLF2 gene rearrangements (Hertzberg et al., 2010).

Deletions in IKZF1 are also often found in DS-ALL, estimated at 24-35% (Hertzberg et al., 2010; Buitenkamp et al., 2012), as are deletions in the PAX5 gene (12-22%) (Kearney et al., 2009; Lundin et al., 2012; Buitenkamp et al., 2012). Patients with an IKZF1 deletion or a PAX5 deletion have decreased overall survival compared to those without these deletions (Buitenkamp et al., 2012).

Treatment

ALL-DS is treated similarly to ALL in those without Down syndrome. However, some additional modifications and supportive care guidelines are often employed in their treatment, including the use of discontinuous dexamethasone during delayed intensification and adding leucovorin rescue after intrathecal methotrexate (Maloney, 2011). Down syndrome patients have increased susceptibility to methotrexate, with higher rates of mucositis, gastrointestinal toxicity, and hepatotoxicity. Some trials have decreased the methotrexate dosage, increasing the dose only if tolerated. Additionally, Down syndrome patient have a higher risk of hyperglycemia after corticosteroids and asparaginase therapy due to alterations in glucose metabolism.

Prognosis

In some studies, children with ALL-DS have been found to have poorer outcomes than children with ALL without Down syndrome, sometimes demonstrating increased induction failures, higher relapse rates, and increased therapy-related mortality. The poorer outcomes are thought to be due, at least in part, to increased sensitivity to methotrexate side effects, and increased susceptibility to infection. The latter susceptibilities are thought to be enhanced by the inherent immunodeficiencies of Down syndrome. However, more recently, with appropriate prognostic group identification based upon favorable and unfavorable cytogenetic features, ALL-DS has been found to have comparable outcomes to ALL not associated with Down syndrome (Maloney et al., 2010; Maloney, 2011). In addition, Buitenkamp et al., 2014 found favorable prognostic factors to include diagnosis < 6 years of age and a WBC 9/L.

In those who relapse, ALL-DS has a lower event-free survival and lower overall survival compared to those with ALL without Down syndrome, usually due to induction deaths and treatment-related mortality (Meyr et al., 2013). These relapses usually occur late (more than 6 months after completion of therapy) (Meyr et al., 2013; Buitenkamp et al., 2014).

In those who undergo a hematopoietic cell transplant (HCT), post-transplant relapse often occurs, with a probability of 54% within 3 years in one cohort, with an overall survival at 3 years of 29% (Hitzler et al., 2014).

Genes involved and proteins

JAK2 (janus kinase 2)

Location
9p24.1

Protein
Protein tyrosine kinase involved in cytokine receptor signaling pathways.

Somatic mutations
Mutations often occur in the pseudokinase domain at or around R683 in exon 16 and result in constitutive kinase activity.

IKZF1 (Ikaros family zinc finger 1)

Location
7p12.2

Protein
Zinc-finger DNA-binding protein that is a transcription factor associated with chromatin remodeling. It is a transcription regulator of lymphocyte differentiation.

Somatic mutations
Usually deletions.

PAX5 (paired box gene 5)

Location
9p13.2

Protein
Paired box transcription factor which has a role in B-cell differentiation, involving regulation of CD19.

Somatic mutations
Usually deletions.

KRAS (Kirsten rat sarcoma 2 viral oncogene homolog)

Location
12p12.1

Protein
RAS oncogene that is a member of the small GTPase family.

NRAS (neuroblastoma RAS viral oncogene homolog)

Location
1p13.2

Protein
RAS oncogene that is a member of the small GTPase family.

CRLF2 (cytokine receptor-like factor 2)

Location
Xp22.33

Protein
Encodes cytokine receptor-like factor 2 which is a lymphoid signaling receptor that dimerizes with interleukin-7 receptor (IL7R) to form a receptor for thymic stromal lymphopoietin (TSLP). This complex (CRLF2/IL7R/TSLP) can stimulate cell proliferation through activation of STAT3 and STAT5.

Somatic mutations
Most commonly, translocations occur with P2RY8 or IGH. In addition to the translocations, in some patients activating mutations in CRLF2 can also occur.

P2RY8 (purinergic receptor P2Y, G-protein coupled, 8)

Location
Xp22.33

Protein
Encodes a G-protein coupled purinergic receptor (P2Y, G-protein coupled, 8).

Somatic mutations
Through an interstitial deletion, the first noncoding exon of this gene hybridizes with the coding region of CRLF2.

IGH (Immunoglobulin Heavy)

Location
14q32.33

Protein
Immunoglobulin heavy chain.

Somatic mutations
Through a translocation, this gene hybridizes to CRLF2.

Result of the chromosomal anomaly

Hybrid gene

Note
The P2RY8/CRLF2 fusion is much more common than the IGH/CRLF2 fusion.

Description
An interstitial deletion in the pseudoautosomal region 1 (PAR1) of Xp22.3/Yp11 occurs in the P2RY8/CRLF2 fusion, hybridizing the first noncoding exon of P2RY8 to the entire coding region of CRLF2 [del(X)(p22.33p22.33)/del(Y)(p11.32p11.32)].
Alternatively, a translocation occurs between CRLF2 and IGH resulting in t(X;14)(p22;q32)/t(Y;14)(p11;q32).

Detection
These fusions can be detected by FISH or RT-PCR.

Fusion protein

Oncogenesis
Results in overexpression/dysregulated expression of CRLF2.

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Leukaemia Section

Review

Myelodysplastic syndrome with excess blasts

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Abstract

Myelodysplastic syndrome with excess blasts (MDS-EB) represents the most clinically aggressive end of the continuum of the myelodysplastic syndromes (MDS). All MDS are characterized by clonal, ineffective hematopoiesis with maturation defects and increased apoptosis resulting in peripheral blood cytopenias, abnormal myeloid maturation (dysplasia) and variable risk of progression to bone marrow failure and/or acute myeloid leukemia. Progressive degrees of restricted myeloid maturation represented by abnormally increased numbers of morphologically-defined blasts in the blood and/or bone marrow is the key feature separating MDS-EB from the other myelodysplastic syndromes and is strongly associated with increased risk of disease progression and decreased survival. Metaphase chromosome analysis of bone marrow myeloid cells is the cornerstone of documenting clonal hematopoiesis to establish the diagnosis of MDS and for risk stratification of patients with confirmed MDS. Molecular analyses are becoming increasingly utilized for diagnosis and prognosis.

