Role of Laminin in Oral Carcinogenesis

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Abstract: Oral carcinogenesis is characterized by significant alterations occurring at the phenotypic and genotypic level resulting in uncontrolled proliferation and evasion of apoptosis. With growing tumor mass, a switch of metabolism and angiogenesis becomes important for the further development of the disease. Invasion and subsequent metastasis of the malignant cells are basic requirement for tumor promotion and progression. Cell migration plays an important in embryogenesis, inflammatory immune response, wound healing and cancer invasion. One of the important factors responsible for the tumor progression is the alteration seen in extracellular matrix proteins. Extracellular matrix (ECM) includes a group of structural proteins, glycoproteins, and proteoglycans that function as a physical scaffold to maintain tissue structure and provides biochemical signals to modulate cellular function. Basement membranes are thin layers of ECM that form the supporting structure under epithelial and endothelial cells. The protein composition of basement membrane is mainly inclusive of type IV collagen, laminins, entactins, and proteoglycans. Laminin is biologically active part of the basement membrane and influences cell differentiation, migration and cell adhesion. They are an important and biologically active component of the basal lamina, influencing cell differentiation, migration, and adhesion. Laminin reflects the integrity of basement membrane better than the other extracellular matrix (ECM) proteins and thus, may be used as a marker suggestive of the basement membrane status during tumorigenesis. Oral squamous cell carcinoma is an important epithelial malignancy and altered laminin expression in OSCC is an important process in its invasion and metastasis. An understanding of the role of laminin in OSCC may aid in its utility as a biomarker to determine the prognosis and treatment planning of OSCC.

Keywords: Laminin, Oral Cancer, Oral pre-cancer, Basement membrane proteins.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is a neoplasm of epithelial origin with high prevalence rate in developing countries of the world accounting for over 90% of the reported malignancies of the oral cavity [1]. The disease is of multifactorial etiology with tobacco and alcohol being the primary risk factor and may arise de novo or from oral potentially malignant disorders [2]. Oral carcinogenesis is a complex process characterized by significant alterations occurring at the phenotypic and genotypic level, which can be correlated to specific processes essential for its progress and development. With growing tumor mass, a switch of metabolism and angiogenesis becomes important for the further development of the disease. During later stages of tumor progression, cancer cells acquire invasive properties to spread to distant tissues and form metastases [3].

Cell migration is an important event involved in embryogenesis, wound healing, immune surveillance, angiogenesis and neoplastic tumor dissemination and metastasis [4]. During these events, the extracellular environment, signal the cells to either migrate or slow down and thus become sessile [5].

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Extracellular matrix (ECM) is a complex mixture of structural proteins, glycoproteins, and proteoglycans that are of two types namely the interstitial matrix and the basement membrane [6]. Basement membranes are thin layers of ECM that form the supporting structure under epithelial and endothelial cells [7]. The protein composition of basement membrane is mainly inclusive of type IV collagen, laminins, entactins, and proteoglycans [8]. ECM is a major component of tumor microenvironment with significant involvement in cancer development and progression. The alteration in the ECM proteins are known to provide necessary to promote cancer cell proliferation, migration, and invasion [9, 10]. Laminin is biologically active part of the basement membrane and influences cell differentiation, migration and cell adhesion. To date, five α, three β and two γ chains have been identified, which form at least twelve different laminin isoforms with distinct tissue distribution [11]. The isoform laminin-5 also called nicein, epiligrin or kalinin, ana3b3g2 heterotrimer, is a component of transitional and stratified squamous epithelia, lung mucosa and other epithelial glands [12].

The occurrence of OSCC either de novo or from precursor lesions is well documented. The transformation of the normal epithelial cell into a tumor cells bestows certain cellular and molecular features which aids in its survival and proliferation. Various proteins found in the basement membrane and the

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components of the stromal tissue undergoes modification and alteration and these alterations may aid in better understanding of the carcinogenesis model [13]. Thus, the aim of this review is to describe the role of laminin in oral carcinogenesis and to highlight its potential role in cancer therapy and prognosis.

BASEMENT MEMBRANE AND ITS ASSOCIATED PROTEINS

Basement membranes are thin sheets of extracellular matrix (ECM) present at the basal side of every epithelium. They are predominantly made of high molecular weight multi-domain proteins that either polymerize or bind to other basement membrane proteins [11]. The binding of basement membrane proteins to cellular receptors, such as integrins and dystroglycan, is required for the assembly [14].

The ultrastructure of basement membrane consists of a three-dimensional network of irregular strands referred to as “cords” whose thickness averages around 3–4nm. Immunostaining reveals that the cords are composed of collagen IV, laminin, heparan sulfate proteoglycan, entactin, and fibronectin [15]. Laminin is detected in the cords as diffuse material within which thin wavy lines may be distinguished [16].

The main functions of basement membrane are cell adhesion, diffusion barrier and regulation of cell growth [17]. Secondly, the basement membrane acts as a molecular sieve (permeability barrier) with pore size depending on the charge and spatial arrangement of its component glycosaminoglycans [18]. The basement membrane acts as a mechanical barrier thereby preventing malignant cells from invading the deeper tissues. Lastly, the basement membrane probably controls cell organization and differentiation by the mutual interaction of cell surface receptors and molecules in the extracellular matrix [19].

Basement membrane is known to play a role in the epithelial-to-mesenchymal transition of the tumor cells on invasion which contributes to tumor spread and metastasis owing to mesenchymal like phenotype of these cells [20]. Basement membrane and its associated proteins play an important role in cancer cell migration. Metastasizing cells migrate through the stroma to reach blood or lymph vessels, where they can be carried to other organs [21].

