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p53 and cancer stem cells
The mevalonate connexion

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The role of p53 in the biology of mammary epithelial stem cells (SC) is well established. p53 may counteract SC expansion by several mechanisms, including restriction of self-renewing divisions and block of reprogramming of somatic/progenitor cells into SCs.[1] p53 regulates the polarity of cell division in mammary SCs. p53 is often inactivated by loss or mutation in breast cancer. This inactivation favors symmetric divisions of cancer SCs, contributing to tumor growth.[2] Two recent studies demonstrate an unexpected link between p53 and stem cell biology that include a metabolic pathway, the mevalonate pathway.

Freed-Pastor and colleagues[3] studied the effects of mutated p53 on breast cancer cells. They showed that depletion of the mutated form of p53 reverses the oncogenic potential of breast cancer cell lines by inducing a normal-like phenotype characterized by the formation of acinilike structures.

Ginestier et al.[4] studied the pathways important to the biology of breast cancer stem cells (BCSCs). They compared the gene expression profiles of breast cancer cell lines in suspension (tumorospheres, supposed to be enriched in BCSCs) and adherent cultures. Genes of the mevalonate pathway were overexpressed in the tumorospheres.

The mevalonate pathway leads to cholesterol synthesis, protein farnesylation and protein geranylgeranylation. By modulating the pathway with inhibitors specific to each of these three end products, both studies identified protein geranylgeranylation as the important mediator of both p53-mutated oncogenic effects and stem cell biology. A small-molecule inhibitor of the geranylgeranyl transferase 1 (GGTI) enzyme reduced the growth and invasive morphology of p53-mutated breast cancer cells and reduced the breast CSC subpopulation both in vitro and in human primary breast cancer xenografts.

Deciphering the gain of function of a p53 mutant in oncogenic transformation is challenging and proposes an alternative to the common dogma, presenting p53 mutation as a classical loss of wild-type p53 tumor-suppressive activity. Actually, the mutated form of p53 has been shown to have neomorphic activities regulating transcriptional activity by recruiting either NFY of VDR.[5,6] Freed-Pastor and colleagues[3] showed that these newly identified oncogenic effects of mutated p53 are mediated through the transcriptional activation of genes involved in the mevalonate pathway, which are regulated by sterol regulators element-binding proteins (SREBPs).

Ginestier and colleagues[4] found that the effect of GGTI on the CSC subpopulation is mediated by the inactivation of RHOA and subsequent increased accumulation of P27kip1 in the nucleus. This is in agreement with previous observations in mouse embryonic stem cells.[7] Thus, the aggressive phenotype of BCSCs may be due to sustained isoprenylation of small GTPases and subsequent induction of cell migration and deregulation of the cell cycle trough P27 retention and degradation in the cytoplasm (**Fig. 1**). The identification of more key targets of geranylgeranylation in CSCs should provide information on both stem cell biology and oncogenesis.

Thus, these two studies have established another direct link between p53 and stem cell biology and, surprisingly, it involves a metabolic pathway. Taken together, they suggest a potential role of the mutated form of p53 on the deregulation of the self-renewal/differentiation program of CSCs through activation of the mevalonate metabolism (**Fig. 1**). CSCs drive tumor growth and metastasis, and their eradication is necessary to cure a cancer. This can be achieved by targeting key pathways regulating CSC biology. The mevalonate pathway and geranylgeranylation thus now appear as excellent potential therapeutic targets. All the more so, since they also mediate p53-mutated oncogenic effect. Interestingly, a clinical trial involving mevalonate metabolism blockade, using statins as a preventive treatment, reported a decreased incidence of basal tumors, which are known to frequently harbor p53 mutations.[8] Moreover, activation of the mevalonate pathway was specifically found in BCSCs isolated from basal cell lines but not from luminal cell lines.[4] These observations underline the opportunity to use GGTI treatment as a new anti-CSC therapy in basal breast carcinomas, which lack adapted targeted therapies.

More generally CSCs, which have conserved many properties of normal SCs, seem to have developed several mechanisms activating metabolic activities that preserve them from oxidation, senescence, DNA damage and stimulate the production of energetic metabolites. The definition of these mechanisms will allow the development of new therapeutic strategies.

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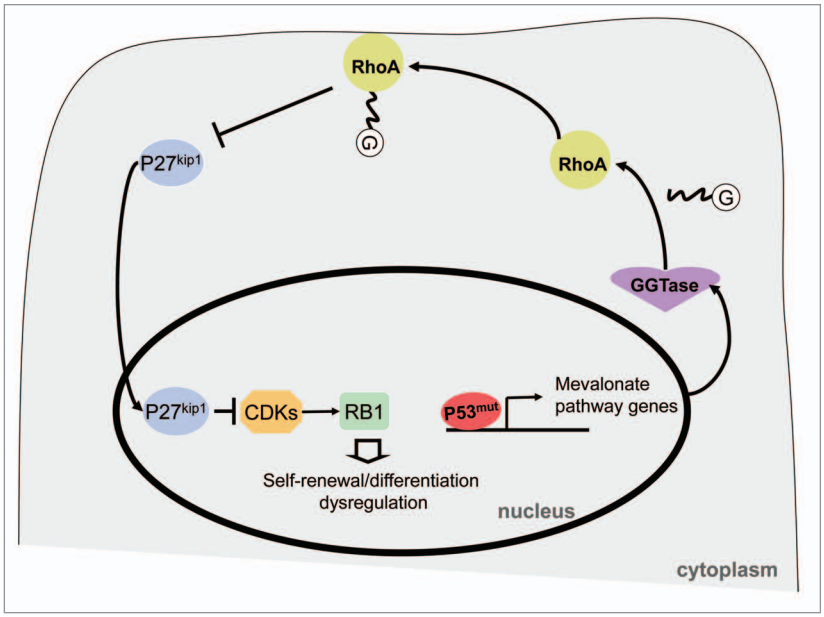

Figure 1. Schematization of the potential relationship between mevalonate metabolism and cell cycle control in a CSC mutated for p53. The mutant form of p53 acts as a transcription factor that induces the expression of enzymes involved in mevalonate metabolism. The mevalonate pathway activates RHOA, which needs to be geranylgeranylated to translocate to the membrane. Activated RHOA protein is known to regulate P27kip1 by enhancing its degradation and inhibiting its translocation to the nucleus, where it controls the cell cycle stages that regulate stem cell fate by allowing equilibrium between self-renewal and committed cell fate decision.

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