

IN THE SPOTLIGHT

Soil Amendments That Slow Cancer Growth

Clare M. Isacke¹ and Mary Helen Barcellos-Hoff²

Summary: The recognition that the tumor microenvironment contributes to tumor survival, growth, and response to therapy provides the rationale for considering it a therapeutic target. The article by Alspach and colleagues in this issue provides evidence that p38MAPK acts posttranscriptionally to promote the tumor-permissive secretory phenotype of both cancer-associated and senescent fibroblasts, and that p38MAPK inhibitors already in clinical trials have significant therapeutic potential. *Cancer Discov*; 4(6); 637-9. ©2014 AACR.

See related article by Alspach et al., p. 716 (8).

Cancer research over the last quarter century has focused almost exclusively on identifying the molecular features of cancer cells based on the idea that genomic changes are in and of themselves the drivers of cancer. Thus, in their original review, Hanahan and Weinberg (1) attributed the six hallmarks of cancer to genetic alterations within the cancer cell. Similarly, experimental rodent models of cancer focused predominantly on “targets,” that is, the genome of the cell that underwent neoplastic transformation, which afforded a great deal of insight into pathways that are deregulated by genetic aberrations and paved the way for targeted therapeutics.

This focus on the cancer cell genome overshadowed the essential contribution of the tumor microenvironment. The genetic changes occurring in cancer cells were known to affect the microenvironment, but their acquisition was considered to be stochastic. A notable exception was Folkman’s (2) early recognition that vascularity could be the Achilles heel of tumors. Even so, antiangiogenic targets are often conceived of as a means of depriving the autonomous cancer cell of nutrients rather than modifying a necessary cellular partner in neoplastic growth.

As reflected in the updated Hanahan and Weinberg (3) review, the past decade has witnessed increasing acknowledgment that the tumor microenvironment provides the context for carcinogenesis. We now recognize that the key to malignant cells successfully seeding cancer is proper amendment of the soil during neoplastic progression, and that for cancer to evolve from early dysplastic lesions into invasive cancer, malignant cells must continue to modify the tissue in an organ-specific manner to facilitate survival. Thus, the acquisition of mutations, such as activation of oncogenic signaling pathways, by early cancer cells not only promotes cancer cell

growth but may also act on the surrounding tissue to recruit and activate stromal cells and reprogram the microenvironment. Therapeutically targeting the tumor microenvironment is now attractive because, compared with the variable routes taken by cells to become cancers, the response of tissues to cancer is relatively consistent. This idea raises the possibility that controlling and eliminating cancer may be more readily achieved indirectly via the tissue microenvironment (4).

Cancer-associated fibroblasts (CAF) are biologically distinct from resident tissue fibroblasts and are functionally polar opposites. Normal stroma can actively suppress tumor growth, but a shift of programming converts quiescent fibroblasts into CAFs, whose action promotes tumorigenesis (5). Intriguingly, senescent fibroblasts, which accumulate with age, also display protumorigenic activity (6). Comparison of the secretory phenotype of CAFs and senescent fibroblasts revealed an overlap in expression of secreted factors referred to as senescence-associated secretory phenotype (SASP) factors (7). These observations raise the question of how this common secretory phenotype is regulated and whether it provides a therapeutic opportunity.

The new study by Alspach and colleagues (8) in this issue describes a posttranscriptional mechanism mediated by p38MAPK activity on AUF1 to stabilize SASP mRNA species common to both CAFs and senescent fibroblasts (Fig. 1). The studies are carefully laid to make a compelling argument in support of their major conclusion that p38MAPK inhibitors, now in clinical trials for other disease states, may be useful in cancer therapy by targeting the stromal cell contribution to cancer growth.

The best-understood mechanism for regulating mRNA decay rate is that mediated by binding of factors, such as AUF1, to AU-rich elements (ARE) in the 3'-untranslated regions (UTR). AREs are present in 5% to 8% of genes and, importantly, these include those encoding SASP protumorigenic factors such as IL6, IL8, GM-CSF, and CCL20. AUF1 (also known as HNRNPD/heterogeneous nuclear ribonucleoprotein D) is a family of four proteins, derived by alternative splicing of a common mRNA precursor, that bind as dimers or higher-order structures to AREs to promote mRNA degradation, most likely via the deadenylation-dependent mRNA decay pathway. To effect this degradation, AUF1 needs to recruit accessory factors, one of which is the chaperone HSP27. As shown previously (9), phosphorylation of HSP27

