Tumor suppression by p53 involves inhibiting an enabler, FGF13

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There is growing evidence for the notion that certain alterations in tumor cells are not necessarily so-called “drivers” that initiate or maintain the neoplastic state. The idea that there are also “enablers” that facilitate or enable cancer cells to proliferate under conditions of stress has been gaining traction. This idea has great translational potential, as such factors can represent novel targets for therapeutic intervention. In PNAS, Bublik et al. (1) propose that the fibroblast growth factor 13 (FGF13) protein exerts just such effects during tumorigenesis. Intriguingly, the authors show that these effects are under the transcriptional regulation of the tumor suppressor p53. Understanding the molecular bases of this well-characterized role for p53 in human cancer has been an active area of research and

remains elusive. The Bublik et al. study provides yet another possible mechanism: that p53 has the ability to dampen or down-regulate the activity of “enablers,” such as FGF13.

FGF13 is a member of the FGF superfamily. Although it shares some homology to the well-studied members that interact with cell surface receptors, FGF13 is one of several that have not been implicated in playing such a role (2). Rather, this group, which includes FGF11–FGF14, all appear to have intracellular localization and functions (3). In the Bublik et al. study (1) the focus is on FGF13 and its role in the nucleolus. Data are presented in support of the idea that FGF13 down-regulates expression of ribosomal RNA (Fig. 1), and this serves a proteostatic role (4). In cells whose proliferation is driven by oncogenic activation, such as mutated Ras, there is an excessive level of protein synthesis that can result in intracellular stress, including increases in unfolded proteins. Bublik et al. (1) suggest that the role of FGF13 is to dampen this, thereby allowing tumor cells to proliferate under such stress-inducing conditions. In such a scenario, it is the oncogene, such as Ras, that drives proliferation, whereas the enabler, FGF13, facilitates the survival of such cells. This is a concept that had been previously put forth and provides another source of targets for intervention in cancer therapeutics (5).

What is especially intriguing about this scenario is that it appears to be negatively regulated by the tumor suppressor p53 (Fig. 1). Bublik et al. (1) show in their study that p53 can transcriptionally repress expression of both FGF13, as well as a micro-RNA, miR-504, that is contained within the FGF13 gene. miR-504 had previously been shown to target the TP53 mRNA, thereby reducing expression of wild-type p53 (6). Bublik et al. (1) “connect the dots” to argue that a feedback loop in which p53 repression of miR-504 enforces its own expression by preventing the microRNA from targeting the TP53 mRNA is thus created (Fig. 1).

p53 has a well-characterized role in human cancer, where it is often found to be persistently expressed as a mutated protein (7, 8). p53 is a transcription factor that binds in a sequence-specific manner to genomic response elements and thereby influences gene expression,

Fig. 1. FGF13 and miR-504 are in a negative regulatory loop with the tumor suppressor p53 and control proteostasis. Bublik et al. (1) present data to argue that p53 negatively regulates at the transcriptional level the expression of FGF13, as well as a microRNA miR-504 that is encoded within the context of the FGF13 gene. miR-504, in turn, down-regulates p53 expression. FGF13 is shown to act within the nucleolus by suppressing ribosomal RNA synthesis. It is proposed that FGF13 exerts a protective effect by dampening protein synthesis in tumor cells that are proliferating in an uncontrolled manner.

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resulting in a variety of cell fate outcomes, including cell cycle arrest and apoptosis, among others (9). Mutation of the TP53 gene in human tumors typically results in the expression of a protein that no longer can bind to DNA, and thus is defective for regulation of genes that contain such p53 responsive elements. p53 has been well-studied to have two main cellular outcomes, apoptosis and cell cycle arrest, which if sustained lead to senescence (9). Thus, it was unexpected when several different laboratories using in vivo mouse models demonstrated that these apoptotic and cell cycle effects of p53 were not needed for tumor suppression (10–12). More recently, it has been shown that another p53-mediated response, ferroptosis, may be a key player in tumor suppression (13, 14). The current study by Bublik et al. (1) adds another possible role for wild-type p53 in preventing cancer development, namely negatively regulating FGF13 expression and its effects on ribosomal RNA synthesis in the nucleolus.

p53 has previously been implicated in responding to ribosomal or nucleolar stress via mechanisms involving its negative regulator Mdm2. Mdm2 is a ubiquitin ligase that acts to inhibit p53 in two ways. First, it targets p53 for degradation via ubiquitination and the proteasome. Second, Mdm2 binds to p53 in a region that is needed for transcriptional activation and prevents relevant cofactor binding (15). A number of studies have shown that disruption of the nucleolus or induction of ribosomal stress leads to an inhibition of Mdm2 activity toward p53, thereby activating p53-dependent cellular responses (16–18). Because FGF13 is shown by Bublik et al. (1) to inhibit ribosomal RNA synthesis, it is intriguing to speculate that there may be an interplay with p53 involving a nucleolus-dependent mechanism. Actinomycin D has been thought to activate p53

because of its effects at also inhibiting ribosomal RNA synthesis (16, 17). Thus, it is possible that FGF13 may similarly signal to p53 by the same underlying molecular mechanism. FGF13 expression would activate p53, whereas the up-regulation of miR-504 would antagonize such an effect. It will be important to explore this issue directly in future studies.

Much of the data generated by Bublik et al. (1) has come from studies in cell culture. It remains to be seen how relevant these findings will be either in vivo or in human tumor samples. Furthermore, the role of p53 status in how particular tumor cells engage the FGF13 pathway is of critical importance. Bublik et al. note increased expression of FGF13 in subsets of human tumors. But it is unclear whether this is because of loss of wild-type p53-mediated repression or some distinct, p53-independent mechanism, perhaps related to oncogenic activation. Although the role of FGF13 as an “enabler” rather than a “driver” is consistent with the Bublik et al. data, it also remains to be directly demonstrated whether FGF13 overexpression can contribute to initiation of oncogenesis in relevant settings. This is a challenging question to address, as it will be difficult to distinguish between a direct, cooperating oncogenic role versus one in which oncogenic events can be facilitated through its overexpression. In either case, the notion that nucleolar FGF13 can serve as a new means for therapeutic intervention in appropriate cancer settings still is deserving of exploration.

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