tumor chemosensitivity. In response to DNA damage, E2F1 is acetylated by PCAF and it is selectively recruited onto the P1p73 promoter to elevate TAp73 protein levels and to induce apoptosis. We show that hSirt1, PCAF and E2F1 co-immunoprecipitate and are co-recruited in vivo onto the P1p73 promoter. hSirt1 represses E2F1-dependent P1p73 promoter activity and inhibits its activation in response to DNA damaging drugs. The sirtuins inhibitor nicotinamide (NAM) induces p73 and APAF transcription but not affect the apoptotic target genes caspase 7 and Bim or the cell cycle genes DHFR and cyclin A. We also found that hSirt1 deacetylates PCAF in vitro and modulates both basal and p300-mediated acetylation of PCAF. In cells exposed to apoptotic DNA damage nuclear NAD^+ levels decrease and inactivate hSirt1, without altering either hSirt1 interaction with PCAF or hSirt1 binding to the P1p73 promoter. PCAF release from hSirT1 repression favours the assembly of transcriptionally active PCAF/E2F1 complexes onto the P1p73 promoter and p53-independent apoptosis. Indeed, doxorubicin-induced p53-independent apoptosis of Hep3B cells is potentiated by nicotinamide or specific hSirt1 siRNAs and abrogated by the hSirt1 activator resveratrol (RES). Finally, we show by qPCR that hSirt1 is highly expressed in human HCCs and its expression inversely correlates with TAp73 expression. Our results reveal that hSirT1 is a selective regulator of E2F1 transcription and identify hSirt1 and PCAF as potential targets to modulate liver tumor cell survival and chemioresistance irrespective to p53 status.

doi:10.1016/j.dld.2006.12.065

3 YEARS OF ADEFOVIR AND LAMIVUDINE COMBINATION THERAPY MINIMIZES THE RISK OF GENOTYPIC RESISTANCE TO ADV IN LAMIVUDINE RESISTANT PATIENTS

P. Lampertico[a], M. Viganò[a], E. Manenti[a], M. Iavarone[a], G. Lunghi[b], E. Del Ninno[a], M. Colombo[a]

[a] *Department of Gastroenterology, IRCCS Maggiore Hospital and University of Milan, Milan, Italy*
[b] *Department of Hygene, IRCCS Maggiore Hospital and University of Milan, Milan, Italy*

Background and aims. The risk of developing genotypic and clinical resistance to adefovir and virological breakthrough in lamivudine resistant patients treated long-term with a combination of adefovir and lamivudine is unknown.
Patients and methods. One hundred and forty five lamivudine resistant patients with chronic hepatitis B (84% HBeAg neg, 73% cirrhotics) were treated for more than 1 year (median: 30 months, range 12–65) with 10 mg/daily of adefovir added to ongoing lamivudine. HBV DNA was assessed every 2 months by Versant 3.0 and drug resistance was assessed by INNO-LiPA HDR V2 assay in viremic patients every year.
Results. Serum HBV-DNA became undetectable in 99/145 (68%), 70/92 (76%) and 43/52 (83%) patients after 1, 2 and 3 years, respectively. None of the patients who achieved undetectable HBV DNA or maintained persistently detectable viremia, showed >1 log rebound of HBV DNA compared to on-treatment nadir. Moreover, genotypic resistance for rtN236T was not identified in any patient. By converse, the rtA181T/V mutation was found in 4 (3%), 1 (1%), and 1 (2%) serum samples at 1, 2 and 3 years, respectively (overall, 6 patients, 4%). All the 5 patients with the rtA181T mutation, but not the one with the rtA181V, had a mixed viral population with the wild-type sequence rtA181A. The rtA181T/V mutants were already detected at baseline in 3 patients, as a mixed viral population with rtA181A. Despite the presence of HBV viral strains with rtA181T/V mutations, serum HBV DNA became undetectable in 4 of 5 patients during 6–12 months of follow-up. Overall, after 3 years of combined therapy, de-novo emergence of rtA181T mutation and persistence of >4 log copies/ml of serum HBV DNA were observed in 1 patient (0.7%), only. By converse, lamivudine-associated resistance mutations were confirmed in 93% of the samples, the pattern being similar to baseline.
Conclusions. Adefovir and lamivudine combination therapy is an effective strategy in lamivudine-resistant patients, since it minimizes the risk of genotypic resistance to ADV and prevents both virological rebound and clinical resistance up to 3 years.

