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Review

Extracellular matrix: A dynamic microenvironment for stem cell niche ☆

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ABSTRACT

Background: Extracellular matrix (ECM) is a dynamic and complex environment characterized by biophysical, mechanical and biochemical properties specific for each tissue and able to regulate cell behavior. Stem cells have a key role in the maintenance and regeneration of tissues and they are located in a specific microenvironment, defined as niche.
Scope of review: We overview the progresses that have been made in elucidating stem cell niches and discuss the mechanisms by which ECM affects stem cell behavior. We also summarize the current tools and experimental models for studying ECM–stem cell interactions.
Major conclusions: ECM represents an essential player in stem cell niche, since it can directly or indirectly modulate the maintenance, proliferation, self-renewal and differentiation of stem cells. Several ECM molecules play regulatory functions for different types of stem cells, and based on its molecular composition the ECM can be deposited and finely tuned for providing the most appropriate niche for stem cells in the various tissues. Engineered biomaterials able to mimic the *in vivo* characteristics of stem cell niche provide suitable *in vitro* tools for dissecting the different roles exerted by the ECM and its molecular components on stem cell behavior.
General significance: ECM is a key component of stem cell niches and is involved in various aspects of stem cell behavior, thus having a major impact on tissue homeostasis and regeneration under physiological and pathological conditions. This article is part of a Special Issue entitled Matrix-mediated cell behaviour and properties.

1. Introduction

All cell types are in contact with the ECM, a complex and dynamic network of macromolecules with different physical and biochemical properties [1,2]. Although the ECM was once considered an inert supportive scaffold, the fundamental role of ECM in key aspects of cell biology became increasingly evident in last two decades. By either direct or indirect action, ECM regulates cell behavior and plays essential roles during development [3]. Indeed, the ECM is a dynamic and versatile compartment and by modulating the production, degradation, and remodeling of its components, it can support organ development, function and repairing [4,5]. On the basis of the relative amounts and organization of the different ECM components, this molecular scaffold is peculiar for each tissue and reflects the specific functions required for the cells present in that tissue. Moreover, the structural, biochemical and functional diversity of ECM components confers well-defined physical, biochemical and biomechanical properties to the ECM. Physical properties such as rigidity, porosity, topography and insolubility are able to influence various anchorage-related biological functions, like cell division, tissue polarity and cell migration [6]. From a biochemical point of view, the ECM displays both direct and indirect signaling properties, since it can act directly by binding cell surface receptors or by non-canonical growth factor presentation [3]. A key concept in ECM biology regards how the biomechanical properties of the ECM can influence cell behavior. Indeed, ECM stiffness is an essential property by which cells sense the external forces and respond to the environment in an appropriate manner, a process known as mechanotransduction [7–13] (Fig. 1). Importantly, all these characteristics and properties are strongly interconnected and one can influence the others. This becomes even more evident when considering that cell–ECM connection is a reciprocal interaction in which cells continually remodel the ECM present in their microenvironment, and these dynamic modifications of the ECM direct cell behavior [3]. It is therefore not surprising that alterations in a specific ECM component or in a player of its regulation can have a remarkable impact on the biochemical, biomechanical and physical properties of the ECM, leading to disorganized network and ultimately failure of organ homeostasis and function.

Stem cells are defined by three essential features, as they are *i) undifferentiated cells* able to give rise both to *ii) differentiated daughter cells*

Abbreviations: ECM, extracellular matrix; CBCs, crypt base columnar cells; HFSCs, hair follicle stem cells; HSCs, hematopoietic stem cells; ISCs, intestinal stem cells; NSCs, neural stem cells; SGZ, subgranular zone; SVZ, subventricular zone

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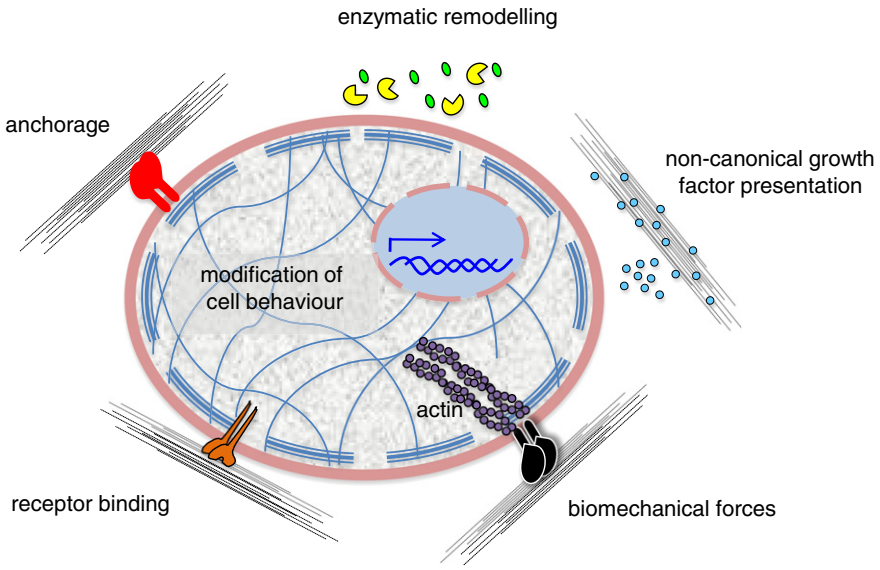

