Chapter 6

TUMOR-MICROENVIRONMENT INTERACTIONS:
The Selectin-Selectin Ligand Axis in Tumor-Endothelium Cross Talk

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Abstract: Interactions of cancer cells with components of their microenvironment are crucial determinants in the decision making process which determines whether the cancer cells will progress towards a highly malignant phenotype or whether they will stay dormant or disappear altogether. The tumor microenvironment is composed of a plethora of soluble and cellular components. Many of these components deliver signals to tumor cells and thus modulate their phenotype thereby driving tumor progression. This chapter focuses on the interaction of tumor cells with endothelial cells through endothelial selectins and their fucosylated ligands expressed by the tumor cells. Comparisons are drawn between the utilization of this interaction axis by inflammatory leukocytes and by tumor cells.

Key words: tumor microenvironment; metastasis; endothelium; selectins; selectin-ligands; fucose; FX enzyme; transendothelial migration; extravasation
1. **THE ROAD TO METASTASIS IS PAVED WITH SEVERAL INVASION EVENTS**

Metastasis is the principal cause of treatment failure, poor prognosis, morbidity and mortality in cancer patients. Invasion of surrounding or distant tissues by cancer cells is the critical event in neoplastic diseases. An understanding of the molecular mechanisms involved in this process will aid in the identification of specific therapeutic targets that may allow tailored therapies for patients with metastasis or even the prevention of cancer progression.

There are several distinct events in the metastatic cascade in which cancer cells invade surrounding tissues. Detached cells from the primary tumor lesion equipped with the proper machinery (e.g., proteinases and other lytic enzymes; motility etc.) invade the extra cellular matrix on their way to the blood or lymph vasculature. Some cells invade these vessels and enter the circulation (intravasation). The next invasion event is transendothelial migration of the tumor cells into the surrounding tissue. This event is also termed extravasation. Those cancer cells that survive all the previous steps may form metastases at distant sites.

Intravasation and, in particular extravasation of tumor cells, require a close and intimate cross talk between tumor and endothelial cells. Such interactions are, however not unique to tumor cells. Other extravasating cells, most notably inflammatory leukocytes also interact with vascular endothelium in the inflammatory process. In fact, our comprehension of tumor cell extravasation is based on mechanisms underlying leukocyte-endothelium interactions leading to the extravasation of the leukocytes.

This review will focus on the involvement of the selectin-selectin ligand axis in cancer-endothelium interactions.

2. **MICROENVIRONMENT-DRIVEN MOLECULAR EVOLUTION OF CANCER CELLS**

The concept that cancer cells are autonomous with respect to growth factor requirements has prevailed for a long time (Haran-Ghera, 1965; Noble and Hoover, 1975; Chigira et al., 1990; Hanahan and Weinberg, 2000). Cancer autonomy has been ascribed to the capacity of cancer cells to produce and respond to their own growth factors delivering autocrine proliferation signals (Herlyn et al., 1990; Berthois and Martin, 1989; Sporn and Roberts, 1985).