The role of p21 in ionizing radiation induced premature senescence

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Background: Current investigations believe that the DNA damage response (DDR) signals, long term cell cycle arrest and activation of p53 or p16 pathway are responsible for the stress-induced senescence. However, the molecular mechanisms of p21 in stress-induced senescence such as ionizing radiation are still unknown.

Materials and Methods: Human melanoma A375 cells were irradiated with X-rays generated by a Faxitron RX650, or heavy ions generated by the HIRFL (Heavy Ion Research Facility of Lanzhou, Institute of Modern Physics, Lanzhou, China). The senescence associated β-galactosidase, p53 and p21 protein expression levels and cell cycle progression in irradiated cells were measured to identify the senescent cells and related characteristics.

Results and Conclusions: We found that 5 Gy of X-rays could induce significant numbers of senescent cells but not apoptotic cells in human melanoma A375 cells, the SA-β-Gal positive cells reached to more than 80% on the 5th day after exposure (Fig.1A). On the other hand, the long term cell cycle arrest and activation of p53 and p21 were responsible for radiation-induced senescence (Fig.1B-C). Knock down of p21 protein expression by siRNA rescued the radiation-induce cellular senescence (Fig.2). In p21-upregulated cells, high levels of p21 induced Aurora A kinase decline, which ultimately resulted in mitosis skip and senescence entry at tetraploid G1 phase. In contrast, cells without p21 expression could not induce Aurora A kinase degradation, which led to G2 arrested cells enter into M phase followed by apoptosis. Our work highlights the p21 functions in the radiotherapy and provides insights into the multiple roles of p21 as a cell cycle regulator cells (Fig.3).

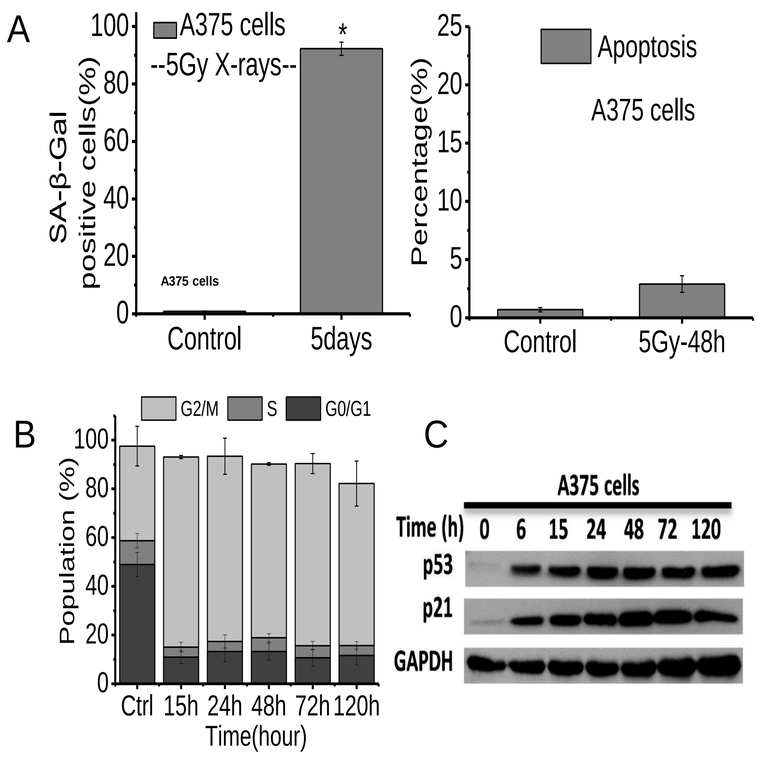

Fig.1 Cellular senescence (SA-β-Gal positive cells, panel A), long-term cell cycle arrest (panel B) and p53/p21 activation (panel C) were induced by ionizing radiation in A375 cells.

