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Role of Type IV Collagen in Oral Squamous Cell Carcinoma.

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ABSTRACT

Oral squamous cell carcinoma is most common malignancy affecting the oral cavity. It is characterized by invasiveness and migration of malignant cells to form metastases at distant sites which causes proteolytic destruction of basement membrane components. The major aspect of tumor cell invasion and metastasis is the interaction between cancer cells and basement membrane components such as collagen, proteoglycans, glycoproteins. Type IV collagen is main component of basement membrane that helps to maintain continuity and integrity of the basement membrane which is most affected during degradation processes by neoplastic cells. Multiple studies have shown expression of type IV collagen in OSCC as an early event in carcinogenesis and is used to study biological behaviour of tumor.

Keywords: Collagen type IV, Basement membrane, Metastasis

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INTRODUCTION

Oral squamous cell carcinoma represents 95% of all forms of head and neck cancer, and encompass at least 90% of all oral malignancies. It is the third most common malignancy in south-central Asia.[1] According to a report of Government of India, approximately 2–2.5 million cases of cancer exist with around 7–9 lakhs new cases being diagnosed every year.[2] Its pathogenesis is multifactorial, associated with cigarette smoke, alcohol and snuff, papilloma virus as well as vitamin deficiencies. Histologically, the lesion passes through various phases (preneoplastic damage) until the ultimate formation of a cancer. This carcinogenesis may be associated with precancerous lesions (such as leukoplakia, erythroplakia and mixed). [1]

Infiltration is a key prerequisite for cancer metastasis and basal lamina has been identified as a crucial structure in the regulation of tumor invasion and metastasis. Basal lamina is the main component of extracellular matrix, composed of type IV collagen, laminin, entactin proteoglycans and glycosaminoglycans. Type IV collagen is important as a structural backbone of the basement membrane.[3] Its attachment to the basement membrane can effectively prevent harmful substances from penetrating the basement membrane to the lamina propria. In Carcinogenesis, collagen IV gradually reduced was fragmented, collapsed, or even dissolved completely, thus providing channels for cancer cells to invade the lamina propria.[4] The loss of continuity of collagen IV can help us in early diagnosis and the prediction of the biological behaviour of the oral lesions.[5]

TYPE IV COLLAGEN

Type IV collagen is a unique member of the large collagen superfamily which occurs only in the basement membrane and is a nonfibrillar collagen that makes up about 50% of all basement membranes [6]and consists of a glycoprotein called Laminin, which cements non-fibrillar type IV collagen in the lamina densa to the epithelial cells and is coated on each side by a glycosaminoglycan(GAG) – Heparan Sulfate. It was first discovered by Kefalides in 1966.[7]

STRUCTURE OF TYPE IV COLLAGEN

The type IV collagen composed of two α1(IV)and one α2(IV) chains extensively exists in a mammalian body, while other forms of type IV collagen with chain compositions of α3(IV) α4(IV) α5(IV), and α6 are limited in their localizations.[8]

The triple helical α chains of type IV collagen are encoded by six distinct genes from α1(IV) to α6(IV) they are located on three different chromosomes and are paired in a head-to-head manner: COL4A1-COL4A2 on chromosome 13q34,2 COL4A3-COL4A4 on chromosome 2q36,2 and COL4A5-COL4A6 on chromosome Xq22.[9]

Type IV collagen chain consists of three domains: an N-terminal 7S domain, a middle triple-helical domain, and a C-terminal globular noncollagenous (NC1) domain. It is speculated that the six chains of type IV collagen self assemble to form predominantly three sets of triple-helical molecules that self associate via their NC1 domains and their middle triplehelical regions to form spider web-like scaffolds that interact with the laminin network and form a basic basement .membrane scaffold. [9]

