Chapter 1

CHANGING EXTRACELLULAR MATRIX LIGANDS DURING METASTASIS

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Abstract: Cellular homeostasis is achieved by cells continuously sending and receiving information, through cell-cell contacts, signals from the surrounding extracellular matrix (ECM), or from soluble hormones and growth factors. During cancer progression, these normal signals may be altered in a variety of ways forcing extracellular and intracellular changes to occur that will favor metastasis. Altering ECM ligands is a major mechanism by which transformed cells metastasize. One way in which ECM ligands change is through alterations in ECM composition. Another mechanism is through proteolysis of ECM proteins causing the release of growth factors or cryptic ECM peptides called matrikines. In this chapter, we will discuss changes that occur in ECM and examine how these changes are important for successful cancer metastasis.

Key words: extracellular matrix; matrikine; protease; cell adhesion molecules

1. ORGANIZATION OF THE EXTRACELLULAR MATRIX

The extracellular matrix (ECM) is a complex network of proteins surrounding cells, serving as a structural element in tissues. The ECM provides cells with information about their environment and thus influences tissue development. The basal lamina (BL) which surrounds epithelial cells is a highly structured, specialized form of ECM. The BL is a component of the basement membrane (BM), and are thin, specialized forms of ECM that surround muscle, fat, peripheral nerve cells, and all epithelial and endothelial cells (1). The ECM also includes the interstitium, which surrounds connective tissue cells and separate islets of epithelial cells.
BLs are responsible for tissue compartmentalization, acting as a barrier for cells. BLs are found at the dermal-epidermal junction of skin; at the base of all lumen-lining epithelia of the digestive, respiratory, reproductive, and urinary tracts; underlying capillary endothelium and venules; around Schwann cells in the nervous system; surrounding fat cells, skeletal muscle, and cardiac muscle cells; and at the base of parenchymal cells of exocrine and endocrine glands.

The BL varies to some extent from tissue to tissue based on which matrix proteins are secreted by surrounding cells, but its basic components include: collagen, elastin, proteoglycans, and “anchorage” proteins such as laminin, fibronectin, vitronectin, and entactin that serve as attachment sites for epithelial cells (2, 3). Other ECM components that modulate cell-matrix interactions include thrombospondin, tenascin, and osteonectin. The BL consists of two networks that can self-assemble independently of each other and are then connected by entactin (3-5). The first network is formed by laminins, which assemble through N-terminal interactions of the three short arms and give dynamic flexibility to the BL and signals that lead to cell polarization. The second network consists of type IV collagens and gives structural stability to the BL. The BL components are well-conserved throughout evolution, indicating the importance of correct BL proteins for the development of multicellular life.

1.1 Laminin

Laminins (LM) are a family of large (400-600 kDa) cross-shaped heterotrimers composed of an α, β, and γ chain that are each separate gene products. LMs are secreted by epithelial cells, endothelial cells, myoblasts, and monocytes. Self-assembly of LM isoforms into a network occurs when the three short arms interact via the N-terminal globular domains (LN modules) (6).

Currently, there are sixteen different LMs described in tissues (7), with five α, three β, and three γ chains identified, and a theoretical possibility for up to forty-five different trimers; indicating that it is likely that new chain combinations have yet to be discovered. However, certain chains are never seen paired with each other, so the actual number of combinations is probably much smaller (8, 9). LM is involved in cell adhesion, migration, differentiation, and neurite outgrowth. Each LM trimer is thought to transmit a unique set of signals to a cell, as a genetic knock-out of each LM chain in mice exhibit unique phenotypes (8).