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

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Abstract

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 suggest a novel non-cell-autonomous tumor suppressive regulation mediated by p53 that is central for maintaining organism homeostasis.

Liver is an important secretory organ that consistently manages various insults in order to retain whole-body homeostasis. Importantly, it was suggested that the tumor-suppressor p53 plays a role in a variety of liver physiological processes and thus it is being regarded as a systemic homeostasis regulator. Using high-throughput mass spectrometric analysis, we identified various p53-dependent liver secretome profiles. This allowed a global view on the role of p53 in maintaining the harmony of liver and whole-body homeostasis. We found that p53 altered the liver secretome differently under various conditions. Under physiological conditions, p53 controls factors that are relatedmainly to lipid metabolism and injury response. Upon exposure to various types of cancer therapy agents, the hepatic p53 is activated and induces the secretion of proteins related to additional pathways, such as hemostasis, immune response, and cell adhesion. Interestingly, we identified a possible relationship between p53-dependent liver functions and lung tumors. The latter modify differently liver secretome profile toward the secretion of proteins mainly related to cell migration and immune response. The notion that p53 may rewire the liver secretome profile suggests a new noncell autonomous role of p53 that affect different liver functions and whole organism homeostasis.

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