Colloqui della Classe di Scienze

Anno Accademico 2015/2016

Sala Azzurra | Palazzo della Carovana
Scuola Normale Superiore
Piazza dei Cavalieri, 7 - PISA

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ore 15.00

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Regulation of self-renewal in cancer stem cells

Abstract

Recent findings support the concept that cells with the properties of stem cells (SC) are integral to the development and perpetuation of several forms of human cancer, and that eradication of cancer stem cells (CSC) may be essential to achieve cancer cure. However, direct proof of these concepts is still lacking, mainly due the scarcity of appropriate model systems. We have recently defined a number of CSC-specific biological properties and underlying molecular mechanisms, using mouse models of i) leukaemia, obtained by transgenic expression of the PML-RAR, mutant NPM or AML1-ETO leukemia-associated oncogenes; and ii) mammary tumor, obtained by transgenic expression of the ErbB2 oncogene. We found that self-renewing divisions of CSCs are more frequent than normal counterparts, unlimited and symmetric, thus contributing to increasing numbers of SCs in tumoral tissues. SCs with targeted mutation of the tumor suppressor p53 possess the same self-renewal properties of cancer SCs, and their number increases progressively in the p53-null pre-malignant mammary gland. We showed that p53 signaling is attenuated in ErbB2-driven tumors, and that pharmacological re-activation of p53 induced restoration of asymmetric divisions in cancer SCs and tumor growth reduction, without affecting rates of apoptosis or proliferation on additional cancer cells. These data demonstrate that p53 regulates polarity of cell division in mammary SCs and suggest that loss-of-p53 in epithelial cancers favors symmetric divisions of CSCs, contributing to tumor growth. As a further mechanisms of extended self-renewal in cancer stem cells, we have demonstrated that up-regulation of the cell-cycle inhibitor p21 is indispensable for maintaining self-renewal of leukaemia SCs (LSCs). Expression of leukaemia-associated oncogenes in normal hematopoietic SCs (HSCs) induces DNA damage and activates a p21-dependent cellular response that, in turn, imposes cell-cycle restriction and triggers repair of the damaged DNA. This effect of p21 prevents the physiological exhaustion of HSC self-renewal, which occurs in time owing to accumulation of DNA damage, and confers an advantage to HSCs when they hyper-proliferate, as it occurs during stress or after full transformation (for example, in the LSCs), thus explaining the role of p21 in the maintenance of the self-renewal potential of LSCs. Finally, I will discuss unpublished data showing the contribution of immune-surveillance to the elimination of DNA-damaged SCs, and the underlying role of p21.

Elaborazione a cura del Servizio Comunicazione e Relazioni Esterne | SNS

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