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Review

Laminins and cancer stem cells: Partners in crime?

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ABSTRACT

As one of the predominant protein families within the extracellular matrix both structurally and functionally, laminins have been shown to be heavily involved in tumor progression and drug resistance. Laminins participate in key cellular events for tumor angiogenesis, cell invasion and metastasis development, including the regulation of epithelial-mesenchymal transition and basement membrane remodeling, which are tightly associated with the phenotypic characteristics of stem-like cells, particularly in the context of cancer. In addition, a great deal of studies and reports has highlighted the critical roles of laminins in modulating stem cell phenotype and differentiation, as part of the stem cell niche. Stemming from these discoveries a growing body of literature suggests that laminins may act as regulators of cancer stem cells, a tumor cell subpopulation that plays an instrumental role in long-term cancer maintenance, metastasis development and therapeutic resistance. The accumulating evidence in this emerging research area suggests that laminins represent potential therapeutic targets for anti-cancer treatments against cancer stem cells, and that they may be used as predictive and prognostic markers to inform clinical management and improve patient survival.

Contents

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1. Introduction

The extracellular matrix (ECM) represents a complex network comprised of macromolecules regulating tissue development and homeostasis. Its role is instrumental to regulate cell adhesion, migration, proliferation, and differentiation under normal physiological conditions [1]. In cases when the dynamics of ECM is deregulated, it undergoes structural and compositional remodeling and contributes significantly to progression of malignant tumors [2]. Laminins, one of the major glycoprotein families present at the basement membrane (BM) of the ECM [1], which separates epithelial and endothelial cells from connective tissues, have been heavily implicated in tumor angiogenesis, invasion and metastasis [3]. Signaling pathways induced by various laminin isoforms interact with their associated receptors at the surface of cancer cells and promote cancer hallmark capabilities and tumor progression [4]. While being significantly involved in the tumorigenic processes including epithelial to mesenchymal transition (EMT) and BM remodeling during invasion, which are directly associated with stem-like properties, laminins have also been reported to regulate the phenotype and differentiation of normal stem cells. As a major component of the BM that forms the stem cell niche and affects stem cell behavior, laminins can either maintain the self-renewal capacity and differentiation potential across a range of stem cell types for culturing purposes *in vitro* [5–8], or guide the differentiation of multipotent stem cells into a variety of specialized cell types to be used in medical applications [9]. Given the crucial roles of laminins for cancer progression and stem cell functions, the regulation and impact of laminins on cancer stem cells (CSCs) has become an emerging area of research interest. CSCs represent a subset of tumor cells that typically exhibit the ability to self-renewal and thereby sustain the long-term growth of tumors [10]. In addition, they often display multi-potent capabilities, giving rise to partially and/or terminally differentiated tumor cells and thereby contributing to intra-tumor phenotypic heterogeneity [11]. This unique subpopulation within tumors has been considered as one of the main driving forces resulting in therapeutic resistance and post-treatment tumor recurrence, leading to treatment failure and decreased overall survival [12]. Emerging and accumulating studies suggest that ECM proteins including laminins are very likely to play critical roles in promoting the stem cell phenotype and sustaining the growth of CSCs, which further promotes the metastatic potential and strengthens drug resistance against anti-cancer therapeutics. This paper will first review with the well-described role of laminins in cancer progression and in the promotion of metastasis development and drug resistance, then focus on how laminins affect normal stem cells and finally discuss the existing evidence concerning the ability of laminins to sustain CSC growth and maintain their key features and functions.

2. Laminins

Laminins are a family of αβγ heterotrimeric glycoproteins usually present in the basal lamina of the BM [1]. These macromolecules, secreted and incorporated as part of the ECM, are often found to be at least 400 kDa. The laminin family of glycoproteins is an integral part of the structural scaffolding of tissues and is vital for their maintenance and survival. More than 15 laminin isoforms have so far been described *in vivo* in humans, the name of which is chosen according to the respective composition in one of the five α, four β, and three γ chains [13]. As an example, laminin-521 (LN-521) is comprised of a α5 chain (encoded by the *LAMA5* gene), a β2 chain (*LAMB2* gene), and a γ1 chain (*LAMC1* gene). Laminins are ubiquitously expressed but the expression of specific isoforms is cell- and tissue-dependent (Table 1), recognized by integrins and other cell-surface receptors [14,15]. Altered function and/or expression of laminins can result in a wide range of cellular defects and abnormal conditions; such as silencing of the α2 chain leads to muscular dystrophy and peripheral nerve defects [1,16]. In relation with their role during morphogenesis and development [17,18], dysregulated ECM proteins (Table 1) including laminins can play a role in tumor progression through interactions with cell-surface receptors and cytoplasmic signaling pathways [18,19].

3. Laminins in advanced cancer

One of laminins' most established roles in normal cells and tissues is to promote cell adhesion and migration, which is also widely demonstrated in tumor cells [20]. Other than being involved in the development of early stage cancers, laminins along with their specific cell-surface receptors have been largely shown to participate in the invasive and metastatic level of cancer progression. Dysregulated interactions between cells and laminins are main features of malignant disorders. For instance, survival of epithelial cells depends on signals from ECM proteins of their natural niche, particularly LN-332 [1], and lack of the appropriate signals leads to anoikis, a form of apoptosis caused by inappropriate cell-ECM contacts [21], in normal cells. Progression of cancer implies leaving the natural niches by the malignant cells and surviving anoikis either by overexpression of ECM proteins by the malignant cells or by altering of the ECM-cell membrane receptors triggered cellular signaling [21]. During tumor invasion, progressive ECM remodeling includes the cleavage as well as proteasome-mediated degradation of ECM components, leading to loss of BM barrier and to a discontinuous pattern of laminin expression. Remodeling of the vascular BM is also frequently noticed during angiogenesis and metastasis [19,22].

Immunohistochemical staining employed in many studies have revealed the abnormal distribution pattern of laminins during invasion, as well as suggesting that some of these altered patterns may provide information about prognosis or other clinical outcomes. Following the development of tumor progression, an *in vivo* model of highly metastatic squamous cell carcinoma presented gradual degradation of the BM integrity at the metastasized lymph nodes as shown by stepwise depletion of the two major BM components: laminin and type IV collagen [23]. In bladder cancer, expression of laminin-332 as reflected by the level of γ2 chain is potentially associated with the specific tumor grade and stage, further determining the risk of tumor progression [24]. Laminin-332 essential for the integrity of the BM appeared to be up-regulated in the more advanced squamous cell carcinoma instead of in the oral dysplastic lesions [25]. The above findings along with other results [26,27] highlighted the potential of laminin-332, and more particularly of its γ2 chain, as an invasion and malignant transformation marker, acting *via* a direct interaction with α6β4 and α3β1 integrin and possibly other laminin-specific receptors [28]. Low laminin expressions were reported to be potentially associated with higher susceptibility to recurrence after surgery in pancreatic head cancer [29]. A significant number of cases containing intense laminin staining were correlated in a group study with patients developing liver metastasis after affected by gastrointestinal cancers [30,31]. These studies demonstrated the correlation between altered laminin expression and poor prognosis or tumor recurrence, highlighting the importance of closer follow-up coupled with adjuvant therapy on cancer patients who exhibit unusual loss of BM barriers. The expression pattern of laminins tend to be up-regulated in invasive cancer cells, as well as in the capillaries of invading carcinomas, for instance the well characterized α4 chain in blood vessels. The α3 B chain in laminin-3B11 as a newly identified vascular isoform however, appears to be down-regulated upon TNF-α activation and interferes with angiogenesis in breast metastasis

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