The remodeling of BRG1, the ATPase subunit of SWI/SNF complex, induces senescence in mesenchymal stem cells

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Chromatin state is fundamental for gene expression. Chromatin remodelling factors can modify the balance between euchromatin and heterochromatin by acting as main regulators of gene expression and then self-renewal, proliferation and differentiation properties of stem cells. However, their activity is modulated by chromatin remodelling factors that operate at the highest hierarchical level [1]. Studies on these factors are crucial to dissect molecular pathways governing the biology of stem cells. SWI/SNF complexes are ATP-dependent chromatin remodeling enzymes that have been shown to be required for cell cycle control, apoptosis and cell differentiation in several biological systems [2]. The aim of our research was to investigate the role of these complexes in the biology of mesenchymal stem cells (MSCs). To this end, in MSCs, we silenced the ATPase subunit of SWI/SNF (*BRG1*).

Silencing of *BRG1* expression induced a significant increase of senescent cells. This was associated with decrease of apoptosis. Of interest, *BRG1* downregulation induced an increase of heterochromatin.

At the molecular level these phenomena were associated with activation of *RB2/P130*- and *P53*-related pathways. Senescence was associated with reduced expression of some stemness-related genes.

Previous studies showed that senescence processes were induced by ectopic expression of BRG1 as well [3].

Together these data suggest that BRG1 belongs to a class of genes having a tightly regulated expression. Indeed, a subtle alteration in their expression levels may disrupt the normal function of cells. One possible explanation to clarify why certain genes may require a precise and accurate control is that these specific genes regulate or are involved in balancing disparate downstream pathways possessing mutually opposite activities. This may be the case of BRG1, which can modulate gene expression in either positive or negative mode.

References

[1] Martens J.A., Winston F. 2003. Recent advances in understanding chromatin remodeling by Swi/Snf complexes. Curr. Opin. Genet. Dev. 13: 136-142.

[2] Saha A., Wittmeyer J., Cairns B.R. 2006. Chromatin remodelling: the industrial revolution of DNA around histones. Nat. Rev. Mol. Cell Biol. 7: 437-447.

[3] Napolitano M.A., Cipollaro M., Cascino A., Melone M.A., Giordano A., Galderisi U. 2007. Brg1 chromatin remodeling factor is involved in cell growth arrest, apoptosis and senescence of rat mesenchymal stem cells. J. Cell Sci. 120: 2904-2911.