



Conclusions and perspectives

The current reports by Rentschler et al. and Aanhaanen et al. clearly demonstrate that accessory pathway formation underlying ventricular preexcitation arises as a consequence of erroneous development of the AV canal myocardium. A hierarchical network of transcription factors, including *Tbx2/3/5*, *Nkx2.5*, *GATA4*, and *Msx2*, governs normal development of the AV canal under the regulation of Notch and BMP signaling (10). Contrary to previous reports demonstrating that Notch signaling restricts BMP2 and *Tbx2/3* to the AV canal during early embryogenesis (16, 17), the expression level of BMP2 was unchanged in Notch1-activated mice (1). Our understanding of the pathophysiology of ventricular preexcitation will be broadened by further characterization of the genetic program for AV canal development.

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Address correspondence to: Issei Komuro, Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan. Phone: 81.6.6879.3631; Fax: 81.6.6879.3639; E-mail: komuro-ty@umin.ac.jp.

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Growing a tumor stroma: a role for granulin and the bone marrow

Andrew Bateman

Endocrine Research Laboratory, Royal Victoria Hospital, Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada.

The tumor stroma is critical in cancer progression; understanding its formation is therefore important biologically and therapeutically. In this issue of the JCI, Elkabets et al. report on the generation of data in mice that lead them to propose that certain tumors can stimulate the growth of a second otherwise quiescent or indolent tumor in the same animal by stimulating stromal formation. Granulin-expressing Sca^+Kit^- hematopoietic progenitor cells in the bone marrow of the tumor host were required to mediate this effect. These data shed new light on the importance of the bone marrow in tumor growth and the role of granulin in carcinogenesis.

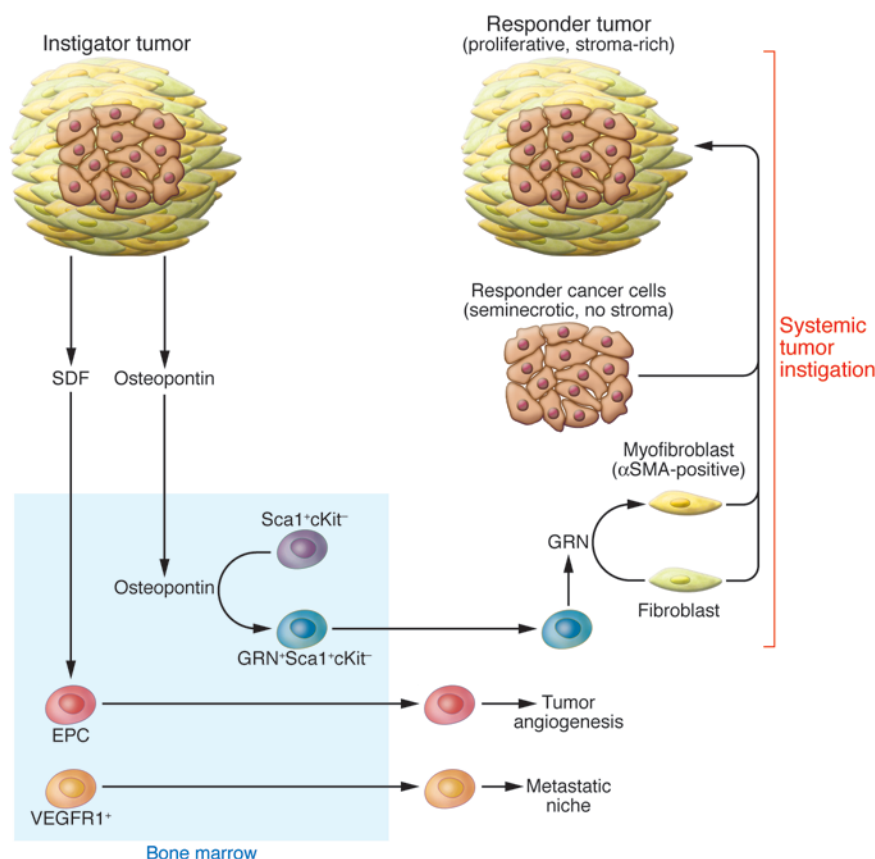
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Background: systemic tumor instigation

