DEVELOPMENT

A tumor suppressor shuts down a signal gradient

p53 shuts down the spatial signaling of a morphogen and prevents clonal cell expansion

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The most frequently mutated tumor suppressor gene in human cancers is *TP53* (*1*). Loss-of-function mutations lead to expansion of a mutated cell and its progeny in epithelial tissues, including sun-exposed regions of the skin, which can progress to invasive cancers. Upon stress, such as DNA damage, p53 becomes phosphorylated or acetylated, modifications that promote its stabilization and the activation of genes that cause cell cycle arrest, cellular senescence, or cell death (*1*). One might expect that clonal expansion triggered by the loss of p53 results from dysregulation of these canonical functions. On page 78 of this issue, Gan *et al.* (*2*) report that this expansion is instead driven by activation of a gradient of Wnt (wingless-related integration site) signals that promotes epidermal stem cell self-renewal. Controlling signaling gradients, rather than the absolute amount of a signal, may be a mechanism through which cancer-associated mutations achieve long-term tissue colonization.

Despite extensive knowledge about p53 functions, the molecular mechanisms by which it suppresses tumorigenesis remain unresolved (*3*). In response to stress, p53 is acetylated at multiple lysine residues, and mutations at the three acetylation sites in the DNA-binding domain prevent it from mediating cell cycle arrest, programmed cell death (apoptosis), and senescence. This mutation in mice (*Trp53*$^{3KR/3KR}$; *Trp53* is the mouse homolog of human *TP53*) also prevents tumor formation because mice lacking *Trp53* (*Trp53*$^{-/-}$), but not *Trp53*$^{3KR/3KR}$, develop early-onset spontaneous lymphoma (*4*). This raises the possibility that tumor suppression does not depend on p53 canonical functions.

During tissue homeostasis, the balance between cell self-renewal and cell differentiation maintains a constant cell number (*5*). Oncogenic mutations can impair this balance, leading to the expansion of a mutated cell into a clonal population as the result of excess stem cell divisions and a failure to differentiate. For example, during basal cell carcinoma initiation, cells harboring a mutation in *Smo* (which encodes the Smoothened protein) exhibit enhanced self-renewing divisions and a block of differentiation, leading to the establishment of preneoplastic lesions (*6*). Although *Trp53* deletion or *Trp53*^{R248W} expression (a dominant-negative mutation that inactivates p53 protein) (*7*) do not increase the rate of mouse epidermal stem cell proliferation, they promote self-renewal, giving rise to more stem cells (without causing cells to divide faster or more frequently). Gan *et al.* did not observe this in mouse epidermal *Trp53*$^{3KR/3KR}$ clones. This suggests that *Trp53*$^{-/-}$-mediated clonal expansion is likely the consequence of an imbalance toward self-renewing cell divisions rather than uncontrolled proliferation, through mechanisms independent of the loss of p53's canonical functions.

To decipher the molecular mechanism by which p53 controls epidermal cell self-renewal, Gan *et al.* hypothesized that genes controlling self-renewal would be shared between wild-type p53 (*Trp53*^{WT}) and *Trp53*^{3KR}. Upon identifying common, differentially regulated genes by *Trp53*^{WT} and *Trp53*$^{3KR/3KR}$ in epidermal cells from both mouse strains (through epigenetic and transcriptional analyses), the authors performed an in vivo genetic screen by molecularly perturbing each of 1113 candidate genes and assessing the impact on self-renewal. They narrowed the list to three genes: *Sfrp1* (*secreted frizzled-related protein 1*), *Lrp1* (*low-density lipoprotein receptor-related protein 1*), and *Usp22* (*ubiquitin-specific protease 22*). The expression of these genes was up-regulated in *Trp53*^{WT} and *Trp53*$^{3KR/3KR}$ epidermal cells, where there was decreased self-renewal. Notably, all three genes had been previously reported as potential negative regulators of the Wnt signaling pathway.

In the mouse skin, Wnt signaling is best known for regulating hair follicle stem cells and sebaceous gland function (*8*). It acts as a morphogen that directs spatial patterning of cells, cell fate, and tissue morphogenesis of the skin. However, loss of β-catenin or wntless (Wls), constituents of the Wnt signaling pathway, also decreases interfollicular epidermal stem cell proliferation (*9*, *10*). Consistent with the idea that p53 up-regulates the expression of inhibitors of Wnt signaling in the epidermis, Gan *et al.* demonstrated that p53 deletion or silencing the expression of *Sfrp1*, *Lrp1*, or *Usp22* in mouse epidermal cells increased activity of Wnt signaling and clonal expansion. Conversely, overexpression of *Sfrp1*, *Lrp1*, or *Usp22* in *Trp53*$^{-/-}$ epidermal cells decreased Wnt activity and clonal expansion. Thus, p53 regulates Wnt activity in the epidermis by controlling the expression of these three genes.

Gan *et al.* further found that p53 deletion leads to a gradient of Wnt activity within the expansion of mutated clones, with the highest activity in the center of the expansion and decreasing radially toward the edges. This spatial distribution was established only by suppressing the expression of the soluble Wnt inhibitor *Sfrp1*. The authors hypothesize that the Wnt gradient, rather than a specific level of Wnt signaling, is responsible for the rapid expansion of p53-deficient clones.

Gan *et al.* uncover a new role for p53 in gatekeeping aberrant cell renewal. In this model, the unrestrained expansion of p53 mutant cells is driven by the generation of a Wnt activity gradient within the mutant clones. It is not clear whether p53 loss in other tissues, or other oncogene or tumor suppressor gene mutations, also modulate Wnt signaling in the skin. Yet to be determined, as well, are the mechanisms by which Wnt signaling itself promotes renewal in this context. p53 puts the brakes on establishing a gradient by activating three inhibitors of Wnt action. However, even in the absence of a gradient, Wnt might still promote clonal expansion. Too much Wnt signaling can decrease renewal and lead to cell differentiation, as observed during hair (*11*) or Paneth cell differentiation in the intestine (*12*). This means that the promotion of stem cell renewal requires the right dose of Wnt signaling.

Sometimes a stem cell mutates and turns on its Wnt signaling pathway permanently, as observed in intestinal crypts. However, clonal expansion of such cells has been attributed to their secretion of Wnt inhibitors to eliminate wild-type neighbors (*13*, *14*). This is a key step in the early stages of intestinal cancer. Whether a similar mechanism occurs in the epidermis remains to be determined. The approach of Gan *et al.* opens the possibility of unraveling clonal expansion and cell competition in response to other oncogenic hits and in other locations. □

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