STRUCTURE AND FUNCTION OF LAMININ

Laminin is a multifunctional, 900kDa mosaic extracellular matrix (ECM) glycoprotein expressed predominantly in the basement membrane structure. It is produced by the cell and is transported extracellularly to be deposited in the basement membrane zone [22]. Laminin reflects the integrity of basement membrane better than the other extracellular matrix (ECM) proteins and thus, may be used as a marker suggestive of the status of intact or degraded basement membrane during tumorigenesis [23]

An important function of laminin is to interact with receptors anchored in the plasma membrane of cells adjacent to basement membranes to regulate multiple cellular activities and signaling pathways. Structurally, laminins are composed of a few independently folded, distinct domains, number, location and size, as well as varying with other molecular components of the basement membranes [24]. Every basement membrane contains several members of the laminin family, which determines structural diversity and their physiological functions [23].

Nearly 30 years ago, stroma from the Engelbreth–Holm–Swarm (EHS1) tumor was purified and found to contain large amounts of a novel non-collagenous glycoprotein which was termed laminin. The first laminin trimer thus isolated was named as EHS-laminin. The chains of EHS-laminin were first called A, B1 and B2. EHS-laminin has been renamed laminin-1 and the chains of laminin-1 named α1, β1 and γ1. Currently this molecule is known as Ln-111 and in addition to this a sum of around fifteen other distinct laminins have been found in mammals [25].

All laminins are heterotrimers composed of one of five α chains, one of three β chains and one of three γ chains (in mammals) found in five, four, and three genetic variants, respectively. Out of all possible combinations, a total of sixteen laminin isoforms have been characterized biochemically [26]. Laminin appears as cross-shaped molecules; the long arm of the cross (~80 nm length) is an α helical coil formed from all three chains, whereas the three short arms (35–50 nm) are composed of one chain each [24]. The homologous short arms are composed of a distal laminin N terminal (LN) domain that is followed by tandem repeats of laminin type epidermal growth factor-like (LE) domains, interspersed with globular domains of unknown structure [23]. The trimeric proteins intersect to form a cross-like structure that can bind to other cell membrane and extracellular matrix molecule. The three shorter arms bind to other laminin molecules thereby aiding in the formation of sheets. The long arm binds to cells thus anchoring the organized tissue cells to the membrane.

Sixteen laminin trimers have been identified till date which are combinations of different alpha-, beta-, and gamma-chains [15].

- The five forms of alpha-chains are: LAMA1, LAMA2, LAMA3 (which has three splice forms), LAMA4, LAMA5
- The beta-chains include: LAMB1, LAMB2, LAMB3, LAMB4
- The gamma-chains are: LAMC1, LAMC2, LAMC3

FUNCTION

Laminins are associated with type IV collagen networks through various proteins such as entactin, fibronectin and perlecan. These interactions along with the binding of laminin to the cell membranes contribute to cell attachment and differentiation, cell shape and movement, maintenance of tissue phenotype, and promotion of tissue survival [27].

ROLE OF LAMININ IN ORAL CARCINOGENESIS

Laminin is associated with an aggressive cancer phenotype by being a potent regulator of cell adhesion and cell migration [28]. In colorectal cancer, anal cancer, pancreatic and gastric cancers differential γ2 localization or expression levels have been shown to be of prognostic value [29, 30]. Expression of Ln-332, particularly γ2, is implicated in progression of head and neck cancers.

In OSCC, inflammation will increase cytokines and growth factors that may enhance laminin expression near the tumor-host interface as a protective mechanism. Also, worsening grades of tumor cause expression of mutated p53 which displaces laminin from cytoplasm towards tumor-host interface resulting in an overall increase in laminin at the interface [31]. Increased laminin expression at tumor-host interface in turn decreases inflammation creating a pro-tumorigenic niche and also acts in concert with proteases like matrix metalloproteinases thus destroying the formed basement membrane and favoring invasion and metastasis [32]. Furthermore, it has been claimed that laminin-5 promotes cell migration and/or invasion after the c2 chain has been cleaved by MMPs (MMP-2 and membrane type 1 MMP) secreted by cancer cells or neighboring stroma cells [33].

Several literature studies have reported an association between altered laminin expression and oral carcinogenesis. Tosios *et al.* (1998) suggested that the discontinuity of the basement membrane corresponds to the progression of the neoplastic transformation process in oral epithelium [34]. Further, overexpression of laminin-5 was found only in OSCC and not dysplastic lesions indicating the utility of laminin-5 as a potential marker for the intraoperative assessment of cancer excision margins and could also be used as a target for chemotherapeutic agents [35]. Loss of laminin expression along with that of E-cadherin and collagen IV distribution in oral premalignant and malignant lesions is associated with the neoplastic transformation and are higher in metastatic nodules [36]. Higher laminin-5 γ2 expression was associated with high-intensity tumor budding leading to the assessment that this was associated with invasive phenotype of neoplastic cells and creating a permissive environment for tumor invasion [33]. Several other studies have also found decreased distribution of laminin with increasing grade of oral squamous cell carcinoma thereby suggesting that laminin might be useful to evaluate histological differentiation and aggressiveness of OSCCs [37]. Additionally, laminin-5 plays an important role for tumor migration and shows an increased expression in areas of direct tumor/stroma interactions [38].

CONCLUSION

It can be concluded that the decreased laminin expression in the basement membrane of oral squamous cell carcinomas and the structural change may affect the basement membrane integrity and favor tumor invasion. Thus, laminin expression in basement membrane may be a useful parameter to evaluate histologic differentiation and aggressiveness of oral squamous cell carcinoma. Also, laminin can be adopted as a useful marker in evaluating the histological differentiation and aggressiveness of oral carcinoma. Targeting the laminin antibody using specific chemotherapeutic agents may serve as an effective anti- cancer therapy thereby aiding in appropriate cancer management.

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