The collagenous domain consists of a repetitive Gly-X-Y amino acid sequence in which X and Y are often proline and hydroxyproline, or lysine and hydroxylysine. This stretch of amino acids provides for the structural integrity of the type IV collagen protomer and suprastructure.[7]The presence of cysteine- and lysine-rich residues at the amino terminus is essential for interchain crosslinking of four triple-helical molecules through disulfide bonds and lysine-hydroxylysine crosslinks. The crosslinked tetramer is heavily glycosylated making it resistant to collagenase activity.[6] (figure 1)

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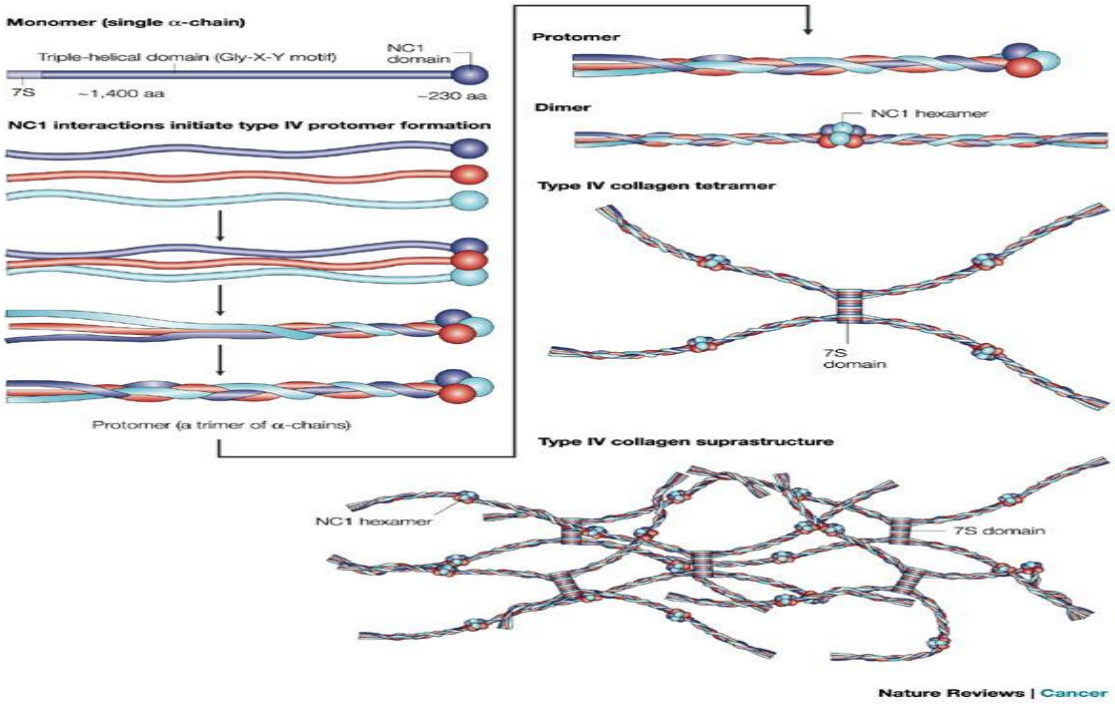

Figure 1 : Structure of type IV collagen (Courtesy: Kalluri R. Basement membranes: structure, assembly and role in tumour angiogenesis.Avaliable from http:// www.nature.com/reviews/cancer)[10]

DEGRADATION OF TYPE IV COLLAGEN

Basement membranes are composed of highly complex arrays of 50 glycoproteins along with laminin, plays an important role in cell adhesion, migration, differentiation, and growth. Type IV collagen degradation products also play an important role during angiogenesis, tissue remodeling, and cancer progression.[9]

The expression level of type IV collagen is regulated by matrix metalloproteinases (MMPs) and their inhibitors, the tissue inhibitors of metalloproteinases (TIMPs). Gelatinases secreted by fibroblasts, macrophages and Type IV collagen proteinases include the proteolytic zinc-containing enzymes MMP-2 and MMP-9 can induce partial or widespread loss of the BM by degradation of type IV collagen, and contribute to invasion and metastasis.[3]

INVASION AND METASTASIS OF ORAL SCC

Tumor invasion is the first step in the complex multi-step process that leads to the formation of metastasis. Tumor invasion into stroma and vascular system is a prerequisite to the development of distant metastasis, which involves attachment of tumor to the basement membrane, degradation of extracellular matrix components, migration of malignant cells to the stroma and ultimate invasion to the surrounding blood vessels or lymphatic channels.[11]

Three-step hypothesis has been proposed concerning tumor cell invasion.

