

REVIEW

Waking up dormant tumors

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Abstract

As appreciation grows for the contribution of the tumor microenvironment to the progression of cancer, new evidence accumulates to support that the participation of stromal cells can extend beyond the local environment. Recently, Elkabets and colleagues demonstrated a systemic interaction between cancer cells and distant bone marrow cells to support the growth of otherwise indolent tumor cells at a secondary site, raising thought-provoking questions regarding the involvement of stromal cells in maintaining metastatic dormancy.

Background

Research in recent years has highlighted the interactions between cancer cells and stromal cells as crucial determinants of cancer progression [1]. Stromal cells of the tumor microenvironment, which includes fibroblasts, endothelial cells, immune cells and more, actively participate in the tumorigenic process and have become important therapeutic targets in cancer [2]. In addition to local stromal interactions within the tumor microenvironment, tumors appear to have a systemic effect that can influence cancer progression, primarily via the stimulation of bone marrow cells [3].

In a previous study 3 years ago, McAllister and colleagues [4] reported that certain tumors (termed 'instigators') can foster the growth of otherwise indolent tumors (termed 'responders') at a distant anatomical site via the activation and recruitment of bone marrow cells. However, the identity of the activated bone marrow cells and their specific contribution had not been determined.

Article

Researchers from McAllister's group at Brigham and Women's Hospital have now determined the identity of

the activated bone marrow cells responsible for stimulating the growth of otherwise indolent tumor cells and further characterized the impact of the activated bone marrow cells on these responding tumors [5]. In addition, they have identified a molecular mechanism by which the activated bone marrow cells facilitate growth of the responding tumors.

Histological analysis of the responding tumors stimulated by the bone marrow cells demonstrated a greater desmoplastic reaction with increased distribution of alpha-smooth muscle actin-positive myofibroblasts and excess collagen deposition. Elkabets and colleagues [5] determined that the myofibroblasts are not bone marrow derived; thus, the bone marrow cells are not differentiating into myofibroblasts but rather activating the myofibroblasts within the tumor microenvironment.

Fluorescence-activated cell sorting (FACS) analysis of the activated bone marrow cells identified them as a Scd1+cKit population of hematopoietic progenitors. While this population of bone marrow cells also exists in mice bearing non-instigating tumors, only the Scd1+cKit population from mice bearing instigator tumors can stimulate the growth of responding tumors. Gene expression profiling of the Scd1+cKit populations from instigator-bearing mice and non-instigator-bearing mice identified that the bone marrow cells from instigator-bearing mice exhibit increased expression of granulin, a secreted growth factor of the epithelin family.

In the absence of activated bone marrow cells, recombinant granulin alone was able to stimulate the growth of indolent tumor cells with an accompanying desmoplastic reaction. Notably, assessment of granulin expression in human breast cancer samples demonstrated that high granulin expression is significantly correlated with the most aggressive breast tumor subtypes and reduced patient survival.

Viewpoint

The role of granulin in promoting tumorigenesis has been previously investigated [6] and its potential as a therapeutic target has been explored via the use of a monoclonal antibody against granulin, which was able to inhibit tumor growth in a dose-dependent manner [7]. However, many of these studies have focused on the function of granulin as expressed by cancer cells; the

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study by McAllister's group [5] is the first to identify a stromal contribution of granulin to tumorigenesis.

Activated bone marrow cells expressing granulin are recruited to the tumor microenvironment to stimulate the growth of otherwise indolent tumor cells. Noting the hematopoietic source of granulin, this raises an interesting question as to whether the assessment of granulin levels in the serum may serve as a prognostic marker for relapse in cancer patients. Additionally, one might also draw a parallel between the indolent responding tumors of these experiments and the dormant metastases of cancer patients. In this case, is bone marrow-derived granulin one of the factors responsible for waking up dormant metastases?

Osteopontin was previously identified as the molecule secreted by the instigator tumor, which activates the bone marrow cells [4]. Is the continued presence of the instigator tumor necessary to maintain activation of the bone marrow cells? Or do the bone marrow cells remain activated despite removal of the instigator tumor? The answers to these questions will have implications on the therapeutic efficacy of primary tumor resection and additional measures that may need to be taken in order to suppress metastatic outgrowth. Even after primary tumor resection, there may be other sources of osteopontin or additional mechanisms that activate bone marrow cells. A greater understanding of the mechanisms underlying bone marrow activation may have important clinical implications for maintaining metastatic dormancy.

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Competing interests

The authors declare that they have no competing interests.

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