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The origins of tumor-promoting inflammation

Tanya Bondar and **Ruslan Medzhitov**
HHMI and Department of Immunobiology, Yale University School of Medicine, New Haven, CT 0651 USA

Ruslan Medzhitov: ruslan.medzhitov@yale.edu

Abstract

Inflammation is increasingly recognized as an essential component of tumor development, but the origin of tumor-associated inflammation remains largely unknown. In this issue of *Cancer Cell*, Ben-Neriah and colleagues find that chronic stress initiates senescence-inflammatory response (SIR), which can promote tumorigenesis in the absence of exogenous inflammatory triggers.

Cellular senescence may be compared to a differentiation program in its dramatic effects on cell morphology, metabolism, and chromatin structure. Yet physiological roles of senescence remain poorly understood.

Because senescence induces permanent cell cycle arrest, it is thought to function to suppress tumor development (Rodier and Campisi, 2011). However, it is unclear why senescence is used instead of apoptosis, which would permanently eliminate oncogenic cells. The phenomenon of cell senescence is in many ways analogous to T cell anergy, where autoreactive and potentially harmful T cells are rendered unresponsive to stimulation. Why anergic and apparently unwanted T cells are not eliminated by apoptosis remains unknown. Likewise it is unclear why senescent cells are retained rather than eliminated?

One possible clue to this puzzle is that in addition to cell cycle arrest, senescent cells may have non-cell-autonomous roles based on their secretory activity. Indeed, senescence-associated secretory phenotype (SASP) is a common feature of senescent cells (Rodier and Campisi, 2011). They primarily release proinflammatory cytokines, chemokines, and extracellular-matrix remodeling factors. Many of these proteins are critical in promoting tissue repair and can be produced in larger quantities by macrophages in response to infection or damage.

The view of senescence as a form of tissue repair response may explain another paradox of cell senescence: in some contexts it has a tumor-promoting effect. Tumor growth has features of deregulated tissue repair, but what initiates this repair response is unclear. Tissue repair accompanies the inflammatory response induced by tissue injury. However, how these responses are induced in tumors remains poorly understood despite increasing appreciation of their critical role in tumor development (Ben-Neriah and Karin, 2011).

Correspondence to: Ruslan Medzhitov, ruslan.medzhitov@yale.edu.

A study in this issue of *Cancer Cell* establishes new functional links between tissue stress, senescence, low-grade inflammatory response, and tumor progression (Pribluda et al., 2013). To introduce these findings, we first need to address the terminology of senescence and inflammation, which is often inconsistent and even confusing.

By being implicated in diverse biological processes, both “senescence” and “inflammation” terms have been stretched far beyond their original definitions, often creating challenges in use and interpretation. Senescence is often defined by an arbitrary number of optional markers, predominantly phenotypic and not always present together. Every single hallmark of senescence has been found dispensable for at least some of the senescence states described. Even permanent growth arrest, the most definitive feature of senescence, can be missing in some cases. For example, senescent hematopoietic stem cells defined in physiological ageing or genotoxic stress display multiple senescent markers while retaining partial proliferative capacity (Rossi et al., 2007). Because of this vague terminology, senescence phenotypes reported in different studies sometimes show little overlap.

Similarly, “inflammatory responses” differ greatly depending on the nature of the inducer, responding cells, etc. Both senescence and inflammation are induced by stress and share some components. Not surprisingly, what is defined as a senescence response in one setting may be more similar to an inflammatory response in this same setting, rather than to a senescence response in a different setting.

This terminological paradox and its elegant resolution are the starting point of the paper by Ben-Neriah and colleagues (Pribluda et al., 2013). In their study, mice with enterocyte-specific ablation of *Csnk1a1* (single knockout, SKO) or *Csnk1a1* and *p53* (double knockout, DKO) yield pre-neoplastic or malignant stages of intestinal carcinogenesis, respectively. Wnt pathway is activated in SKO cells but does not result in tumor development, as it is counteracted by chronic DNA damage response and senescence. The senescence appears p53-dependent, as growth arrest and p21 expression are ablated in DKO enterocytes, which rapidly progress to malignancy.

