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High expression of CUL4A promotes the growth of hepatocellular carcinoma

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More and more findings demonstrate that dysfunction of ubiquitin-proteasome pathway contributes to aberrant cell growth and differentiation in Hepatocellular Carcinoma (HCC), a highly aggressive malignancy. As one member of Cullin family, CUL4A E3 ubiquitin ligases known to regulate cell cycle DNA replication, DNA repair and chromatin remodeling. In recent years, CUL4A is involved in tumorogenesis and development in human cancers. In this study, we attempt to analyze the expression pattern of CUL4A in the HCC and to explore its possible roles in the development and progression of HCC. Firstly, we investigated CUL4A expression of cancerous and their paired paracancerous tissues from HCC patients by immunohistochemistry (IHC) and analyzed its correlation with clinicopathological indices. Next, the effects of CUL4A on cell proliferation were examined in cultured HCC cell line by cell growth curve assay. IHC analysis showed that CUL4A expression in HCC tissues was significantly higher than that of the corresponding adjacent tissues. Importantly, CUL4A expression in HCC tissues was positively correlated with tumor size, tumor differentiation, TNM stage, and lymphatic and venous invasion. Cell growth curve assay showed that CUL4A siRNA inhibited the growth of both BEL7402 and HepG2 cells. This study demonstrates that CUL4A played anti-tumor roles in hepatocarcinogenesis by accelerated cell growth and migration. This work provides new insights into the biological role of CUL4A in carcinogenesis and provided a new candidate target for clinical therapy of HCC.

Financial support: This work was supported by grants from the National Science Foundation of China (No. 81171642, 81372211, 81300297), the Foundation for Outstanding Young Scientist in Shandong Province (No. BS2011YY032), the Independent Innovation Foundation of Shandong University (IIFSDU, 2012TS174), the Shandong Science and Technological Development Project (SDSTDP, 2013GSF11859).

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The combinatory effects of PPAR-gamma agonist and Survivin inhibition on the cancer stem-like phenotype and cell proliferation in bladder cancer cells

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The strategies for PPAR activation or Survivin inhibition are proposed as the potentials for cancer therapy. However, it is still unknown whether the combination of these two approaches can be developed as a rational regimen with enhanced efficiency in the inhibition of tumor cells. In this study, we investigate the combinatory effect of PPAR-gamma agonist and Survivin inhibition on bladder cancer cells. We found that, in the human bladder cancer cell lines T24 and 5637, the natural PPAR-gamma ligant 15d-PGJ_2 significantly decreased the cell proliferation and loci formation. The increase in the proportion of apoptotic cells was observed in the cells 48 hours after 15d-PGJ_2 treatment. Furthermore, 15d-PGJ_2 substantially inhibited the levels of stemness-related genes in these cells. The ability of sphere formation was absolutely suppressed in the cells treated with 15d-PGJ_2. More importantly, the downregulation of Survivin with siRNAs significantly enhanced 15d-PGJ_2 -mediated induction of cell apoptosis and inhibition of sphere formation. Accordingly, we also found that Survivin inhibition significantly enhanced 15d-PGJ_2-induced production of reactive oxygen species (ROS) in bladder cancer cells. Taken together, these findings suggest that the combination of 15d-PGJ_2 and Survivin inhibition may be a potential for the therapeutical manipulation of bladder cancer.

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Evidence-based cancer care requires development of patient population-specific molecular biomarkers

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Colorectal cancer (CRC) is the third most common cancer in the world. The pathologic stage, most commonly used for prognosis, may not be the best indicator of outcome, since patients with tumors of identical stage have different treatment responses and outcomes. Thus, there is a need to identify markers of therapy efficacy (predictive), disease recurrence, and patient survival (prognostic). Due to contradictory results, no marker has achieved acceptable clinical utility. These differences may be due to technical discrepancies, under-powered study populations, an admixture of different proportions of racial/ethnic/geographic groups, or to different tumor sites within the colorectum, tumor stages, and/or patient demographics. For example, our studies have suggested that abnormal nuclear accumulation of p53 in CRCs is a strong indicator of poor patient survival of non-Hispanic Caucasians (CAs) with proximal colon tumors; however, it has no prognostic value for AAs or CAs with distal or rectal tumors[1]. In AAs, but not CAs, the Pro/Pro phenotype correlates with a higher incidence of missense p53 mutations, nodal metastasis, and higher mortality due to CRC[2]. Lack of or decreased expression of Bcl-2 as a strong predictor of early disease recurrence and of a poor prognosis, particularly among patients with Stage II tumors[3]; in contrast, increased expression of $p27^{Kip-1}$ is an indicator of good prognosis for patients with Stage III tumors[4]. Patients with CRCs expressing high levels of Bax have worse survival when they receive chemotherapy; however, patients treated only with surgery and with CRCs lacking Bax expression had higher mortality than those with high Bax expression[5]. Further, analysis of a panel of six miRNAs suggests that, after treatment, patients with higher levels of miRNA-21 have an increased risk of death for CAs. For AA patients, but not for CAs, the higher levels of miR-181b indicate a poorer prognosis[6]. Thus, potential confounding variables, such as tumor stage, location, and patient race/ethnicity should be taken into consideration in evaluating the clinical utility of molecular biomarkers.

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The effect of hypoxia on human skeletal muscle: molecular and cellular analysis

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The effects of a hypobaric, hypoxic environment and exercise performed under extreme conditions, such as at high altitudes, are intriguing physiological aspects that need to be investigated directly on human climbers. Their skeletal muscle is one of the main tissues that can suffer from hypoxia and physical challenges, which will both define the muscle adaptation and the molecular signature of regenerative capacity. We investigated the muscle regenerative capacity characterizing satellite cells isolated from Vastus Lateralis muscles biopsies obtained from six male volunteers (40 ± 14 years old) before and after the return from the Himalayan Expedition during which they were exposed to hypoxia living for about 30 days at 5,000 m a.s.l. Muscle needle biopsies were used for RNA isolation. A high-density oligonucleotide microarray technique was performed. The human oligonucleotide gene set consisting of 21,329 (70-mer) oligonucleotides (Operon version 2.0), designed on the basis of the Human Unigene clusters. Arrays were scanned and recorded fluorescence intensities were subjected to LOWESS normalization. The expression of each gene was defined as the log base-2 of the ratio between the intensity of cyanine-coupled aaRNA from post-expedition and those from pre-expedition samples. Our study shows that satellite cells were altered by hypobaric, hypoxic environments and exercise performed at high altitudes. Of note, in human skeletal muscle after this 5,000 m a.s.l. expedition, satellite cells showed a significantly lower ability to regenerate skeletal muscle, in respect to before this high-altitude expedition. This impairment appears to be due to reduced satellite cell activity, consistent with their decreased myogenicity and fusion ability. Furthermore, at the transcriptional level several pathways, such as cell cycle, myogenesis, oxidative metabolism, proteolysis and sarcomeric protein synthesis, were found dysregulated[1,2].

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