The reactive (or desmoplastic) stroma is an aberrant fibrous tissue that surrounds can-

cer cells (1). It is formed from fibroblasts, adipocytes, inflammatory cells, and vascular cells and is further characterized by the presence of myofibroblasts (1). Myofibroblasts display properties not usually associated with fibroblasts in healthy tissue, such as the expression of αSMA , and secrete high levels of matrix proteins such as collagen I (1). The molecular properties of tumor stroma are predictive of disease outcome (2), with the stromal cells, in particular the myofibroblasts, stimulating tumor growth, invasion, and metastasis (1). For example, molecular crosstalk between cancer cells

**Figure 1**

The role of GRN⁺Sca1⁺cKit⁻ BMCs in systemic instigation and the formation of tumor stroma. Cells from an aggressively growing primary tumor, the instigator, secrete the circulating signal osteopontin. This mobilizes a population of Sca1⁺cKit⁻ BM progenitor cells that express high levels of the secreted glycoprotein GRN. The GRN⁺Sca1⁺cKit⁻ BMCs travel to the site of inoculation of a second cancer cell type, the responder, that grows poorly in mice. GRN⁺Sca1⁺cKit⁻ cells enhance the assembly of the tumor stroma by stimulating the differentiation of fibroblasts into α SMA-expressing myofibroblasts. The stroma, in turn, supports the successful growth of the otherwise quiescent or indolent responder cells, resulting in a proliferating stroma-rich carcinoma outgrowth (7). The process whereby an aggressive primary tumor promotes the outgrowth of another otherwise indolent tumor is called systemic instigation. Interrupting the paracrine GRN signal during systemic instigation or preventing the mobilization of the GRN⁺Sca1⁺cKit⁻ BMCs might prove therapeutically useful in preventing the formation of reactive tumor stroma, thereby inhibiting tumor progression (7). The role of GRN⁺Sca1⁺cKit⁻ BMCs as local regulators of tumor progression is compared to other proposed mechanisms of BM/tumor interaction. For example, the BM may provide progenitor cells directly; in the example shown, tumor fibroblasts secrete stromal-derived factor-1 (SDF), which mobilizes endothelial progenitor cells (EPC). These contribute to angiogenesis (16). Other hematopoietic progenitors, for example VEGFR1⁺ cells, may assist in the creation of prometastatic niches (17).

and myofibroblasts, mostly in the form of growth factor signaling (1, 3), promotes invasive growth of cancer cells (1, 3).

Several mechanisms have been put forward to explain how the tumor stroma forms, including through the recruitment and differentiation of cells in or near the tumor (1), through the recruitment into the tumor of circulating BM-derived cells, such as mesenchymal stem cells and fibrocytes (1, 4), and through epithelial-mesenchymal

transition of cancer cells (1). A previous study by McAllister, Weinberg, and colleagues (5) defined in mice an additional mechanism that they called systemic instigation. Underpinning this mechanism is the concept that a circulating signal is secreted from an aggressively tumor-forming breast cancer cell line, which is called the instigator tumor, that results in tumor outgrowth and the acquisition of a reactive stroma in a second otherwise quiescent or

indolent breast cancer cell line, known as the responder. If the instigator tumor is absent, the responder cells fail to expand and may even become necrotic (Figure 1).

Systemic instigation acts through BM cells (BMCs). The instigator tumor secretes the prometastatic factor osteopontin (6), which then mobilizes Sca1⁺cKit⁻ cells from the BM. The Sca1⁺cKit⁻ BMCs accumulate at the responder tumor and stimulate reactive stroma formation (ref. 5 and Figure 1). However, how these Sca1⁺cKit⁻ BMCs stimulate formation of a reactive stroma has not been defined (5). This point has now been addressed in this issue of the *JCI*, where Elkabets et al. (7) report for the first time the mechanism by which Sca1⁺cKit⁻ BMCs instigate the formation of a reactive stroma in indolent responder tumors in mice.

