

Rational targeting of distinct p53 mediators in stem cells

Tao Cheng

Chinese Academy of Medical Sciences & Peking Union Medical College, China

Puma is a direct p53 target gene that encodes a potent BH3-only pro-apoptotic protein. Loss of Puma was shown to profoundly lead to long-term survival of mice mainly via tissue stem and progenitor cell protection following lethal ionizing radiation (IR) but interestingly did not increase tumorigenesis in the long-term survivors. Recently, using the mouse strains deficient in Puma, p21 or p53, we also found that PUMA is an independent mediator of the negative effect of p53 on the induction of pluripotent stem cells (iPSC). PUMA deficiency led to a better survival rate associated with reduced DNA damage and fewer chromosomal aberrations in iPSC whereas loss of p21 or p53 resulted in an opposite outcome. Noticeably, our data also suggest an apoptosis-independent mechanism of Puma within the target cells. To further explore novel mechanisms, we obtained Puma-deficient mouse embryonic stem cells (ESC) or iPSC and hematopoietic progenitor cells to investigate whether Puma is directly involved in double strand break (DSB) DNA repair in stem or progenitor cells. Our results show that Puma-deficient stem and progenitor cells exhibited a significant higher DSB repair activity via homologous recombination (HR). Given these findings, PUMA may serve as a distinct and desirable target for therapeutic stem cell manipulations.

chentx@UPMC.EDU / chengt588@gmail.com