Fig. 1. Regulation of cell behavior by ECM. The effects exerted on cells by ECM can be differently mediated. The ECM can directly bind different types of cell surface receptors or co-receptors (red, orange, black), thus mediating cell anchorage and regulating several pathways involved in intracellular signaling and mechanotransduction. Moreover, the ECM can act by non-canonical growth factor (cyan) presentation and be remodeled by the action of enzymes (yellow pie), which can release functional fragments (green).

and *iii)* cells that retain their stemness by *self-renewal* [14]. Embryonic and adult stem cells have different capabilities to produce differentiated cells, a property known as *potency*. Cells present in the early embryo until the blastocyst stage are pluripotent, since they produce all differentiated cell types present in the body, whereas fetal and adult stem cells are able to produce multiple cell lineages (multipotent) or a single differentiated cell lineage (unipotent). In adult tissues, stem cells are usually in a quiescent state and in order to undergo self-renewal they have to enter the cell cycle, divide and generate a progeny of undifferentiated cells [15,16]. With this mechanism, the stem cell pool is maintained and the long-term homeostasis and regeneration of tissues can be preserved throughout the entire lifespan [17]. The choice of a stem cell to undergo self-renewal is carried out by two cell division mechanisms, which fulfill two different requests by the tissue [18]: *i) asymmetric* self-renewal, in which each stem cell divides into one stem and one differentiated cell, allows maintaining a constant number of stem cells, which is generally sufficient under physiological conditions; *ii) symmetric* self-renewal, in which each stem cell originates two daughter stem cells, leads to an expansion of the stem cell pool, a condition required after tissue injury or in diseased conditions causing loss of differentiated cells [19]. In the asymmetric cell division, the mitotic process leads to polarization and asymmetric segregation of components essential for the cell fate determination so that, once cell division is completed, one daughter cell has received RNAs, proteins and other molecules that maintain the undifferentiated program, whereas the other cell receives lineage commitment factors. In the symmetric cell division, the two daughter cells receive the same factors and the decision for commitment and differentiation is not linked to mitosis, rather it is a later event that can involve the newly formed cells [17]. Symmetric or asymmetric divisions are not mutually exclusive, and a mixture of these two mechanisms can be used on subsequent divisions. During mid to late gestation, some mammalian progenitor cells are able to make a developmentally regulated transition from largely symmetric to predominantly asymmetric divisions. Similarly, adult stem cells dividing asymmetrically under steady-state conditions retain the capability to divide symmetrically to restore stem cell pools depleted by injury or disease [19].

Stem cells reside in a dynamic, specialized microenvironment, denoted as '*niche*', which provides extracellular cues to allow stem cell survival and identity. Moreover, the niche dynamically regulates stem cell behavior, maintaining a balance between quiescence, self-renewal and differentiation [20,21]. Despite their high potential to proliferate, the niche maintains stem cells in a quiescent and low metabolic state to prevent stem cell exhaustion [22]. Moreover, the niche is thought to protect stem cells from the accumulation of gene mutations that may lead to their malignant transformation into cancer cells [23]. Increasing evidence indicates that deregulation of the stem cell niche plays a key pathogenic role in a number of diseases associated with tissue degeneration, aging and tumorigenesis [24]. Both quiescent and active stem cell subpopulations coexist in several tissues, in separate yet adjoining locations [15,23]. In these niches, the precise regulation of the balance between symmetric and asymmetric divisions is critical for maintaining proper stem cell number and for fulfilling the needs for differentiated cells within the surrounding tissue [20]. The ability of a stem cell to seed in its niche represents one of the most important features of the niche itself, and the proper binding between stem cells and their niche is essential to maintain the stem cell pool for long-term self-renewal. Thus, the niche establishes a sort of crosstalk between the state and necessity of the tissue and the proper functioning of the stem cell pool [25,26]. Since its first definition originally proposed in 1978 for the hematopoietic microenvironment [27], the concept of the niche has increased in complexity (Fig. 2). Niches are highly specialized for each type of stem cell, with a defined anatomical localization, and they are composed by stem cells and by supportive stromal cells (which interact each other through cell surface receptors, gap junctions and soluble factors), together with the ECM in which they are located. Moreover, blood vessels carry systemic signals and provide a conduit for the recruitment of inflammatory and other circulating cells into the niche, whereas neural inputs transmit distant physiological cues to the stem cell microenvironment. The diverse and dynamic composition of the ECM provides controlled biochemical, physical, structural, and mechanical properties to the different niches. In addition, secreted or cell surface factors, signaling cascades and gradients, as well as physical factors, such as shear stress, oxygen tension and temperature, contribute to control stem cell behavior in a well-orchestrated manner [25,26]. Not only the niche components influence stem cell behavior, but also the interactions between stem cells and their niche are reciprocal, since stem cells are able to remodel the niche and secrete ECM components in response to the signals they receive from it [28–30].