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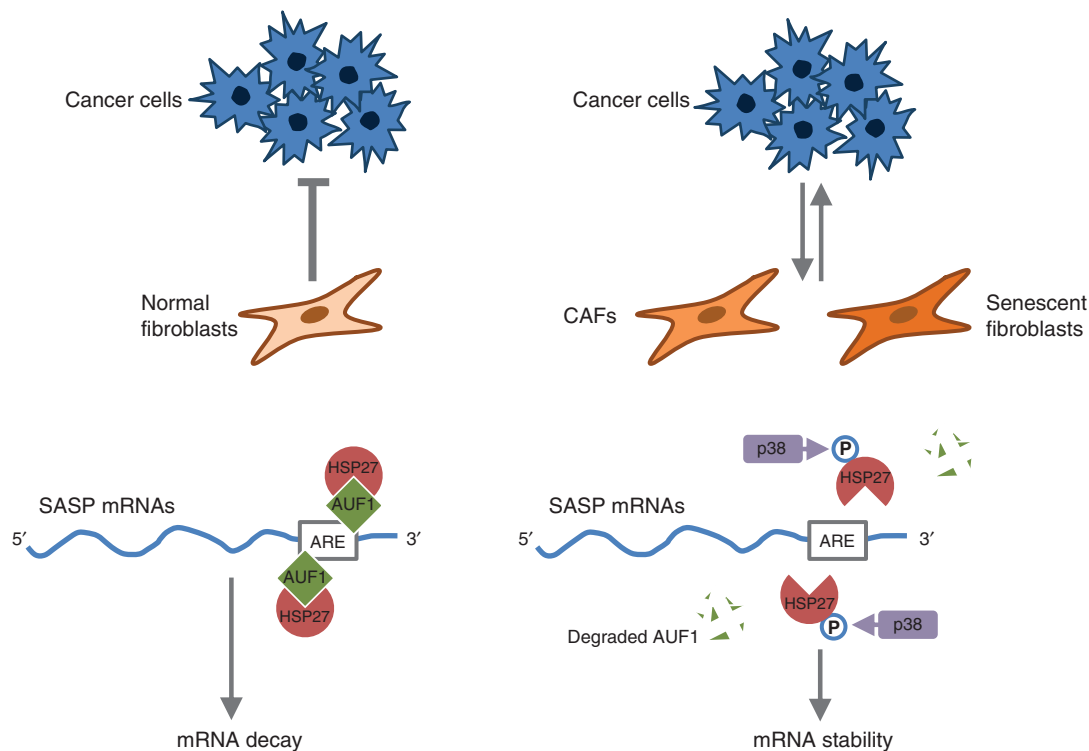


Figure 1. Activity of p38MAPK in cancer-associated and senescent fibroblasts. Whereas normal fibroblasts can play a tumor-suppressive role, CAFs and senescent fibroblasts that are characterized by secretion of SASP factors can promote tumorigenesis. AUF1 and associated factors, including HSP27, mediate mRNA degradation by binding to SASP mRNAs containing AREs in their 3'-UTRs. Stability of SASP mRNAs is enhanced by p38MAPK, which phosphorylates HSP27 to promote proteosomal degradation of AUF1. Targeting p38MAPK both reverses the enhanced SASP mRNA stability and attenuates tumorigenicity.

by the stress-activated kinase p38MAPK results in proteosomal degradation of AUF1 and consequent mRNA stabilization. A key feature of the study by Alspach and colleagues (8) is to provide a link between p38MAPK, AUF1, and the posttranscription regulation of key SASP components, such as IL6 and IL8, in CAFs and senescent fibroblasts. Crucially, they then provide strong data from models demonstrating that targeting p38MAPK in the stroma both inhibits the development of tumor growth and attenuates the growth of established tumors, thus highlighting p38MAPK as a potentially relevant target.

Consistent with this notion, Alspach and colleagues (8) show that the stroma of breast cancer is enriched in SASP proteins. These promising data underscore a gap in the study in that the functional demonstration relies exclusively on cancer cell lines. Future experiments might use primary human cancers and fibroblasts in xenograft models, which would enable testing of whether p38MAPK inhibition can be generalized to diverse human tumors and genetic backgrounds. An alternative would be a murine model of carcinogenesis, whether from exogenous exposure or genetic manipulation, in which the generation of tumors is evaluated in the context of stromal cells that are unable to activate p38MAPK or respond to the inhibitor. An additional area of interest for future studies would be to understand the interplay between senescent fibroblasts and oncogene (or other)-induced senescence of tumor cells. Although there is strong evidence that oncogene-

induced senescence acts as a tumor-suppressive mechanism in tumor cells, it is now appreciated (and supported by the data presented in the current study) that the accompanying associated senescence of stromal fibroblasts can, conversely, be protumorigenic (10). Although Alspach and colleagues (8) report no effect of p38MAPK inhibitors on their tumor cell lines, it will be important to confirm in more complex models that these inhibitors predominantly act on the stromal compartment. Meanwhile, as is discussed in this study, p38MAPK inhibitors are currently in phase II and III trials for a variety of inflammatory diseases. Although tumor incidence will not be a primary endpoint in these studies, the trials will provide valuable information on the tolerability and side effects of treating patients with these inhibitors and potentially speed up their introduction into the oncology setting.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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