KEYWORDS
Myelodysplastic syndrome, blast, mutation, karyotype, chromosome, deletion, monosomy.

Identity

Other names

Refractory anemia with excess blasts (W.H.O. 2001, W.H.O. 2008, F.A.B. 1976, F.A.B 1982). Myelodysplastic syndrome with excess blasts is the W.H.O. 2016 s name.

Clinics and pathology

Disease

Myelodysplastic syndrome with excess blasts (MDS-EB) is a clonal disorder of hematopoietic stem cells (HSC) characterized by morphologically disordered maturation ("dysplasia") and restricted maturation of the myeloid lineages in the bone marrow resulting in ineffective hematopoiesis, cytopenias, increased blasts (5-19% of blood or bone marrow nucleated cells), and increased risk of progressive bone marrow failure and/or developing acute myeloid leukemia. Disease-specific morbidity and mortality is related to cytopenias, i.e. anemia, neutropenia, and thrombocytopenia resulting in infection and/or bleeding, due to progressive bone marrow failure and/or development of acute leukemia.

Phenotype/cell stem origin

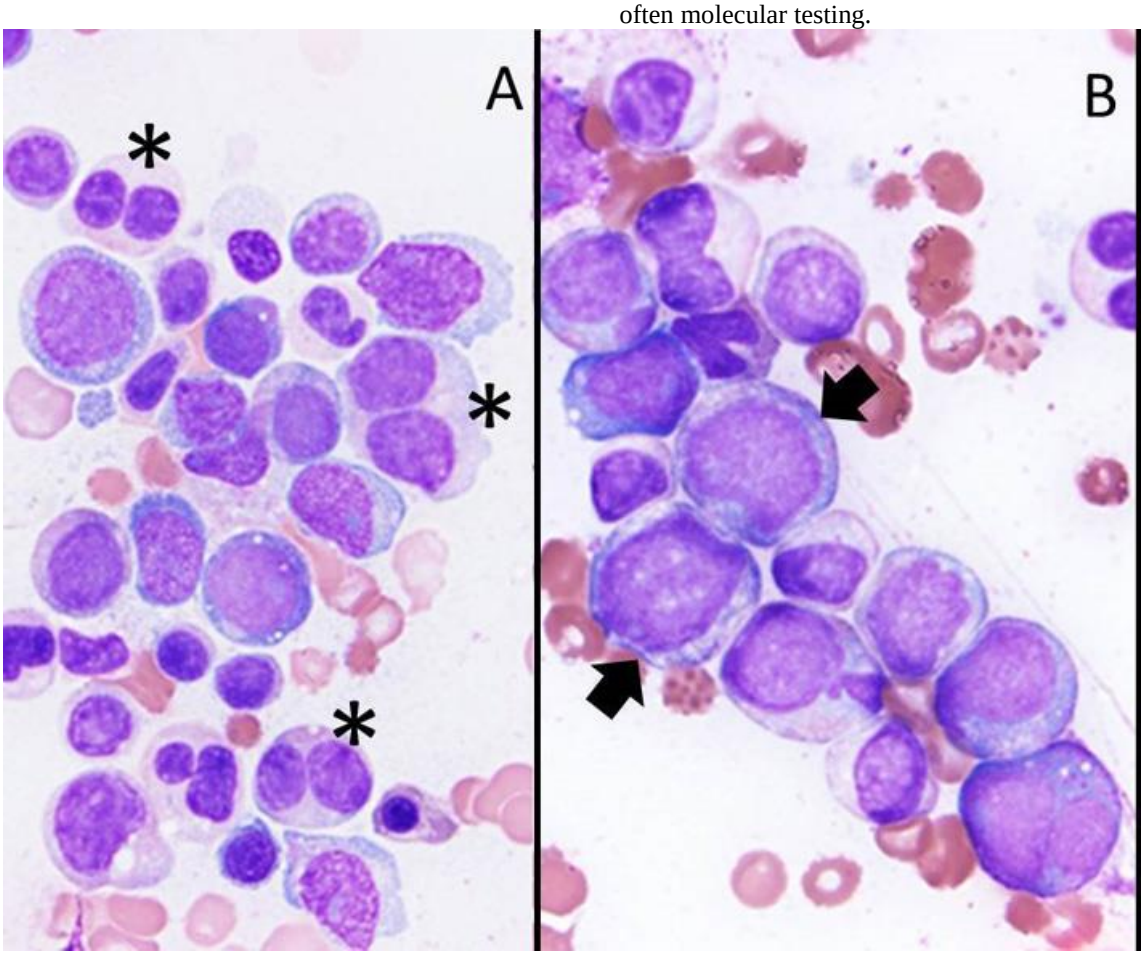
Recent work suggests that the leukemia stem cell in myelodysplastic syndromes is a specific hematopoietic stem cell with the following phenotype: Lin-, CD34+, CD38-, CD90+, and CD45RA- (Woll et al., 2014).

Epidemiology

Myelodysplastic syndromes may affect individuals of any age, gender or ethnicity. Accurate measurement of the incidence of myelodysplastic syndromes, including MDS-EB, is very difficult to obtain due to underreporting and underdiagnosing, but clearly shows a marked increase incidence with age. Some estimates are as high as 63.9 / 100,000 in people ≥85 y.o. (Cogle et al., 2015). The median age of diagnosis is around 71 years (Pfeilstöcker et al., 2016).

Clinics

Patients may present with asymptomatics cytopenias identified on routine laboratory testing or due to symptoms related to cytopenias, e.g. fatigue or exercise intolerance due to anemia, infections due to neutropenia and/or bleeding due to thrombocytopenia. Diagnosis requires examination of blood and bone marrow for morphological features of disordered maturation of myeloid lineages ("dysplasia") and enumeration of blast cells in blood and marrow correlated with genetic and often molecular testing.



Bone marrow aspirate smear from a patient with MDS-EB (Wright-Geimsa, 1000X). A. Extensive dysgranulopoiesis with marked nuclear-to-cytoplasmic dyssynchrony, numerous "Pelgeroid" segmented neutrophils with bilobed nuclei and hypogranular cytoplasm (∗) and giant forms. B. Increased blasts (arrows).