However, senescence markers SA-β-gal and p19 are still displayed by the highly proliferative DKO cells. Even more surprisingly, both SKO and DKO cells produce elevated levels of numerous inflammation-related factors, which the authors call senescent-inflammatory response (SIR). Although the identities of SIR and SASP genes show little overlap, most belong to the same functional categories. Thus, both SIR and SASP may be viewed as para-inflammation induced by genotoxic stress. Accordingly, senescence can function as two separable stress-induced responses: (1) tumor suppressive, p53-mediated, cell-autonomous growth arrest, which is in essence a prolonged DNA damage checkpoint, and (2) an inflammatory response (SIR/SASP/para-inflammation), which promotes tissue repair by cell-extrinsic mechanisms and may potentially be tumor-promoting.

These results further suggested that inflammation induced by stress in a cell-autonomous manner may be the elusive source of tumor-associated inflammation. Indeed, blocking SIR with non-steroidal anti-inflammatory drugs (NSAIDs) decreased tumor burden in DKO mice and abolished aberrant proliferation and transformed phenotype of DKO organoid cultures. As these cultures are devoid of microbes and immune cells, these experiments illustrate that cell-autonomous initiation of inflammation can play a critical role in oncogenic transformation.

Which of the many SIR genes are responsible for this process, and what is the p53's role in it? SIR genes are elevated in SKO and DKO cells, but induce oncogenic transformation only in DKO cells. In their previous study, Ben-Neriah and colleagues reported that oncogenic transformation of DKO cells is mediated by “the p53-suppressed invasiveness signature”

(PSIS) genes (Elyada et al. 2011). These genes are expressed in DKO but not SKO cells and function in tissue remodeling, cell adhesion, and migration. Now by showing that PSIS expression is dependent on SIR and blocked by NSAIDs, the authors seem to have connected the dots (Pribluda et al., 2013).

But more questions always follow. What is the physiological counterpart of the PSIS program? How does PSIS activation induce hyperproliferation? One possible explanation may be provided by a hypothesis that proliferation of stem cells at steady state and during tissue injury is differentially controlled by cell interactions.

Stem cells generally depend on contacts with their niche for proliferation, survival, and self-renewal. This dependence enables elimination of misplaced stem cells and controls stem cell compartment size. How do stem cells survive and massively proliferate upon tissue injury when the niche is likely to be damaged? Perhaps in this context some injury-induced signals can temporarily license stem cells to survive and proliferate outside the niche and migrate to nearby sites of damage if those “local” stem cells have been destroyed. Niche disruption would induce tissue remodeling, so the production of the licensing signals could be coupled to the remodeling response. This mechanism would ensure that niche-independent proliferation is only allowed when there is tissue damage. Once the tissue structure is restored, the inflammatory response and tissue remodeling cease and proliferation again becomes restricted by contacts with the niche.

Consistent with this hypothesis, NSAIDs only inhibit proliferation of DKO cells in “inappropriate” locations, such as small intestine villi and organoid cultures spheroid bodies. Proliferation within intestinal crypts and their in vitro equivalents (organoid “outpockets”) was unaffected by NSAIDs, consistent with the idea that signals in the stem cell niche sustain proliferation by a distinct mechanism (Pribluda et al., 2013).

Inflammatory factors secreted by senescent cells have been implicated in cancer progression via several non-cell autonomous mechanisms (Ohtani et al., 2013). In contrast, inflammatory and tissue remodeling factors promoting tumor progression of DKO enterocytes are produced and act cell-autonomously. This latter scenario illustrates the principle that oncogenic transformation can be induced by low-grade inflammation resulting from tissue stress (para-inflammation) (Medzhitov, 2008).

References

Ben-Neriah Y, Karin M. Inflammation meets cancer, with NF-kappaB as the matchmaker. Nature immunology. 2011; 12:715–723.10.1038/ni.2060 [PubMed: 21772280]

Elyada E, et al. CKIalpha ablation highlights a critical role for p53 in invasiveness control. Nature. 2011; 470:409–413.10.1038/nature09673 [PubMed: 21331045]

Medzhitov R. Origin and physiological roles of inflammation. Nature. 2008; 454:428–435.10.1038/nature07201 [PubMed: 18650913]

Ohtani N, Hara E. Roles and mechanisms of cellular senescence in regulation of tissue homeostasis. Cancer science. 2013; 104:525–530.10.1111/cas.12118 [PubMed: 23360516]

Pribluda et al., 2013. This issue

Rodier F, Campisi J. Four faces of cellular senescence. The Journal of cell biology. 2011; 192:547–556.10.1083/jcb.201009094 [PubMed: 21321098]

Rossi DJ, et al. Deficiencies in DNA damage repair limit the function of haematopoietic stem cells with age. Nature. 2007; 447:725–729.10.1038/nature05862 [PubMed: 17554309]