Cell Adhesion and Cytoskeletal Molecules in Metastasis

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Cell Adhesion and Cytoskeletal Molecules in Metastasis

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FOREWORD

The ability of an epithelial cell to adhere to its neighbor and to the extracellular environment is an essential process that defines in part, a normal multicellular organism. It is a feature that is fundamental to the development of an organism. Mutations in critical adhesion components will result either in embryonic lethal phenotypes at various stages or lethality shortly after birth. In addition, adhesion structures are essential for the survival of the adult organism, as mutations will also result in defective wound healing responses in a variety of organ systems.

Although many adhesion structures exist that are required for successful epithelial cell adhesion, the focus of this volume is to highlight the necessity for the transformed epithelial cell to adhere either to the extracellular environment via integrin type receptors or to adhere to its neighbor through cadherin complexes during tumor progression. The alteration of the requirements of cellular adhesion during tumor progression and metastasis is the subject of Chapters 1-3.

Cell adhesion structures are normally tightly regulated but their components are corrupted for nepharious purposes such as cancer cell invasion, migration and attachment at a distant site. The cytoskeleton is involved in these processes. In Chapter 4, the actin cytoskeleton and integrin receptors normally engaged in strong stable adhesion structures are discussed as migration determinants. In Chapter 5, a FERM domain protein, known to interact with F-actin, called EHM2, is discussed as a metastasis promoting agent. In Chapter 6, the cytokeratin 6 network of the cytoskeleton is postulated as a critical element in the maturation of a stem cell component within a normal prostate gland.

The molecules involved in cell adhesion structures are uniquely positioned to serve as membrane sentinels for the changing extracellular

environment of a metastatic cell. This is an important requirement of a metastatic cancer cell to survive the dynamic environments encountered during intravasation and extravasation, prior to reaching a distant site. In Chapter 7, the epigenetic regulation of cell adhesion genes is discussed as a potential mechanism to confer transient suppression of cell adhesion genes during the metastatic process. The ability of cell adhesion structures to influence damage responses through the action of cell surface receptors is detailed in Chapters 8 and 9.

The reliance of the cancer cell upon cell adhesion for invasion, migration and survival during and after the journey to a distant site makes it formally possible to block these events using small peptide extracellular adhesion mimetics. Chapter 10 illustrates the potential for generating and targeting epithelial cell surfaces using synthetic D-amino acid peptides.

The reliance of the metastatic cancer cell on a restricted set of adhesion structures derived from normal structures offers the opportunity for the early identification and eradication of circulating tumor cells with a pro-survival and pro-metastatic phenotype. Understanding the minimum elements of the adhesion structures that are selected for and preserved on the cancer cell during tumor progression will offer the possibility of defining adhesion receptors that dictate the metastatic adhesion signature. Stated another way, the metastatic adhesion signature confers an advantage for cancer cell survival and adhesion at the metastatic site; this reveals a potential vulnerability of the successful metastatic cell. Future work defining the metastatic adhesion structure(s) is likely to lead to improved early detection and prevention of cancer metastasis.

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