GRN⁺Sca1⁺cKit⁻CD45⁺ cells mediate systemic instigation

To follow the fate of BMCs during tumor instigation, Elkabets and colleagues performed BM transplants using donor marrow that expressed GFP (7). As expected, GFP⁺ BMCs were recruited to the stroma of responder tumors. However, very few GFP⁺ myofibroblasts were observed in the responder tumor stroma. It was deemed unlikely therefore that Sca1⁺cKit⁻ BMCs were stromal progenitor cells; rather it seemed more likely that they acted in a regulatory capacity to coordinate the assembly of the stroma from other cell types. BMCs from mice with instigator tumors were sorted into Sca1⁺cKit⁻, Sca1⁺cKit⁺, and Sca1⁻ cells and comixed with responder cancer cells before transplantation into mice that did not bear contralateral instigator tumors. Of these three cellular subsets, only Sca1⁺cKit⁻ cells reproduced the effects of an instigator tumor, enabling responder tumors to elaborate a collagen-rich stroma with α SMA⁺ cells. In contrast, Sca1⁺cKit⁻ cells that were harvested from the BM of control mice with either Matrigel or an aggressive tumor that did not instigate the responder tumor in place of the instigator tumor were unable to promote formation of a reactive stroma (7).

Sca1⁺cKit⁻ cells are a subclass of quiescent hematopoietic progenitor cells of ill-defined function present in all mouse BM (8). Elkabets et al. (7) therefore asked in what way stroma-instigating Sca1⁺cKit⁻ BMCs differed from inactive control Sca1⁺cKit⁻ BMCs. No differences were observed in cell-surface markers, with both instigator and control Sca1⁺cKit⁻ BMCs displaying



the hematopoietic marker CD45. However, microarray analyses revealed that instigator Sca1⁺cKit⁻ BMCs expressed greater levels of the *Grn* gene, which encodes the secreted protein Granulin (GRN; sometimes called progranulin, PC-derived growth factor, granulin-epithelin precursor, proepithelin, acrogranin, or TGF- α) (9). Importantly tumor-resident BMCs in responder tumors grown opposite instigator tumors were also GRN⁺, whereas α SMA⁺ myofibroblasts and cancer cells were GRN⁻.

Elkabets et al. (7) then investigated whether GRN might mediate stroma instigation by the GRN⁺Sca1⁺cKit⁻CD45⁺ BMCs. In vivo stimulation of indolent tumors with recombinant GRN fully recapitulated the effect of instigator tumors, promoting the formation of responder tumor foci with an adenocarcinoma-like morphology. GRN induced the differentiation of cultured human mammary fibroblasts into α SMA⁺ myofibroblast-like cells. Responder cancer cells in culture did not proliferate in response to GRN. This suggests that during systemic instigation, the proliferation of responder cancer epithelial cells is not stimulated directly by GRN but likely results secondarily through the increased formation of a reactive stroma. In agreement with this hypothesis, transplantation into mice that lacked instigator tumors of responder cells comixed with normal primary mammary fibroblasts primed in vitro with GRN resulted in the growth of proliferative foci of responder tumor cells (7). Elkabets et al. (7) therefore concluded that GRN⁺Sca1⁺cKit⁻CD45⁺ BMCs mediate systemic instigation of tumor stroma through the secretion of GRN.

