The opposing functions of wild-type and mutant forms of p53

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Cancer develops as a result of deregulation of proto-oncogenes and loss of tumor suppressor proteins. In its normal wild-type form the p53 tumor suppressor protein functions as a DNA sequence-specific transcription factor that regulates hundreds of genes whose functions play roles in preventing cancer such as cell cycle arrest, cell death, senescence, DNA repair, metabolism and others. By contrast, the missense mutant forms of p53 that are found with high frequency in many of the major forms of human cancer regulate hundreds of genes whose products appear to serve the opposite functions of promoting several cancer related properties such as proliferation, survival, motility and invasiveness. The questions we pose address the mechanistic basis for the different activities of wild-type and mutant forms of p53. First, how does wild-type p53 function to regulate target genes that are required to prevent tumor suppression? Second, what are the key activities of tumor-derived mutant forms of p53 that are required for their gain of oncogenic function? Third, how can we harness our knowledge derived from basis research to better diagnose or treat cancer patients? Progress in these areas will be discussed.