Cytogenetics

Metaphase chromosome analysis remains a crucial pillar in the diagnosis and prognosis of patients with MDS. Overall, about 40-50% of all individuals with de novo MDS will show a clonal chromosomal abnormality at the time of diagnosis (Greenberg 2012). Not surprisingly, the likelihood of identifying a clonal chromosomal abnormality is correlated with the severity of the disease, e.g. about 32 %patient's with MDS with single-lineage dysplasia and

Chromosomal abnormalities in myelodysplastic syndromes are myriad, but the most common are unbalanced resulting in net loss/gain of chromosomal material, such as monosomy, deletions and/or unbalanced translocations, and trisomy. Specifically, the incidence of common chromosomal abnormalities in MDS with an abnormal karyotype is: del(5q) (30%), -7/del(7q) (21%), +8 (16%), -18/18q- (7%), 20q- (7%), -5 (6%), -Y (5%), -17/17p- (including isochromosome (17q)) (5%), +Mar (5%), +21 (4%), inv/t(3q) (4%), -13/13q- ID: 1096 (4%), +1/+1q (3%), -21 (3%), +11 (3%), 12p- (2%), t(5q) (2%), 11q- (2%), and t(7q) (2%). MDS-EB is enriched for unfavorable risk abnormalities (i.e. ≥ 3 abnormalities or any chromosome 7 abnormality) as compared to MDS with <5% blasts. (Haase 2017)

The most recent multinational study of prognosis in MDS created a Revised International Prognostic Scoring System (IPSS-R) (Greenberg et al.,2012) stratified chromosomal abnormalities into 5 categories: Very good, good, intermediate, poor and very poor as follows: (Schanz et al, 2012).

In contrast to acute myeloid leukemia (AML), balanced reciprocal translocations are conspicuously uncommon in MDS-EB.

IPSS-R Cytogenetic Risk Categories		
Very Good:	*Single:*	del(11q), -Y
Good:	*Single:*	Normal, del(5q), del(12p), del(20q)
	Double:	including del(5q)
Intermediate:	*Single:*	del(7q), +8, i(17q), +19, any other, independent clones
	Double:	any other
Poor:	*Single:*	inv(3)/t(3q)/del(3q)
	Double:	including -7/del(7q)
	Complex:	3 abnormalities
Very poor:	*Complex:*	Greater than 3 abnormalities

I.

Genes

As about 40% of patients with MDS-EB will have normal metaphase chromosomes, many investigators have sought to use higher-resolution molecular techniques to identify diagnostic, prognostic and predictive molecular aberrations.

The use of FISH for as an adjunct to metaphase chromosome analysis in MDS is controversial. Many physicians routinely request a panel of interphase FISH probes to common and/or clinically significant abnormalities (e.g. -5/5q-, +8, -7/7q-, 20q-, 17p/TP53) a priori for all patients with suspected or confirmed MDS. However, several studies have shown essentially no additional clinically useful information is discovered with this technique if the metaphase study is adequate. Interphase FISH may be useful for specimens without adequate metaphases. Metaphase and/or interphase FISH may also be helpful to clarify subtle abnormalities of metaphase spreads.

Array comparative genomic hybridization (aCGH) and single nucleotide polymorphism array (SNP array) are particularly attractive methods to interrogate the entire genome at a fairly fine resolution to identify the gains and/or losses of chromosomal material that are common in MDS. Additionally, SNP arrays can identify copy-neutral loss of heterozygosity (CN-LAH) which can functionally inactivate tumor suppressor genes, similar to gross monosomies and deletions. These techniques have been shown to confirm most, but not all chromosomal abnormalities concurrently identified in metaphase chromosome analysis. They also detect additional abnormalities in genes or regions implicated in the pathogenesis or prognosis of patients with myeloid neoplasia. The precise clinical significance of detecting these submicroscopic chromosomal abnormalities in patients with MDS is currently under extensive study.

Sequence level techniques, including targeted sequencing of specific genes or broader whole-genome sequencing (WGS) may be used to document clonal hematopoiesis and to provide prognostic and predictive data to patients with established MDS. Targeted sequencing techniques will identify mutations in up to 90% of all MDS patients. Commonly mutated genes include: SF3B1, TET2, SRSF2, ASXL1, DNMT3A, RUNX1, U2AF1, TP53, and EZH2 (Haferlach et al., 2014). The clinical significance of specific mutations is currently evolving (Bejar et al, 2017).

In patients with MDS-EB, the issue of clonality is rarely a question, but the predictive information about which therapies may work for an individual patient may prove highly beneficial, such as mutations of IDH1 /IDH2 that can be targeted by specific drug therapies. In addition, these techniques

have identified novel genetic abnormalities and mechanisms, e.g. chromothripsis, which are improving our understanding of the mechanisms of disease development and progression (Abaigar et al., 2016).

Treatment

Treatment options for patients with MDS-EB include a broad spectrum of options from supportive care, low-intensity therapies, to high-intensity therapies +/- stem cell transplantation. Given that the incidence of MDS-EB is highly positively correlated with age, it is no surprise that many patients will have significant comorbidities and decreased performance status at the time of diagnosis, which are likely to limit their tolerance of higher-intensity chemotherapy and stem cell transplant.

Supportive care options are aimed at ameliorating or lessening symptoms and improving quality of life, such as RBC transfusion to improve symptoms of decreased oxygen carrying capacity or platelet transfusions for bleeding events. Antifibrinolytics may benefit patients who are unresponsive to platelet transfusion. Some patients may also respond to colony stimulating factors such as erythropoietin, granulocyte colony stimulating factor, granulocyte-monocyte stimulating factor and thrombopoietin mimetics.

Low intensity therapeutic options mostly center hypomethylating agents such as 5' azacytidine or decitabine or low-dose cytotoxic chemotherapies such a as cytosine arabinoside. Some patients will respond to immunosuppression (ATG) and/or biological response modifiers (lenalidomide) suggesting an immune-mediated etiology in some individuals.

High intensity treatments are similar to those used for acute myeloid leukemia such as intensive induction chemotherapy, e.g. idarubicin/daunorubicin, cytarabine/fludarabine, topoisomerase inhibitors, etc. +/- allogeneic stem cell transplantation.