Progranulin in human breast cancers

In mice, GRN⁺ cells in both responder and instigator tumors were found only in the stroma (7), suggesting tentatively that instigator tumors may instigate the formation of their own stromal tissue. Although stromal cells in human breast cancers express GRN, Elkabets et al. (7) observed that GRN was also expressed in human cancer epithelial cells (7). They further observed a positive correlation between GRN expression and aggressive, treatment-resistant, triple-negative breast cancers (that is, breast cancers that lack the receptors for estrogen and progesterone, as well as Her2/neu). GRN-positivity also correlated with the size of the tumor and its proliferative index. Kaplan-Meier analyses indicated a relationship between

GRN positivity of breast cancers and worse survival among patients (7). These studies did not differentiate between stromal and epithelial expression of GRN.

The triple-negative state of a breast cancer refers to the lack of expression of the three receptors on the cancerous cells of epithelial origin, not the stroma. Epithelial GRN expression has been associated previously with advanced invasive cancers (9, 10). In previous reports in mice, depleting GRN from cancer cells by mRNA targeting (11) or monoclonal antibody strategies (12) reduced their tumorigenicity, while overexpressing GRN in cells that are only weakly tumorigenic enhanced their malignant properties (13, 14). Taken together, these data suggest a model in which GRN delivered to a tumor by GRN⁺Sca1⁺cKit⁻CD45⁺ BMCs plays a key role in the early stages of tumor development, particularly in stromal formation (7), but as tumors progress, GRN expression is no longer restricted to these cells (7), as cancer epithelial cells acquire the ability to both express and respond to GRN. Fibroblasts in wounds respond to GRN by increased proliferation and migration (15). GRN from cancer epithelial cells may therefore play a similar role in regulating fibroblast activity in the tumor stroma, perhaps even taking over part of the function of GRN⁺Sca1⁺cKit⁻CD45⁺ BMCs, although at this stage that is purely speculative.

Context and questions

BMCs have been implicated extensively in tumor progression and invasion (Figure 1), primarily as the source of myofibroblast precursor cells for the tumor stroma (1, 4) or as endothelial progenitor cells that may be mobilized from the BM and recruited to tumors by tumor-derived chemokines such as stromal-derived factor-1 (16). Nevertheless, the mechanism for stroma formation proposed by Elkabets et al. (7) presents unique features, notably that the GRN⁺Sca1⁺cKit⁻CD45⁺ BMCs recruited to the tumor direct the assembly of the reactive stroma but do not act themselves as precursors for stromal cells. Further work is needed to understand when systemic instigation, working through GRN⁺Sca1⁺cKit⁻CD45⁺ BMCs, contributes to stroma formation and when circulating progenitor cells from the BM are more likely to support the production of a reactive tumor stroma. BMCs promote metastasis by providing favorable local microenvironments in which metastasizing cancer

cells assemble and grow, as exemplified by the formation of prometastatic niches by VEGFR⁺ BMCs (17). Sca1⁺cKit⁻ cells, which are presumably identical or closely related to the GRN⁺Sca1⁺cKit⁻CD45⁺ cells of Elkabets et al. (7), are effective instigators of indolent breast cancer metastasis in mouse lungs (5). Clearly, the role of GRN and GRN⁺Sca1⁺cKit⁻CD45⁺ BMCs in metastasis warrants further research.

As with all novel mechanisms, there are caveats in that suggested by the work of Elkabets et al. (7). Not all aggressively growing primary tumors are instigators of indolent tumors (5). Furthermore, primary tumor resection often promotes the metastasis of distant dormant tumors (18). This is the opposite of what would be predicted from the model of systemic instigation as proposed by Elkabets et al. (7), and it will be important to learn what factors determine why primary tumors can act either as instigators (7) or inhibitors (18) of dormant tumors. Integrating the responder/instigator mechanism definitively into the natural history of cancer progression is clearly an important future goal.

Conclusions

The findings reported in this issue of the *JCI* by Elkabets et al. (7) on the mechanisms by which BMCs regulate the formation of a reactive tumor stroma during systemic instigation enrich our understanding of the interplay between BMCs and cancer; they also reinforce the importance of the tumor stroma in cancer progression and highlight new roles of GRN in tumor growth. This clearly raises the prospect that strategies targeting GRN or the GRN⁺Sca1⁺cKit⁻CD45⁺ BMCs might provide novel therapeutic approaches to blocking, or even reversing, stromal expansion in cancer and that by so doing they might slow or halt the growth of human tumors.