The first step is tumor cell attachment via cell surface receptors for laminin. The anchored tumor cells next secrete hydrolytic enzymes to degrade the matrix. The third step is tumor cell locomotion into the impaired matrix. Type IV collagen is the main component in the extracellular matrices and is degraded by type IV collagenase which is secreted from tumor cells or host cells. Thus, type IV collagen is an important protective component against invasion and metastasis.[11]

Mode of invasion was graded by the method reported by Yamamoto et al as follows:

Grade 1- a well- defined borderline

Grade 2- cords, a less marked borderline;
Grade 3- groups of cells, no distinct borderline;
Grade 4- diffuse invasion

4c-cordlike type, 4d- widespread type[12]

The stage of invasion was graded by the method reported by Anneroth et a1 as follows:

Grade 1- carcinoma in situ and/or questionable invasion
Grade 2- distinct invasion involving only lamina propria
Grade 3- invasion below lamina propria adjacent to muscles, salivary gland tissues and periosteum
Grade 4- extensive and deep invasion replacing most of the stromal tissue and infiltrating jaw bone.[12]

DISCUSSION

BM structure probably presents a natural barrier to the migration of tumor cells. BM is an insoluble flexible structure, which is impermeable to large proteins. It becomes permeable in case of carcinogenesis. Experimental studies on type IV collagen and metastatic activity of tumor cells have been reported.[11]

In a study done by Pankaj et al concluded that there was direct relationship between the presence of type IV collagen and the differentiation degree of SCC cells, that SCC cells loose their capability to form the basement membrane components as they become less differentiated. Similar study by Lalita and Satish found that destruction of the basement membrane is the first step in tumour invasion and metastasis and expression of collagen IV in malignant tissues with high molecular mass showed degradation of collagen IV.[13

Study by Fan et al showed that type IV collagen was found as fragmented, collapsed or even dissolved completely providing channels for cancer cells to invade lamina propria. In well differentiated carcinomas, thick and sparse type IV collagen were found around cancer nest. In moderately and poorly differentiated tumors type IV collagen was destructed around cancer nests which suggest that well differentiated tumors have low malignant potential and weak invasiveness while moderately and poorly differentiated have high malignant potential and strong invasiveness.[3]

Van Cauwenberge et al reported that remnants of basement membrane material may represent areas of partial regression of the neoplasm. It has been well established that these non-cohesive irregular small cords and single cells are more likely to attain access to vasculature and develop metastasis.The invasive front should always be the field of study for alterations in basement membrane in oral squamous cell carcinoma[13] and another study by Daniela Diaconescu concluded that type IV collagen is an indicator of basement membrane disruption and its expression showed an alternated distribution of type IV collagen with a significant loss in all cases of laryngeal cancer, reflecting tumor aggressiveness.[14]

CONCLUSION

The role of the basal lamina in tumor differentiation and growth has been a subject of intensive research. Chemically, basal lamina consist of both collagenous and non collagenous glycoproteins. The scaffold of the lamina densa layers is formed by type IV collagen, which is organized in a netlike fashion. Expression of type IV collagen depended on production and destruction related to enzymatic activity such as metalloproteinases causing rupturing of basal lamina by destruction of type IV collagen causing tumor invasion. Oral squamous cell carcinoma border and its early invasion strongly expresses type IV collagen supporting tumor invasion and thus can be used as marker in early detection break in basal lamina.

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