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Novel p53 target genes secreted by the liver are involved in non-cell-autonomous regulation

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The tumor suppressor p53 is a transcription factor that prevents cancer development and is involved in regulation of various physiological processes. This is mediated both by induction of cell cycle arrest and apoptosis and by controlling the expression of a plethora of target genes, including secreted proteins. It has been demonstrated that p53 may exert its effect in non-cell-autonomous fashion by modulating the expression of genes that encode for secreted factors. In this study, we utilized our microarray data to identify and characterize novel p53 target genes expressed in human liver cells and associated with steroid hormones processing and transfer. We identified the steroid hormones binding factors, sex hormone binding globulin, corticosteroid-binding globulin and cytochrome P450 family 21 subfamily A polypeptide 2, as novel p53 target genes. Their expression and secretion were increased following p53 activation in various hepatic cells. We observed that p53 wild type mice exhibited higher levels of corticosteroid-binding globulin compared with their p53 null counterparts. We demonstrated that the induction of the steroid hormones binding factors can be mediated by binding to specific p53 responsive elements within their promoters. In addition, utilizing conditioned medium experiments we have shown that p53 dependent induction of sex hormone binding globulin secretion from liver cells enhances apoptosis of breast cancer cells. Moreover, depletion of sex hormone binding globulin abolished the induction of breast cancer cells death. The newly identified p53 target genes suggests a novel non-cell-autonomous tumor suppressive regulation mediated by p53 that is central for maintaining organism homeostasis.

Recent Publications

1. Solomon H, Dinowitz N, Pateras IS, Cooks T, Shetzer Y, Molchadsky A, Charni M, Rabani S, Koifman G, Tarcic O, Porat Z, Kogan-Sakin I, Goldfinger N, Oren M, Harris CC, Gorgoulis VG, Rotter V. Mutant p53 gain of function underlies high expression levels of colorectal cancer stem cells markers. Oncogene. 2018 Jan 18
2. Shmuel-Galia L, Klug Y, Porat Z, Charni M, Zarmi B, Shai Y. Intramembrane attenuation of the TLR4-TLR6 dimer impairs receptor assembly and reduces microglia-mediated neurodegeneration. J Biol Chem. 2017 Aug 11; 292(32):13415-13427
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5. Charni M, Rivlin N, Molchadsky A, Aloni-Grinstein R, Rotter V. p53 in liver pathologies-taking the good with the bad. J Mol Med (Berl). 2014 Nov 19.

Biography

Meital Charni-Natan- B.SC degree with high honors and departmental honors in life science, Ben-Gurion University of the Negev, Beer Sheva, Israel. MSc and PhD- Department of molecular cell biology, Weizmann Institute of Science, Rehovot, Israel. Thesis advisor: Prof. V. Rotter Topic: understanding the non-cell-autonomous function of the tumor suppressor p53 in the liver.

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