Escape from p21-mediated Oncogene-induced Senescence Leads to Cell Dedifferentiation and Dependence on Anti-apoptotic Bcl-xL and MCL1 Proteins

Titre	Escape from p21-mediated Oncogene-induced Senescence Leads to Cell Dedifferentiation and Dependence on Anti-apoptotic Bcl-xL and MCL1 Proteins
Type de publication	Article de revue
Auteur	Trécesson, Sophie de Carné [1], Guillemin, Yannis [2], Bélanger, Audrey [3], Bernard, Anne-Charlotte [4], Preisser, Laurence [5], Ravon, Elisa [6], Gamelin, Erick [7], Juin, Philippe [8], Barré, Benjamin [9], Coqueret, Olivier [10]
Editeur	American Society for Biochemistry and Molecular Biology
Type	Article scientifique dans une revue à comité de lecture
Année	2011
Langue	Anglais
Date	2011/04/15
Numéro	15
Pagination	12825 - 12838
Volume	286
Titre de la revue	Journal of Biological Chemistry
ISSN	1083-351X
Mots-clés	Cell Cycle [11], Cell Division [12], Colon cancer [13], Oncogene [14], p21WAF1 [15], senescence [16], Transcription Regulation [17]

Résumé en anglais	Oncogene-induced senescence (OIS) is a tumor suppressor response that induces permanent cell cycle arrest in response to oncogenic signaling. Through the combined activation of the p53-p21 and p16-Rb suppressor pathways, OIS leads to the transcriptional repression of proliferative genes. Although this protective mechanism has been essentially described in primary cells, we surprisingly observed in this study that the OIS program is conserved in established colorectal cell lines. In response to the RAS oncogene and despite the inactivation of p53 and p16INK4, HT29 cells enter senescence, up-regulate p21WAF1, and induce senescence-associated heterochromatin foci formation. The same effect was observed in response to B-RAFv600E in LS174T cells. We also observed that p21WAF1 prevents the expression of the CDC25A and PLK1 genes to induce cell cycle arrest. Using ChIP and luciferase experiments, we have observed that p21WAF1 binds to the PLK1 promoter to induce its down-regulation during OIS induction. Following 4–5 weeks, several clones were able to resume proliferation and escape this tumor suppressor pathway. Tumor progression was associated with p21WAF1 down-regulation and CDC25A and PLK1 reexpression. In addition, OIS and p21WAF1 escape was associated with an increase in DNA damage, an induction of the epithelial-mesenchymal transition program, and an increase in the proportion of cells expressing the CD24low/CD44high phenotype. Results also indicate that malignant cells having escaped OIS rely on survival pathways induced by Bcl-xL/MCL1 signaling. In light of these observations, it appears that the transcriptional functions of p21WAF1 are active during OIS and that the inactivation of this protein is associated with cell dedifferentiation and enhanced survival.
URL de la notice	http://okina.univ-angers.fr/publications/ua9177 [18]
DOI	10.1074/jbc.M110.186437 [19]
Lien vers le document	http://dx.doi.org/10.1074/jbc.M110.186437 [19]
Titre abrégé	J. Biol. Chem.

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[19] http://dx.doi.org/10.1074/jbc.M110.186437