doi:10.1016/j.dld.2006.12.066

CLINICAL SIGNIFICANCE OF SERUM AND LIVER TISSUE SCCA IN CHRONIC HEPATITIS C

L. Cavalletto[a], C. Caberlotto[a], F. Calabrese[b], P. Pontisso[a], E. Bernardinello[a], A. Biasiolo[a], C. Giacometti[b], A. Gottardo[a], A. Gatta[a], L. Chemello[a]

[a] *Department of Clinical and Experimental Medicine, University of Padua, Italy*
[b] *Department of Pathology, University of Padua, Italy*

Background and aim. Recently the ov-serpin squamous cell carcinoma antigen (SCCA) was detected in serum associated with IgM (SCCA-IC) in about one third of the patients with chronic hepatitis. Aim of this study was to relate serum levels and tissue expression of SCCA to histological evolution in chronic HCV infection.
Material and methods. Sixty-three consecutive out-patients (33/30 M/F; mean age ± S.D.: 48.2 ± 12.2 years) with chronic hepatitis C were tested in parallel for SCCA-IC (Hepa-IC, Xeptagen, Italy) and tissue-SCCA (Hepa-Ab, Xeptagen) at the time of biochemical tests and liver biopsy. Statistical evaluation was performed by *T*-test, *U*-test and Chi-square test as appropriate. The accuracy of SCCA-IC to diagnose disease evolution was defined by ROC curve analysis.
Results. Based on histological findings, the study population was grouped in cases without (F0–F2) and with (F3–F6) septal fibrosis. In the table below are shown the most significant results.

	Ishak < F3	Ishak ≥ F3	*p*-level
No. of cases (males)	32 (16)	31 (17)	
Mean age (years) ± S.D.	42.8 ± 12.9	53.7 ± 8.7	0.03
Mean GGT (UI/L) ± S.D.	44.9 ± 40.1	79.3 ± 53.6	0.01
Mean ferritin (ug/L) ± S.D.	115 ± 79	225 ± 148	0.01
Histologic grading: G ≤ 4/G > 4	22/10	11/20	0.01
Steatosis degree: 1/2	24/8	4/17	0.04
Mean SCCA-IC (AU/ml) ± S.D.	181.9 ± 163.3	697.9 ± 976.1	0.01
Tissue-SCCA: positive cases (%)	13 (41%)	24 (77%)	0.01

A significant correlation was found between serum level of SCCA-IC and liver SCCA expression in the same patient ($p = 0.01$). ROC curve analysis in cases without and with liver disease evolution discriminated the value of 190 AU/ml as the best cut-off for the prediction of evolution (AUC = 0.668; sensitivity 48.4%; specificity 84.4%; PPV 75% and NPV 63%).

Conclusions. Serum SCCA-IC appears significantly correlated to SCCA expression in the liver and circulating levels of the serpin are significantly higher in patients with liver disease evolution. This serum marker may represent a simple and reliable predictor of early progression to HCV-related cirrhosis.

doi:10.1016/j.dld.2006.12.067

EFFECT RADIOFREQUENCY THERMAL ABLATION OF HCC LIVER NODULES ON NATURAL KILLER CELLS AND REGULATORY T CELLS

A. Zerbini, M. Pilli, G. Pelosi, G. Menozzi, D. Laccabue, C.S. Cerioni, M.G. Pizzi, S. Schivazappa, C. Ferrari, G. Missale

Unit of Infectious Diseases and Hepatology, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy

Background and aim. Radiofrequency thermal ablation (RFA) of HCC has been shown to enhance tumor-specific T-cell responses in man and animal