CHAPTER 7
Tumor Stroma Formation in Lung Cancer

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1. Introduction

Lung carcinomas are heterogeneous in composition. The malignant cells are surrounded by a specialized connective tissue called stroma, consisting of an extracellular matrix (ECM) and a cellular compartment made of fibroblasts, inflammatory cells and endothelial cells. The ability of carcinoma cells to induce a stroma is a phenotypic trait that is maintained at metastatic sites. Stromal tissue is qualitatively distinct from the connective tissue which develops in inflammatory conditions: for instance, stromal inflammatory and mesenchymal cells have distinct phenotypic characteristics, and specific spliced variants of ECM components, such as fibronectin and tenascin, have been reported in carcinomas. Blood vessels are another essential component of the stroma. A vascular supply is necessary for tumor growth over 2 mm³. This is achieved by the complex multistep

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process of angiogenesis (see chapter by Castronovo et al., this volume). Moreover, the stroma, as opposed to normal connective tissue, is an unstable structure, remodelled throughout tumor development. This plasticity, controlled in part by the neoplastic cells themselves, is the result of a spatially and temporally changing imbalance between the agonist and antagonist stromal mechanisms that control tumor progression.

It is now currently accepted that stroma acts for tumor cells as: (1) a mechanical support, (2) a feeding support and pathway for metabolic wasteproducts, (3) a participant in the control of differentiation, proliferation, adhesion, and migration via a complex network of extracellular signals, and (4) ultimately promotes the tumor invasive phenotype and the metastatic process, although a number of histochemical studies have demonstrated the presence of infiltrating immune cells within carcinomas. Understanding the complex relationships established between neoplastic cells and cellular and non-cellular stroma components may lead, in the near future, to the design of new anticancer treatments targeted against tumor stroma constituents.

2. Extracellular Matrix Components of Lung Carcinomas

2.1. Carcinoma Cell-ECM Interactions are Mediated by Surface Receptors: Integrins, Non-integrins and Cell Surface Proteoglycans

The most extensively studied of ECM receptors is the integrin family, a group of transmembrane $\alpha$ and $\beta$ subunit glycoprotein heterodimers [1, 2]. Integrins play an important role in both tumor cell-ECM and carcinoma cell-stromal cell interactions, especially with endothelial cells and leukocytes. Integrins and the mechanisms coupled to them undergo extensive changes during malignant transformations and tumor progression. For instance, in normal lung tissue $\alpha 6 \beta 4$ integrin was found at a low level, but its expression increased significantly in epidermoid carcinomas and adenocarcinomas, mostly at carcinoma/stroma interfaces [3]. In small cell lung carcinoma (SCLC) cell lines, $\beta 1$ expression is predominantly associated with the $\alpha 3$ subunit (and to a lesser extent, with $\alpha M$ and $\alpha 1$ [4]. This $\alpha 3 \beta 1$ integrin is involved in laminin adhesion of SCLC cells.

Among non-integrins, the laminin/elastin receptors and the collagen receptors-cell surface proteoglycans (including CD44) play a central role. The latter are less specified elements, but provide an important support for cell-ECM interactions.

2.2 Extracellular Matrix Components

The ECM is composed of four major classes of component (collagens, elastin, proteoglycans and hyaluronic acid, and glycoproteins), a wide range