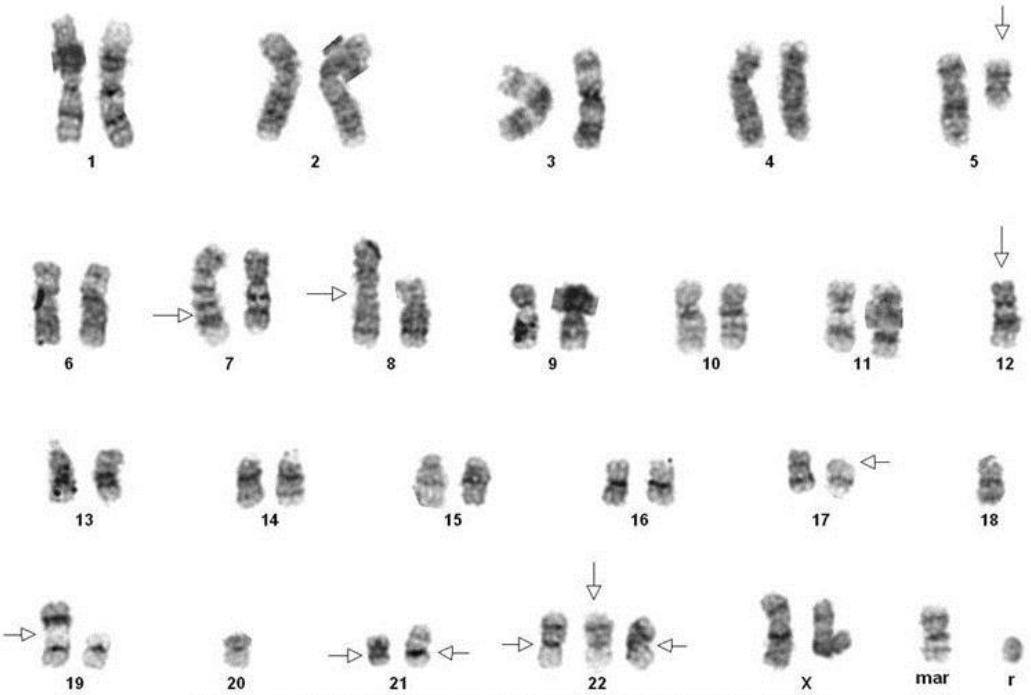
Evolution

MDS-EB is usually a clinically and genomically unstable disease state with a very high rate of progression to death due to bone marrow failure and/or acute myeloid leukemia (>20% blasts). Cytogenetic evolution often accompanies and/or precedes clinical and morphological progression.

Prognosis

The prognosis for patients with MDS has been studied intensively leading to several risk stratification models, e.g. IPSS, IPSS-R and IPSS-RA (ie, IPSS-R including age),the original WHO classification-based Prognostic Scoring System (WPSS) applying transfusion need, its modification using hemoglobin thresholds (WPSS 2011) and its modification including age (WPSS-A), and the Lower-Risk Prognostic Scoring System (LR-PSS). (Pfeilstoeker et al., 2016) The most commonly used system in clinical practice is the IPSS-RA. (Greenberg et al, 2012) These systems all incorporate chromosomal analysis with clinical and morphological features. Most patients with MDS-EB will be stratified into higher-risk categories with median overall survival about 9 months to 2 years and about 50-90% risk of progression to AML within 5 years.

Cytogenetics



46,XX,del(5)(q13q35),der(7)t(7;12)(q32;q13),i(8)(q10),-12,
add(12)(p11.2),del(17)(p11.2),-18,der(19)t(11;19)(q13;p13.3),-20,
add(21)(p11.2),add(21)(p11.2),add(22)(p11.2)x2,+add(22)(p11.2),+r,+mar

Abnormal karyogram from the bone marrow of a patient with MDS-EB showing a highly complex karyotype with numerous monosomies and unbalanced translocations resulting in net loss of chromosomal material. Common abnormalities associated with MDS include del(5q), -7q, del(17p), -18, -20 are illustrated. Karyogram and interpretation provided by Rhett P. Ketterling, M.D., Mayo Medical Laboratories, Rochester, MN, USA.

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Leukaemia Section

Review

Subcutaneous panniculitis-like T-cell lymphoma

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Abstract

Review on Subcutaneous panniculitis-like T-cell lymphoma, with data on clinics and the genes possibly involved.

KEYWORDS
Subcutaneous panniculitis-like T-cell lymphoma; NAV3; IDO1; IFNG; CXCR3; CCL5; ARID1B; SMARCA4; CHD4; MTOR; TSC1

Clinics and pathology

Disease

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a lymphoma derived from cytotoxic α/β T cells that preferentially involves subcutaneous tissue (Gonzalez, Medeiros et al. 1991; Salhany, Macon et al. 1998; Parveen and Thompson 2009). The definition of SPTCL was revised in the 2008 World Health Organization (WHO) classification to exclude cases of γ/δ T-cell origin; these latter cases are now classified as primary cutaneous T-cell γ/δ lymphoma (Harris, Swerdlow et al. 2008).

Etiology

No specific etiologic factor has been identified for SPTCL. Autoimmune diseases occur in approximately 20% of patients and some cases show overlapping histologic features with subcutaneous lupus (Marzano, Berti et al. 2000). The lesions have been associated with rheumatoid arthritis (Levy, George et al. 1997), inflammatory bowel disease (Hoque, Child et al. 2003), and Sjögren syndrome (Yokota, Akiyama et al. 2009) . Lesions occurring following transplantation also have been described; however, a clear association with Epstein-Barr virus or other infectious agents has not been identified (Salhany, Macon et al. 1998; Go and Wester 2004; Bregman, Yeaney et al. 2005).

Epidemiology

SPTCL represents less than 1% of all non-Hodgkin lymphomas. It affects both children and adults with a median age of onset of 35 years. It is slightly more common in women but no racial or ethnic predisposition has been reported (Kumar, Krenacs et al. 1998; Weenig, Ng et al. 2001; Willemze, Jansen et al. 2008).

Clinics

Patients with SPTCL typically present with solitary or multiple painless subcutaneous nodules or plaques. The lesions are most commonly located on the lower extremities but the upper extremities and trunk may also be involved. The lesions may be small or measure several centimeters. The nodules may become necrotic but ulceration is rare (Willemze, Jansen et al. 2008; Parveen and Thompson 2009). Systemic symptoms, including fever, fatigue, and weight loss are reported in approximately half of cases while hemophagocytic

syndrome is seen in 15-20% of cases (Marzano, Alessi et al. 1997).

