Targets of Tumor Suppressor p53 in IGF Signaling as Markers of Cancer

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Abstract—*IGF (insulin-like growth factor) signaling is one of the critical pathway for the growth and development of many tissues and organs. It is an essential process during neonatal and pubertal growth. It promotes cell proliferation and interruppts programmed cell death. IGF system consists of members of the tyrosine kinase receptor family that are IGF-1R, IGF-2R, and the insulin receptor (IR). These receptors get activated by the two ligands IGF-1 and IGF-2. Tumor suppressor p53, recently,is shown to modulate various signaling pathways by targeting the transcription of certain genes . Upon activation and in response to many signals, p53 starts the transcription of many genes thatinduces apoptosis, cell-cycle arrest, or senescence to maintain the machinery of the cell. Conventionally, p53 is thought to do these functions, few of the recent studies revealed the novel functions of p53 in modulating IGF pathway and p53 target certain important genes implicated in this pathway. It controls the transcription of IGFBP (insulin-like growth factor binding protein) 2 and IGFBP3as well as the protease PAPP-A (pregnancy associated plasma protein A) that cleaves both IGFBP4 and IGFBP5. Cleaveage of IGFBP4by PAPP-Ais IGF dependent whereas the cleavage of IGFBP5 is IGF independent. Another important component of the IGF pathway that is targeted by tumor suppressor p53 is IGF1R (insulin-like growth factor receptor 1). p53 induces IGFBP2 and 3 to control the excessive signaling, since both IGFBP 2 and 3 binds to circulating IGF and as result IGF signaling is inhibited. On the other hand p53 downregulates PAAP-A and IGF1R. By decreasing the levels of PAPP-A, IGFBP4 is saved and binds to the free IGF. Tumor suppressor also downregulates IGF1R, upstream of all the other players of the pathway. Taken together, tumor suppressor p53 controls IGF pathway. In the absence of p53 or upon mutations in this gene, IGF pathway gets aberrant and takes a carcionogenic turn. The upregulation and down-regulation of these players of IGF signaling by p53 holds the potential to develop them as biomarkers for the cancer.*