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miR-141, a new player, joins the senescence orchestra

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microRNAs (miRNAs) are short non-coding, single-stranded RNA molecules of:22 nucleotides that either inhibit translation or enhance degradation of mRNA of a target gene. To date, more than 2500 human miRNAs (miRBase v20), regulating a remarkable array of cellular processes and human pathologies, have been identified. In line with recent evidence that certain miRNAs function as tumor suppressors, a new study by Dimri et al. identifies miR-141 as a novel inducer of cellular senescence,[1] a critical intrinsic tumor-suppressive mechanism.

Most cells undergo cellular senescence in culture and in vivo.[2] It is induced by a number of stresses such as oncogenic insults, telomere erosion, and cell culture stress and is a fail-safe mechanism that limits the proliferation of cells at risk of neoplastic transformation. Senescence is regulated by 2 major tumor-suppressive pathways, the intrinsic p53-p21 telomere-dependent pathway and the extrinsic p16-pRb telomere-independent pathway.[3] The polycomb protein BMI1 represses the expression of p16 and plays an important role in blocking replicative senescence by inhibiting the p16-pRb pathway.[2,3] BMI1 depletion in fibroblasts results in induction of p16 and senescence, whereas its overexpression extends the replicative lifespan of fibroblasts undergoing p16-dependent senescence.[2,3]

Several miRNAs are differentially expressed during cellular senescence;[4] some of them may regulate senescence, while others may be regulated by senescence. Certain components of miRNA processing also participate in cellular senescence,[5] such as the ago2-microRNA complex, which represses RB/E2F-target genes in senescent cells.[6] How these factors and miRNAs orchestrate cellular senescence is an important question.

A new report by Dimri et al.[1] shows that miR-141 induces senescence by targeting the 3′ untranslated region of *BMI1* mRNA, leading to suppression of BMI1 expression and upregulation of p16 and other senescence markers. Since p16-positive senescent fibroblasts are present even in early passages,[3] inhibition of endogenous miR-141 resulted in the modest induction of cell proliferation, consistent with the ability of BMI1 to suppress the emergence of p16-positive cells. Interestingly, miR-141 overexpression also resulted in extensive DNA damage, evidenced by γ-H2AX foci and p53 induction, suggesting a possible novel cross-talk with DNA damage response pathway. Importantly, ectopic expression of *BMI1* lacking the miR-141 targeting sequence was sufficient to rescue miR-141-mediated senescence, suggesting that miR-141 specifically targets *BMI1* to induce senescence. Consistent with reduced levels of BMI1 in cells undergoing senescence,[3] Dimri et al. show that miR-141 expression is increased in cells undergoing senescence, suggesting a potential role of miR-141 in triggering senescence.

miR-141 belongs to the miR-200 family of miRNAs that comprises miR-141, -429, -200a, -200b, and -200c based on the sequence homology. The miR-200 family is known to inhibit the epithelial–mesenchymal transition by suppression of ZEB1 and ZEB2, but its ability to either inhibit or promote oncogenesis is controversial and appears to depend on the type of cancer. miR-200c has recently been reported to inhibit BMI1 and suppress the breast cancer stem cell population.[7] Intriguingly, miR-141 and miR-200c are clustered on human chromosome 12p13.31, separated by only a 338-bp spacer sequence. Dimri et al. also showed that miR-200c induces cellular senescence as efficiently as miR-141,[1] consistent with an earlier report that miR-200c induces endothelial cell senescence.[8] These data suggest a very important role of this locus

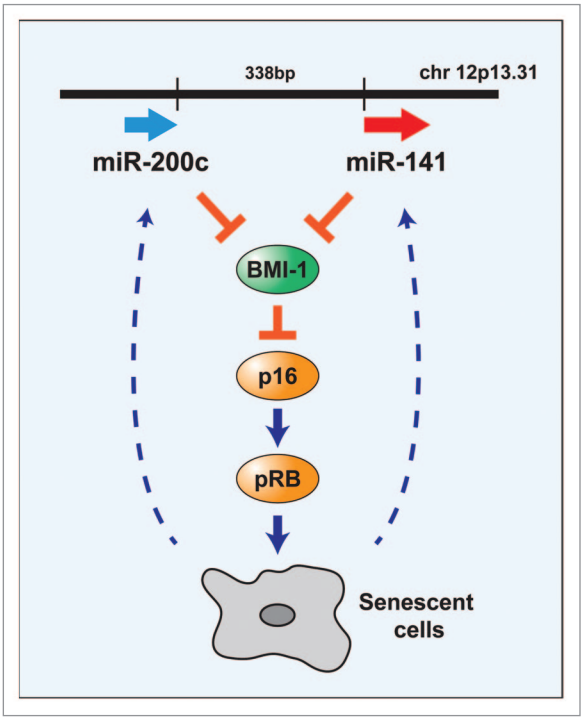

Figure 1. Model for contribution of miR-141 and miR-200c to p16-dependent senescence in human fibroblasts. A positive feedback mechanism in senescent cells possibly upregulates the miR200c/miR-141 locus.

in cellular senescence (**Fig. 1**). What factors regulate this locus will be an important question. Studies by Dimri et al.[1] and other groups[8] implicate oxidative stress in the induction of this locus. ZEB1, target of miR-200c, represses this locus and forms a negative feedback loop. This locus is also known to be regulated by DNA methylation. Furthermore, induction of senescence by other stimuli also triggered miR-141,[1] suggesting a positive feedback loop (**Fig. 1**). Further investigation on upstream regulators of this locus and the functional interaction between these 2 miRNAs is warranted.

Revealing the critical regulators of cellular senescence has clinical relevance for the treatment of age-related diseases and cancer, although the efficacy of each miRNA may be dependent on the type of disease and cancer. This current study by Dimri et al. has identified an important aspect of senescence regulation through miR-141 and should stimulate future studies to elucidate its therapeutic application as well as define its exact role in the complex senescence orchestra that involves many miRNAs and their processing components.

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