Pathology

SPTCL is characterized by a dense subcutaneous infiltrate of small to medium-sized lymphoid cells. The infiltrate involves the fat lobules, usually with relative sparing of septa. Typically, there is minimal involvement of the overlying epidermis and dermis. The adipocytes characteristically show rimming by neoplastic lymphocytes. Macrophages and vacuolated histiocytes with associated fat necrosis and karyorrhectic debris are commonly present (Parveen and Thompson 2009). Erythrophagocytosis by histiocytes is occasionally seen (Gonzalez, Medeiros et al. 1991; Salhany, Macon et al. 1998; Willemze, Jansen et al. 2008).

By immunohistochemistry, the tumor cells have a mature alpha-beta cytotoxic T-cell phenotype and are characteristically positive for CD3 and CD8 and negative for CD4. The cytotoxic proteins granzyme B, TIA-1, and perforin are usually present (Kumar, Krenacs et al. 1998). Rarely, there is co-expression of CD4 and CD8 while the absence of both CD4 and CD8 should prompt consideration of a γ/δ T-cell lymphoma (Santucci, Pimpinelli et al. 2003; Kong, Dai et al. 2008).

In situ hybridization for Epstein-Barr virus-encoded RNA (EBER) is negative in almost all cases (Salhany, Macon et al. 1998).

Treatment

Multi-agent chemotherapy has traditionally been used for the treatment of SPTCL but more recent studies suggest that conservative immunosuppressive agents such as cyclosporine, steroids or chlorambucil may be as effective and should be considered in patients without associated hemophagocytic syndrome (Tsukamoto, Katsunobu et al. 2006). Local radiation therapy has been used effectively in patients presenting with a solitary lesion (Willemze, Jansen et al. 2008). For patients with more aggressive disease, anthracycline-based combination chemotherapeutic regimens with or without stem cell transplantation are frequently used (Go and Wester 2004).

Prognosis

SPTCL generally is a clinically indolent disease with a waxing and waning course. The 5-year disease-specific survival is around 80% (Gonzalez, Medeiros et al. 1991; Salhany, Macon et al. 1998). In most patients the disease remains confined to the subcutaneous tissue, and spread to lymph nodes and internal organs is rare. Patients who develop hemophagocytic syndrome generally have a poor outcome (Aronson, West et al. 1985; Gonzalez, Medeiros et al. 1991). Most previous reports of SPTCL with a rapidly fatal course in the absence of hemophagocytic syndrome are probably attributable to inclusion of γ/δ T-cell lymphomas, which have a much worse prognosis, in the previous classification of SPTCL (Toro, Liewehr et al. 2003).

Genetics

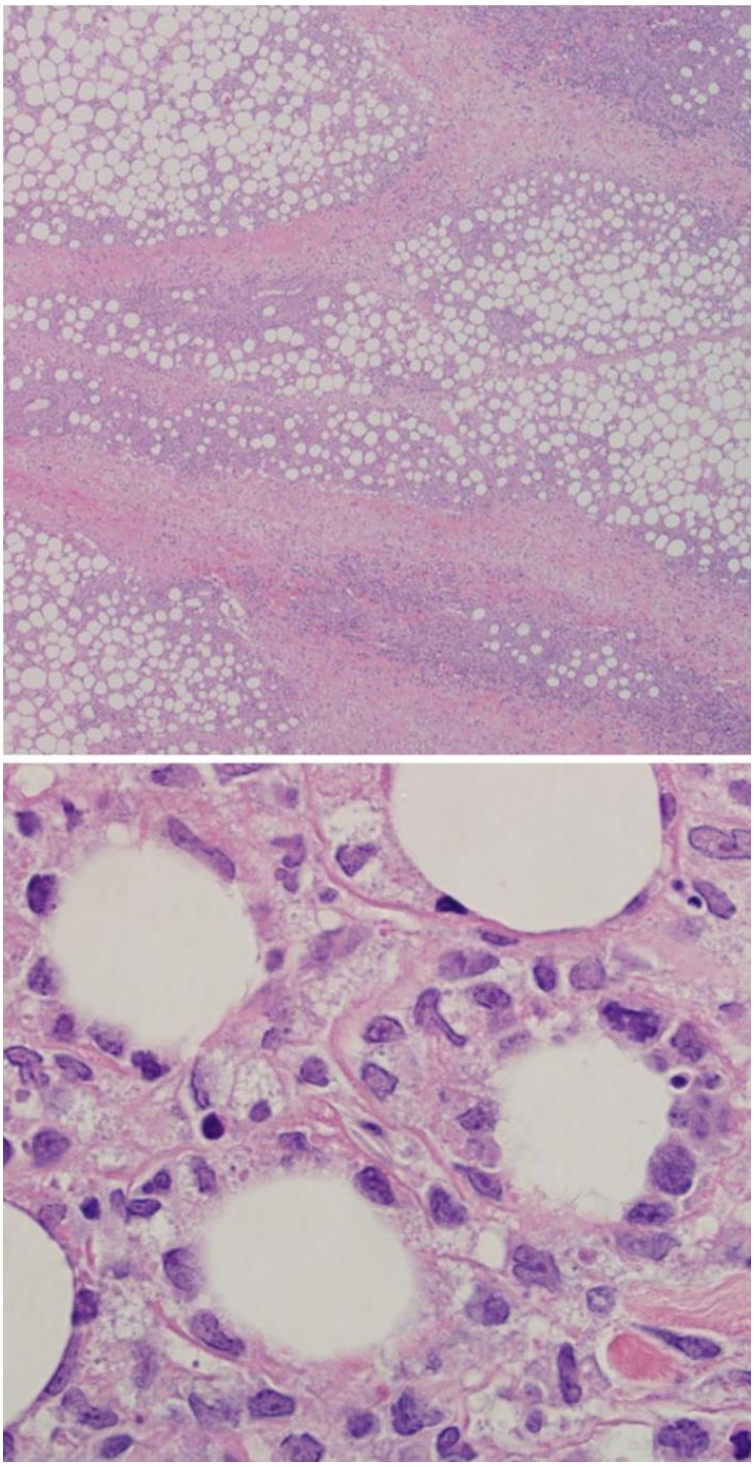
Note

Polymerase chain reaction (PCR) analysis of SPTCL has shown clonal rearrangements of the TCR β, γ, and α genes without evidence of clonal immunoglobulin gene rearrangements (Ghobrial, Weenig et al. 2005; Willemze, Jansen et al. 2008; Kong, Dai et al. 2009).

