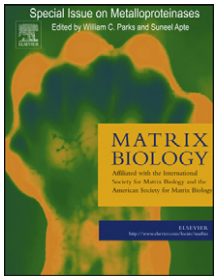
Review



Matrix metalloproteinases in stem cell regulation and cancer

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Abstract

Since Gross and Lapiere firstly discovered matrix metalloproteinases (MMPs) as important collagenolytic enzymes during amphibian tadpole morphogenesis in 1962, this intriguing family of extracellular proteinases has been implicated in various processes of developmental biology. However, the pathogenic roles of MMPs in human diseases such as cancer have also garnered widespread attention. The most straightforward explanation for their role in cancer is that MMPs, through extracellular matrix degradation, pave the way for tumor cell invasion and metastasis. While this notion may be true for many circumstances, we now know that, depending on the context, MMPs may employ additional modes of functionality. Here, we will give an update on the function of MMPs in development and cancer, which may directly regulate signaling pathways that control tissue homeostasis and may even work in a non-proteolytic manner. These novel findings about the functionality of MMPs have important implications for MMP inhibitor design and may allow us to revisit MMPs as drug targets in the context of cancer and other diseases.

Introduction

Development of multi-cellular organisms is mediated by a tightly controlled program of cell fate decisions that determine whether a stem or progenitor cell will proliferate, differentiate or undergo apoptosis. Even in the adult organism, tissue resident stem cells are crucial to mediate tissue homeostasis and replenish the tissue on a daily basis. These cell fate decisions of stem cells within the parenchyma are strongly influenced by extrinsic signals provided by the surrounding microenvironment, or the niche, which consist of extracellular matrix (ECM), adjacent stromal cells as well as extracellular, soluble factors such as growth factors, cytokines and chemokines.

Another group of extracellular factors that play important roles in stem cell niches during development are the matrix metalloproteinases (MMPs). MMPs are a family of zinc-dependent endopeptidases that were firstly described in amphibian tadpole morphogenesis about half a century ago [1]. MMPs have been found to play crucial roles in during tissue remodeling and organ development by rearrangement of the extracellular matrix as well as by specifically modulating signaling pathways through proteolytic interaction with multiple substrate molecules of very diverse nature [2]. However, there is a dark side to these proteinases, in particular when their function or expression goes awry, they can contribute to virtually all steps of tumor progression [3].

In this minireview we will concentrate on the emerging roles of MMPs as secreted factors within stem cell niches during development and how some of these functions may be hijacked during cancer.

MMPs in the stem cell niche

The microenvironment provides the context that dictates the behavior of adult stem cells in normal

tissue homeostasis and in cancer. The stem cell niche consists of a microenvironment of adjacent cells and surrounding extracellular matrix, which provides localized signals and extrinsic factors that save the stem cells from depletion, while preventing uncontrolled self-renewal and proliferation [4].

Due to their ability to cleave, degrade and rearrange ECM molecules, MMPs can modulate a variety of stem cell niches. The hematopoietic stem cell system is one of the best studied examples of adult stem cells and several questions about the composition of their niche have already been solved [5]. MMPs take an active role in shaping the microenvironment of the niche in the bone marrow. MMP9 can cleave and mobilize Kit ligand, which enables bone marrow repopulating cells to translocate to a permissive niche that allows reconstitution after irradiation [6]. MMP14 (MT1-MMP) regulates HIF-mediated gene transcription of chemokines and cytokines within the hematopoietic stem cell niche [7]. These examples illustrate how MMP function can modify the microenvironment of the bone marrow stem cell niche by changing the bioavailability of cytokines and chemokines that affect stem cell function.

Many morphogens bind to components of the ECM, which limits the range of function of these growth factors within tissues. In Drosophila, MMP2 specifically cleaves the ECM component division abnormally delayed (dally)-like protein (Dlp), which renders it incapable of binding to the morphogen wingless (Wg). This could explain how Wg traverses long distances in the Drosophila ovary to promote follicular stem cell proliferation [8]. ECM cleavage by MMPs may also lead to the destruction niche related structures. In the case of human epidermal stem cells, long-term survival is maintained by inhibiting proteolysis through MMP2 and MMP14 in organotypic cultures [9], which otherwise would lead to proteolytic degradation of a stem cell promoting niche.

However, there is much more to the complexity of stem cell regulation by MMPs than simple degradation of the ECM. Our own work recently showed that MMP3 (also called Stromelysin-1) has an impact on the maintenance of adult epithelial stem cells in the mammary gland. These effects of MMP3 are based on its specific capacity to bind and inactivate the noncanonical Wnt ligand Wnt5b. Thereby, MMP3 acts as a regulator of Wnt signaling and may tip the balance towards the canonical side, which leads to increased signaling through β-catenin and expansion of the mammary stem cell pool (Fig. 1). Surprisingly, MMP3 may do so even in the absence of proteolytic activity, since overexpression of inactive mutants of MMP3 and the hemopexin domain alone was sufficient to cause hyperplastic growth in the mammary gland [10]. MMP3's next closest relative within the MMP family is MMP10 (also called Stromelysin-2). Similar to MMP3 in the mammary gland, MMP10 is involved in lung tumorigenesis based on bronchio-alveolar stem cell expansion in the context of Kras-driven lung cancer [11]. Even though a direct substrate or interaction partner for MMP10 was not identified in this study, the authors showed a causative role for MMP10, as Kras-induced lung tumors were significantly diminished in number as well as in size in MMP10-deficient mice. These studies provide interesting examples of how changes in the microenvironment—in this case overexpression or lack of an MMP—can alter the propensity of signaling pathways that promote stem cell expansion leading to increased neoplastic risk.

Regulation of cellular differentiation

The ability of cells to differentiate into cell types with more specialized function and more restricted fate is fundamental to the development of multi-cellular organisms, but also for regenerative processes as well as the daily maintenance of every tissue of the body. The decision of a precursor cell to differentiate is strongly context-dependent and may be influenced by changes in the surrounding microenvironment.

MMPs are potent proteolytic mediators of ECM remodeling, and thereby may provide the necessary changes of the microenvironment triggering cellular differentiation during developmental processes. In this context, MMP14 is required for adipocyte differentiation in vivo, since it may act as a pericellular collagenase that directs the dynamic adipocyte-ECM interactions during white adipose tissue development in a 3D context [12]. In a similar fashion, MMP14 also contributes to mesenchymal stem cell differentiation through promotion of the trafficking behavior of these cells into type I collagen-rich environments [13].

MMPs can also modulate signaling pathways that regulate differentiation. For example, transdifferentiation of pancreatic acinar cells is controlled by MMP7, which is required for activation of the Notch signaling pathway [14]. This process may be crucially involved in a cascade of events leading to acinar-to-ductal metaplasia, a precursor state of pancreatic ductal adenocarcinoma [15]. It remains to be determined whether MMP7 is required for the regulation of the Notch pathway in the differentiation of other cell types.

The abilities of MMPs to influence differentiation processes are sometimes hijacked in cancer. For example, MMP13 can stimulate osteoclast differentiation by activating proteolytic cascades involving cleavage of pre-MMP9 and galectin-3, a suppressor of osteoclastogenesis. This in turn allows MMP13 expressing MDA-231 breast cancer cells to promote a favorable microenvironment for bone metastasis [13].