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16:00~17:00 C1F Auditorium

Cell fate decision by tumor suppressor p53: live or die

Summary

It is widely accepted that the p53 tumor suppressor restricts abnormal or DNA damage-exposed cells before damage to DNA is converted to inherited mutation by induction of growth arrest or by triggering apoptosis. This process depends mainly on the expression of genes that regulate cell-cycle arrest or apoptosis. A critical unresolved issue about the DNA damage response is how the resulting up-regulation of the p53 tumor suppressor can lead either to cell cycle arrest/senescence and DNA repair, or to apoptosis.

p53 is an important component of pathways mediating cellular responses to genotoxic stress by inducing the transcription of a variety of genes that regulate diverse cellular processes including cell cycle progression, apoptosis and genomic stability. However little is known about the mechanism(s) that determines which set of genes i.e. the cell cycle arrest genes or the pro-apoptotic genes are transactivated by p53 under a specific condition. Here we report that Hematopoietic Zinc Finger (Hzf), a novel p53 target gene, modulates p53 transactivation functions by positively regulating genes involved in cell cycle arrest and negatively regulating those with pro-apoptotic functions. We show that Hzf is induced by p53 and directly interacts with its DNA binding domain resulting in preferential transactivation of its cell cycle arrest mediating target genes p21 and 14-3-3σ but inhibition of transactivation of pro-apoptotic target genes such as Bax, Noxa and Perp. Multi-ChIP analysis revealed that upon binding of Hzf, p53 is primarily recruited to the promoters of its cell cycle arrest mediating rather than its pro-apoptotic target genes. Thus p53 overexpression in Hzf wt-MEFs results in cell cycle arrest while in Hzf-/- MEFs, apoptosis is induced. Moreover, shRNA mediated-knock-down of Hzf expression resulted in switching of the p53 mediated response to genotoxic stress from cell cycle arrest to apoptosis. We also found that sustained p53 activation resulted in Hzf degradation concomitant to induction of apoptosis, whereas lack of Hzf degradation favors p53-induced senescence. All of these results demonstrate that Hzf is a critical modulator of p53 transactivation functions and provide novel mechanistic insights into p53 cell fate decisions in response to DNA damage/genotoxic stress.

Since the consequence of the absence or degradation of Hzf protein is irreversible cell death, defects in the Hzf activation pathway may confer resistance to the cytotoxic effect of chemo- and radio-therapeutic agents. Thus, this novel layer of the Hzf pathway may provide important implications for our understanding of DNA damage checkpoint signaling, as well as novel mechanisms of anti-cancer resistance in cancer patients.

Host:

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