Deletion of NAV3 (neuron navigator 3) gene has been identified in approximately 50% of cases by fluorescence in situ hybridization (FISH) and loss of heterozygosity (LOH) assays (Hahtola, Burghart et al. 2008).

Gene expression microarray and quantitative PCR analysis have shown upregulated expression of indoleamine 2,3-dioxygenase (IDO1), an immunotolerance-inducing gene, along with upregulation of Th1 type cytokines, most notably IFNG, CXCR3, and CCL5. Over-expression of these genes may contribute to the formation of an immunosuppressive microenvironment, favorable for the neoplastic T-cells

A recent next-generation sequencing study has identified recurrent mutations in epigenetic modifiers and the PI3K/AKT/mTOR pathway in SPTCL, with mutations in ARID1B, SMARCA4, CHD4, MTOR, and TSC1 each observed in 3/18 cases (Li, Lu et al. 2017).



Subcutaneous panniculitis-like T-cell lymphoma. At low power (top), the tumor can be seen infiltrating the fat lobules. At high power (bottom), cytologically atypical tumor cells can be seen "rimming" the fat spaces.

Cytogenetics

Cytogenetics morphological

Relatively few cases have been analyzed by conventional cytogenetics and no consistent abnormalities have been identified.

Cytogenetics molecular

Several DNA copy number abnormalities have been identified by comparative genomic hybridization (CGH), including losses of chromosomes 1p, 2p, 2q, 5p, 7p, 9q, 10q, 11q, 12q, 16, 17q, 19, 20, and 22, and gains of chromosomes 2q, 4q, 5q, 6q, 13q. Some of these changes overlapped those seen in other cutaneous T-cell lymphomas, whereas alterations of

chromosomes 5q and 13q appeared unique to SPTCL (Hahtola, Burghart et al. 2008).

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Leukaemia Section

Short Communication

t(18;21)(p11;q11)

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Abstract

Chromosome translocation between the short arm of chromosome 18 and the long arm of chromosome 21 including the t(18;21)(p11;q11) is a rare event, reported only in sporadic cases.

KEYWORDS
Chromosome 18; Chromosome 21; Acute erythroleukemia; AML-M6; Acute lymphoblastic leukemia; Follicular lymphoma.

Clinics and pathology

Disease

Acute erythroleukemia (FAB type M6), acute lymphoblastic leukemia (ALL) and follicular lymphoma

Epidemiology

Only 3 cases to date: a 71-years old male diagnosed with acute erythroleukemia (Cigudosa et al., 2003), a female patient with follicular lymphoma (Lestou et al., 2003) and a 27-years old male with B-cell ALL (present case, personal observation).

Prognosis

Unknown (sporadic cases described). The ALL patient relapsed after 7 months of therapy and was alive in the last follow-up 2 years from the diagnosis.

Cytogenetics

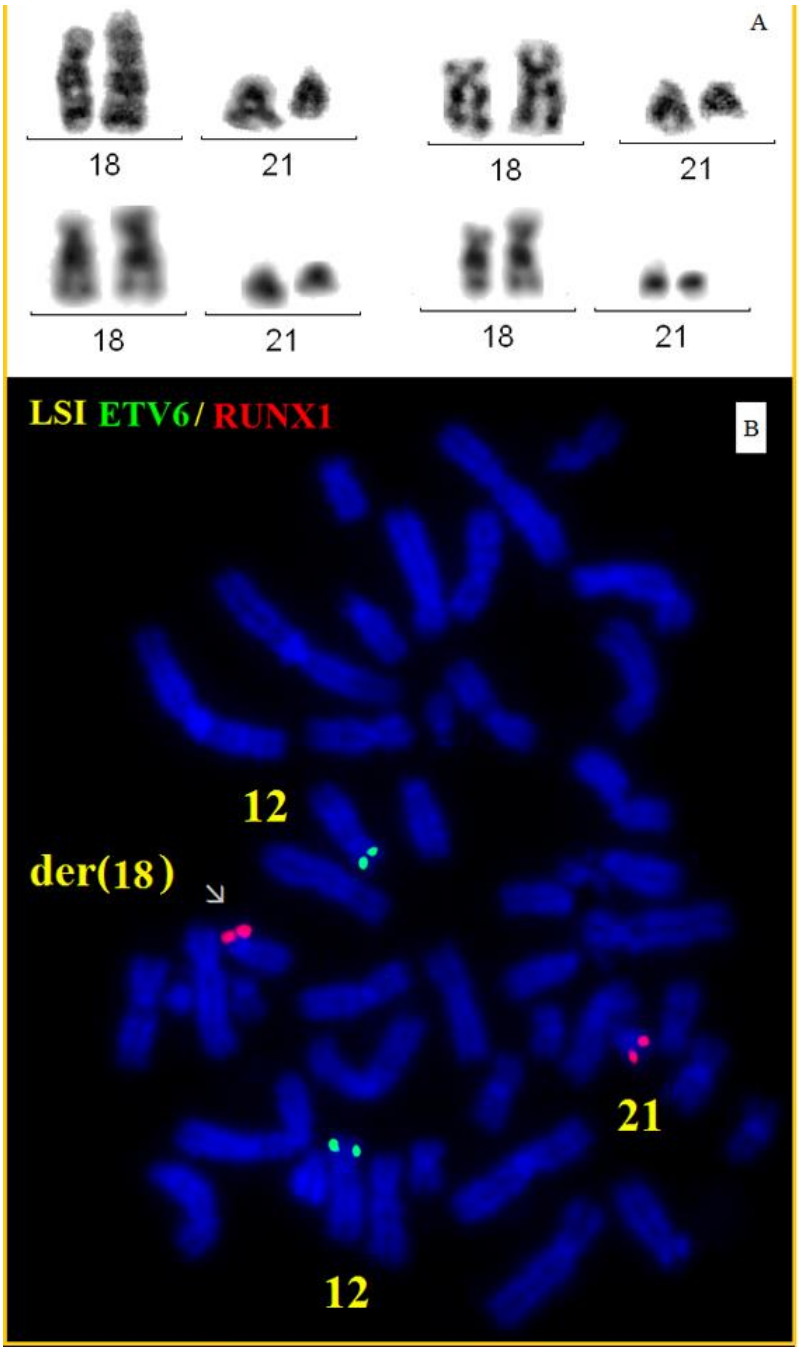
Note
Breakpoints on 18p and 21q are difficult to ascertain in suboptimal preparations.