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Address correspondence to: Andrew Bateman, Endocrine Research Laboratory, Room H.5.21 Royal Victoria Hospital, Research Institute of the McGill University Health Centre, 687 Pine Ave. West, Montreal, Quebec H3A1A1, Canada. Phone: 514.934.1934; Fax: 514.843.2819; E-mail: Andrew.bateman@muhc.mcgill.ca.



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Nuclear receptors take center stage in Th17 cell-mediated autoimmunity

Jennifer J. Heller, Ju Qiu, and Liang Zhou

Department of Pathology and Department of Microbiology and Immunology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA.

Liver X receptors (LXRs) are nuclear receptors involved in cholesterol homeostasis. Notably, they are also expressed by T cells and are involved in regulating T cell proliferation and differentiation. In this issue of the JCI, Cui et al. have elucidated the molecular mechanism underlying the effects of LXR activation on a subset of T cells known as Th17 cells in mice and humans. Specifically, they showed that LXR-induced Srebp-1 inhibits *Il17* transcription by binding to the *Il17* promoter through interaction with the aryl hydrocarbon receptor (Ahr), a transcription factor known to enhance Th17 cell responses.

Heightened immune responses are needed to fight harmful microorganisms, yet those same responses have to be kept from overreacting and attacking the body's normal tissues to cause autoimmunity. This balance is maintained by a complex set of interactions among various immune cells. Th17 cells are a subset of CD4⁺ T cells characterized by the production of high levels of the cytokines IL-17 (also known as IL-17A), IL-17F, and IL-22 (1). They are important for the clearance of certain bacterial and fungal pathogens (1). However, Th17 cells have also been implicated in various human autoimmune diseases and other chronic inflammatory conditions (1). Since the initial discovery that the nuclear retinoic

acid-related orphan receptor γ t (ROR γ t) is key to the differentiation of Th17 cells (2), transcriptional regulation of Th17 cells has been intensively investigated.

Aryl hydrocarbon receptor, an important regulator of Th17 cell differentiation

Aryl hydrocarbon receptor (Ahr), a ligand-dependent nuclear receptor, is among the handful of transcription factors implicated thus far in Th17 cell differentiation (3). Although its endogenous ligands remain elusive, Ahr is best known to mediate the effects of environmental toxins (e.g., the human carcinogen dioxin; ref. 4). Ahr belongs to the basic region helix-loop-helix (bHLH)/Per-Arnt-Sim (PAS) family of proteins (4). Ligand binding to the PAS domain triggers the transcriptional activity of Ahr, inducing target gene expression. Ligand-activated Ahr enhances the expression

of IL-17 and is essential for IL-22 expression (5). Recent data suggest that Ahr may promote Th17 cell differentiation, in part through suppression of Stat1 phosphorylation (6). However, the precise molecular mechanism(s) by which Ahr regulates Th17 cell differentiation still remain elusive.

Role of liver X receptors in regulating immune response

Liver X receptors (LXRs) were originally classified as orphan nuclear receptors. However, it was subsequently determined that both LXR isoforms (LXR α and LXR β) are ligand-dependent transcription factors activated by metabolites of cholesterol that cause a conformational change in the LXR upon binding (7). LXRs form a heterodimer with retinoid X receptor (RXR), which then binds DNA and modulates the expression of various genes involved in regulating cholesterol homeostasis, including *ABCA1*, *ABCG1*, and *SREBP1* (7). More recent studies have expanded the role of LXRs to implicate them as modulators of the immune response (8–11). LXR ligands have been shown to inhibit LPS- or cytokine-induced expression of genes encoding inflammatory mediators such as IL-6 (8), and LXR-dependent gene expression is required for macrophage function in response to bacterial infection (9).

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