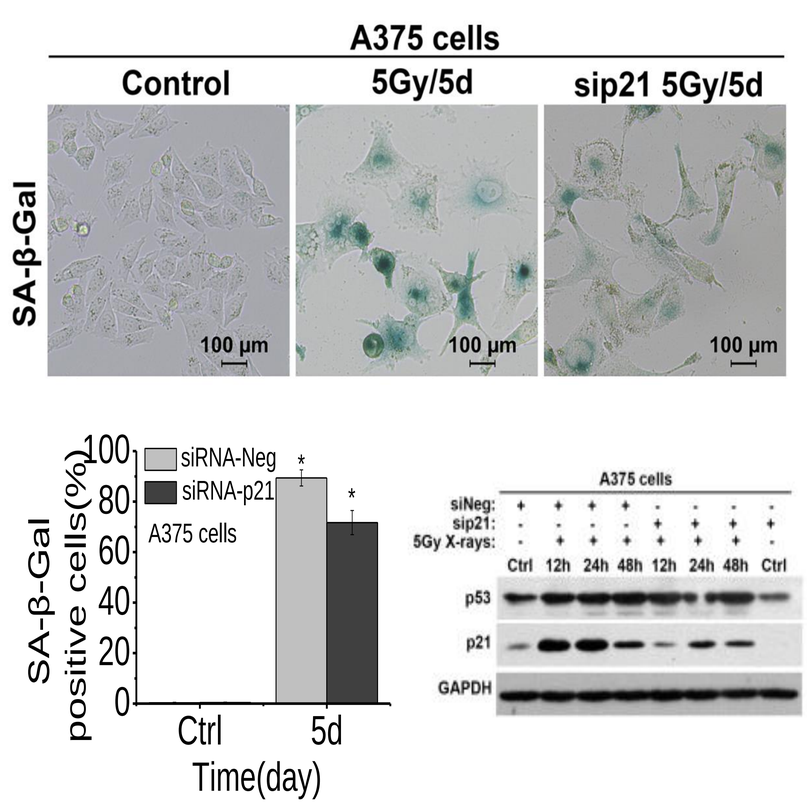

Fig.2 Rescue of radiation-induce cellular senescence by siRNA of p21.
Green-yellow: SA-β-Gal positive cells

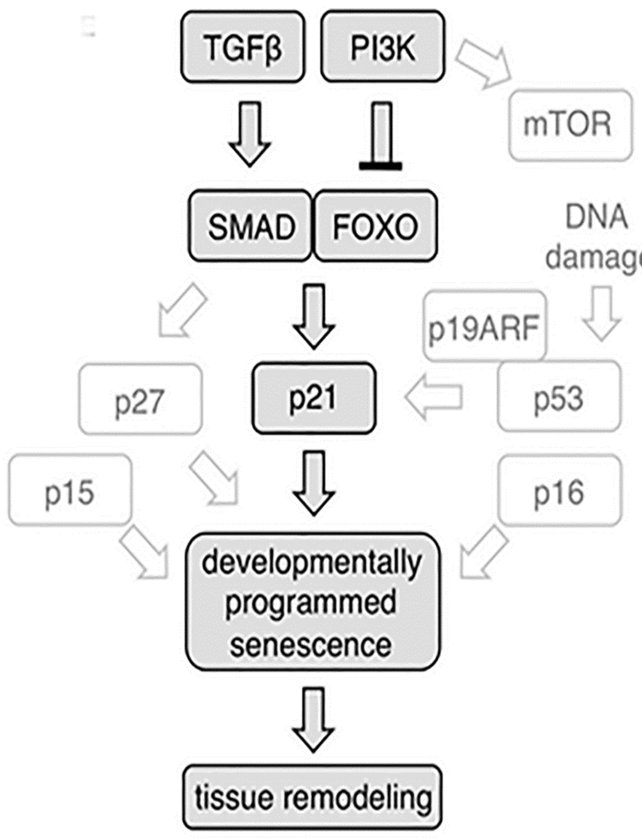

Fig.3 The role of p21 in cellular senescence. Munoz-Espin D, *Cell*, 2013, 155:1104-18

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