Additional anomalies

Associated with del(5)(q13q31) del(5)(q13q31), monosomy 7, hsr and complex karyotype in the AML case (Cigadusa et al., 2003), del(5)(q15q31), +7, t(14;18)(q32;q21) in the lymphoma case (Lestou et al., 2003) and with homozygous 9p deletion (70% of cells), detected by fluorescence in situ hybridization in the present case.

Variants

Genes involved are unknown.



Partial karyotypes with t(18;21)(p11;q11) (A). Fluorescence in situ hybridization with LSI TEL-AML1 probe (Vysis/Abott Molecular, US) probe showing relocation of AML1 (RUNX1) sequences from 21q22 to the short arm of chromosome 18 (B).

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Solid Tumour Section

Review

Kidney: Renal Oncocytoma

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RenalOncocytomaID5132. Atlas Genet Cytogenet Oncol Haematol
Kim HJ, Monzon FA. Kidney: Renal Oncocytoma. Atlas Genet Cytogenet Oncol Haematol 2009;13(4)

Identity

Phylum
Urinary system:Kidney:Adult:Oncocytoma/oncocytosis

Classification

Note
Renal Oncocytoma is a benign renal epithelial neoplasm that comprises approximately 5-9% of renal tubular epithelial tumors.

Clinics and pathology

Note
The first case of renal oncocytoma was reported by Zippel in 1942. Since then this tumor have been described as proximal tubular adenoma with oncocytic features and later oncocytoma became the generally accepted term.

Embryonic origin

Many investigators have suggested that these tumors originate from intercalated cells of the collecting system.

Etiology

Renal oncocytomas can present in familial or sporadic forms. Oncocytomas may be seen in patients with Birt-Hogg-Dube syndrome (BHD, who carry germline mutations in the folliculin gene (FLCN). However, sporadic cases are much more common and have an unknown etiology.

Epidemiology

Renal oncocytomas account for about 5-9% of all renal tumors and occur across a broad age range, peaking in the seventh decade. There is a male predominance (2:1) and tumors are frequently small and found incidentally. A rare association between oncocytoma and angiomyolipoma or tuberous sclerosis has been reported..

Pathology

Macroscopically, renal oncocytomas are well-circumscribed, slightly lobulated solid tumors with generally mahogany brown or dark red cut surface. The tumors are typically solitary, but can be multifocal or bilateral. A central scar is frequently observed. Some cases show involvement of the perinephric fat or rarely the renal vein with no change in prognosis. Microscopically, the tumor is composed of nests and tubular structures made up from oncocytic cells, and is frequently associated with fibrous or edematous stroma. The tumor cells are large round eosinophilic cells with granular cytoplasm that is packed with mitochondria. Nuclei are round and monomorphic and contain small nucleoli. Tumor cells around the central scar are small with scant cytoplasm. Bizarre cells with

pleomorphic nuclei may be present in some tumors and have no affect on outcome. Mitoses and necrosis are not seen. Tumor cells are typically immunoreactive for KIT, S100A (multifocal), and HNF1beta, and are negative for CD10, AMACR and vimentin. CK7 is usually negative or patchy positive with immunoreactivityini single scattered cells; this is in contrast to chromophobe renal cell carcinoma which shows diffuse membranous positivity.

Rare cases that show multiple oncocytic tumors can be referred to as oncocytosis. Oncocytosis, as well as hybrid oncocytic tumors may occur sporadically or in association with Birt-Hogg-Dubé syndrome. .

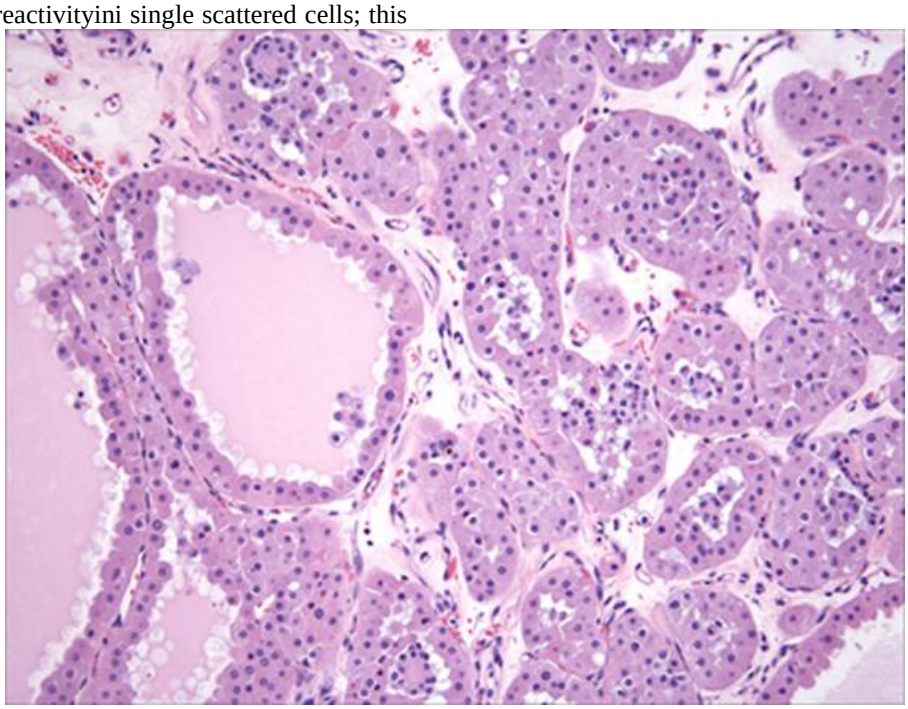

Figure 1A: Oncocytoma is a benign renal epithelial neoplasm. Oncocytomas contain small oncocytic cells with round, regular nuclei that sometimes contain a small nucleolus. Architecturally the tumors are solid, nested or tubular, and are frequently associated with edematous stroma.

