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Hematopoiesis and Fibronectin Receptors

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Introduction

Fibronectin is an extracellular matrix protein produced by a variety of cell types in the bone marrow and widely disseminated throughout the body. The multiple isoforms of this protein are produced by stem cell niche cells. Fibronectin not only provides a scaffold for the cells to adhere to, but it also controls their behavior by attaching to receptors on nearby hematopoietic stem cells and stromal cells. Integrins such $\alpha4\beta1$, $\alpha9\beta1$, $\alpha4\beta7$, $\alpha5\beta1$, $\alpha v\beta3$, Toll-like receptor-4 (TLR-4), and CD44 are identified on hematopoietic stem cells. The study of fibronectin's role in hematopoiesis is difficult due to the lethality of fibronectin knockout during embryonic development and the fact that fibronectin is generated by practically all cell types in mammals.

Using *in vivo* models, however, robust and direct evidence for its activation of myelopoiesis and thrombopoiesis exists. The research of fibronectin receptors revealed that their activation alters the behavior of hematopoietic stem cells, which led to the discovery of other consequences. Only hemolytic stress increased erythropoiesis, and only late phases of lymphocyte differentiation were influenced. Because fibronectin is widely expressed, these interactions in health and sickness must be considered whenever any molecule in hematopoiesis is studied [1,2].

Description

The bone marrow is a one-of-a-kind habitat for hematopoiesis. On the one hand, hematopoietic stem cells in the marrow must be kept throughout life, but they must also respond to sudden changes in the demand for different types of blood cells. They do so by responding to inputs from their environment, nearby cells, or distant organs. A variety of cells surround the stem cells, providing them with a protective environment as well as short-distance signals that enable them to operate. This niche was once assumed to be near bone lining cells or osteoblasts, but more recent research suggests that long-term hematopoietic stem cells are found near endothelium cells. All of these cells are encased in a web of extracellular matrix proteins made by supporting cells. This matrix affects stem cell behaviour by acting on receptors on the stem cells' and supporting cells' surfaces. The matrix can have a wide range of effects since it is made up of a huge number of chemicals that individually affect various receptors. Finally, the matrix acts as a reservoir for growth factors, whose availability varies based on the matrix's composition [3].

Why are fibronectin and its receptors being studied?

In the context of hematopoiesis, several extracellular matrix proteins have been studied, but fibronectin stands out for a variety of reasons. The majority of mammalian cells generate it. Fibronectin is produced by practically all cell types in the bone marrow, including endothelial cells, pericytes, and osteoblasts. Circulating fibronectin also infiltrates a variety of tissues, including bone. As a result, it might be considered an important part of the stem cell niche.

Fibronectin is a chemical that helps cells attach to one another. It's made up of two amino acid chains that are heterodimerized. These chains are made up of structural units that are arranged in three types: type I, type II, and type III. The Extracellular Domain A (EDA), the Extracellular Domain B (EDB), and the variable area are the only three domains that may differ between the two chains (V). Both the EDA and EDB domains are absent from plasma fibronectin. While EDA and EDB can be present or absent, the variable region can be spliced in a variety of ways. Finally, post-translational alterations affect how the molecule interacts with the cells. Fibronectin acts on cell surface receptors to perform a range of activities. Proliferation is regulated, apoptosis is inhibited, migration is aided, and differentiation is regulated. It's not surprising, then, that fibronectin deletion during embryonic development is fatal. Deletion in adulthood utilizing the Cre-LoxP method gave information on a variety of postnatal functions. The availability of multiple isoforms and post-translational modifications, as well as the enormous number of receptors to which fibronectin can bind, allow for such a wide range of actions [4].

Hematopoiesis-related fibronectin receptors

Fibronectin interacts primarily to integrins, which are heterodimers of a subunit that are found on the cell surface. Integrins not only bind matrix and impact intracellular alterations, but cell processes can also change integrin activation states, making them more likely to react to their environment. Five of the fibronectin-binding integrins have been studied in hematopoiesis: $\alpha5\beta1$, $\alpha4\beta1$, $\alpha4\beta7$, $\alpha9\beta1$, and $\alpha v\beta3$, which are all expressed on hematopoietic stem cells.

Because it contains a hyaluronic acid-binding pouch, CD44 is classified as a hyaluronic acid receptor. Various post-translational changes, on the other hand, influence the binding affinity to hyaluronic acid. CD44 can bind fibronectin thanks to the presence of chondroitin sulfate on one of its isoforms. 4-1 and CD44 were discovered to work together to attach stromal cells to fibronectin.

Syndecan-4 is a cell membrane-spanning proteoglycan that can bind to fibronectin. It affects the expression of integrin pairs at the cell surface: when phosphorylated by Src, it speeds up the degradation of integrin pair 51 and promotes the expression of v3. Although it is not found on hematopoietic stem cells, it can be found on monocytes and lymphocytes.

Hematopoiesis begins in the yolk sac early in development, then proceeds to the liver, and finally to the bone marrow. This necessitates stem cell migration to the liver and ultimately to the bone marrow. To be kept in the niche, stem cells must establish an interaction with the stromal cells and matrix once they arrive in the liver or bone marrow. The stem cells may then proliferate, resulting in either a self-renewing stem cell or a cell that begins to differentiate into the numerous blood cell types [5].

Malignancy and fibronectin

The expression of fibronectin is linked to a bad outcome in cancer. It appears to be a component of the pre-metastatic niche. In hematopoietic malignancies, however, this is not the case. Syndecan-4 binding to tenascin-C and 4-1 binding to fibronectin caused apoptosis in malignant hematopoietic cells. Despite the amount of fibronectin around normal hematopoietic cells, normal hematopoietic cells were resistant to syndecan-4-mediated apoptosis. The lack of problems in hematopoiesis in syndecan-4 knockout animals could be explained by low expression of syndecan-4 on normal hematopoietic cells, according to the researchers. Macrophages, on the other hand, express the

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receptor in sufficient quantities to alter cytokine production in response to lipopolysaccharide [4,5].

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Conflict of Interest

The author shows no conflict of interest towards this manuscript.

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