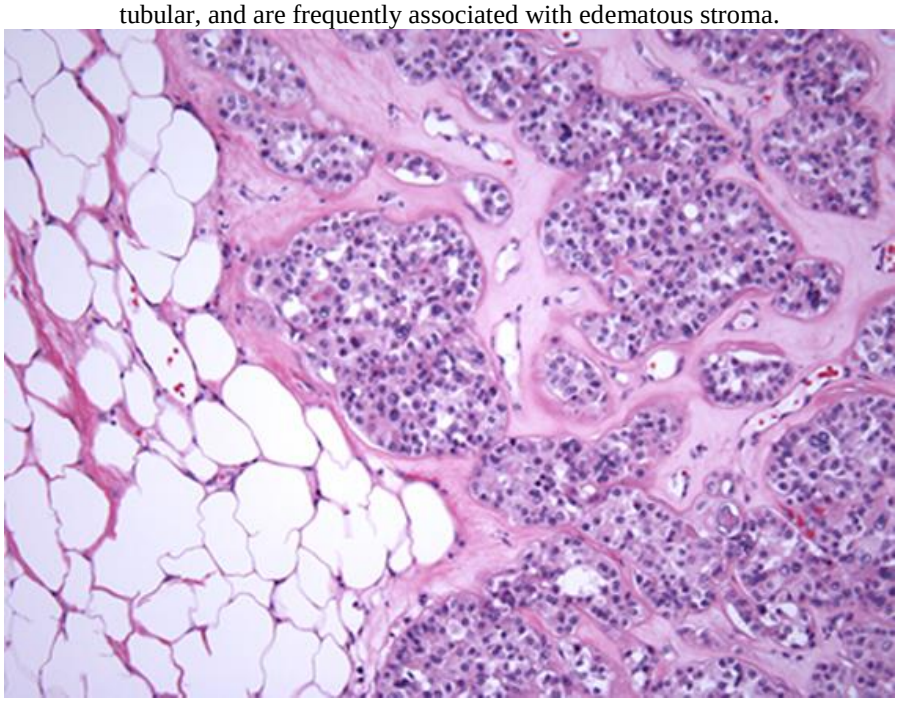

Figure 1B: Occasionally oncocytomas extend into perinephric adipose tissue; this findings has no affect on clinical outcome (i.e., the tumor is still benign).

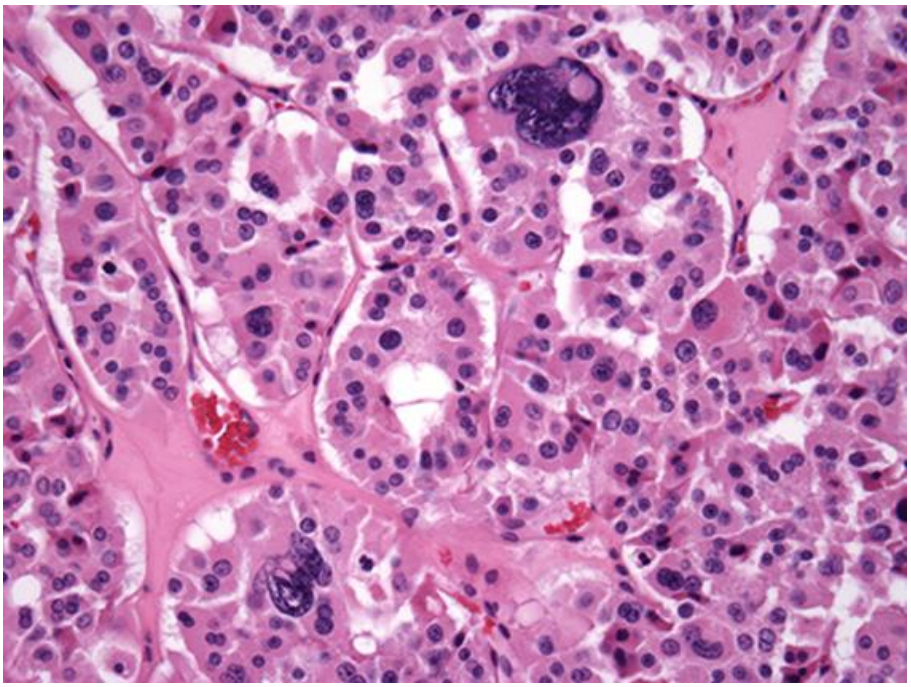

Figure 1C: A small subset of oncocytomas demonstrate nuclear atypia and/or multinucleation. Some think this is due to degenerative change. Regardless, these nuclear features do not affect clinical outcome (i.e., the tumor is still benign).

Treatment

Most patients with RO are treated with nephrectomy. Nephrectomy (radical or partial). Enucleation, wedge resection or ablation may also be considered for treatment options but are less common.

Prognosis

Oncocytomas behave in a benign fashion. Atypical pathologic features, such as nuclear pleomorphism, perinephric fat involvement and extension into renal vein branches do not influence prognosis.

Cytogenetics

Note

Oncocytomas frequently exhibit losses of chromosome 1/1p-, chromosome 14 and/or a sex chromosome. Structural rearrangements of 11q13 have been reported, with t(5;11) and t(9;11) representing the most common translocations. A t(6;9)(p21;p23) has been reported in three cases of oncocytoma (Balzarini et al., 1999; Hudacko et al., 2011). A subset of oncocytomas exhibit non-recurrent numerical or structural abnormalities A normal karyotype is also frequently observed.

One of the diagnostic pitfalls in renal epithelial tumors is distinguishing between benign RO from the eosinophillic variant of chromophobe carcinoma. Many studies have reported that chromophobe RCC shows complex simultaneous losses of chromosomes 1, 2, 6, 10, 13, 17, and 21. Although occasional losses of all these chromosomes have been reported in RO, the simultaneous loss of all these chromosomes has not been seen in oncocytomas.

Genes involved and proteins

Note

Mitochondrial DNA mutations that disrupt components of complex I in the electron transport chain can be found in bilateral and multifocal oncocytomas (Lang et al., 2015).

FLCN (folliculin gene)

Location

17p11.2

Note

Germline mutations in FLCN cause Birt-Hogg-Dubé syndrome, an inherited disorder characterized by follicular hamartomas, renal tumors, pulmonary cysts, and spontaneous pneumothorax. Hybrid oncocytic/chromophobe tumors and chromophobe renal cell carcinomas are the most common renal tumors in Birt-Hogg-Dubé syndrome, but oncocytomas may be seen in a subset of cases. The renal tumors are typically bilateral and multifocal.

Protein

Folliculin is a putative tumor suppressor that plays a role in the regulation of energy homeostasis and AMPK and CC: TXT: mTOR ID: 40639> signaling.

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