Matrix Metalloproteinases in Cancer

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1. INTRODUCTION

The production of proteinase activity has long been thought to be an essential property of tumor cells that allow them to invade and metastasize to distant sites. The “three step theory of invasion” proposed by Liotta and colleagues (1) suggests that potentially invasive cells must first attach to basement membrane proteins via cell-surface receptors, i.e., the integrins. Localized, extracellular proteolytic activity then clears a path for the cell. Finally, the cell has to move into the cleared region, a locomotive process which probably depends on specific chemotactic factors. This invasion process first occurs as a tumor cell breaches the basement membrane at the primary tumor site—an event which signifies a malignant lesion. In order to result in a growth at a secondary site, the process has to be repeated as tumor cells penetrate blood vessels through a process referred to as intravasation. They can be carried to a new location, where a third invasive event must occur to extravasate into the parenchyma of the distant organ. Thus, proteolysis of basement membrane (BM) and extracellular matrix (ECM) components has been viewed as an essential step in tumor invasion and metastasis. Since metastasis is the principal cause of cancer-

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associated mortality, the tumor proteases responsible for BM and ECM degradation have been viewed as accessible targets for therapeutic intervention.

There has been considerable progress over the last decade in identifying the specific proteases contributing to tumor invasion and metastasis. The contribution of members of the matrix metalloproteinase (MMP) family is the topic of this volume, although it must be noted that endoproteases of the serine, cysteine, and aspartyl classes have been associated with invasion and metastasis as well and are likely to have overlapping functions in tumor-mediated matrix degradation. Nevertheless, there have been compelling reports of "proof-of-principle" experiments in which the invasive and metastatic ability of tumor cells has been altered by manipulating the levels of a MMP or the endogenous tissue MMP inhibitors, the TIMPs. It was these observations that provided the driving force behind the development of synthetic MMP inhibitors for cancer therapy.

As the field has matured however, it has become clear that the biology of MMPs in cancer is more complex than originally envisioned. Most of these proteinases are produced by stromal fibroblasts or by infiltrating inflammatory cells as a response to tumor-produced factors. In addition, it has become evident that MMP activity can contribute to early-stage tumorigenesis and to angiogenesis, as well as to the late stage events of invasion and metastasis. In this chapter, we explore the roles played by MMPs in multiple stages of tumor progression, and the preclinical data suggesting a therapeutic benefit to inhibiting these enzymes.

2. MMP EXPRESSION IN HUMAN TUMORS

A striking feature of the MMPs is the abundant expression of multiple family members in malignant disease. In contrast to the absence or relatively low levels of MMP transcripts or protein noted in normal tissues, including those resected with a malignant lesion, a wide variety of human tumors have been reported to express high levels of specific MMP family members. A survey of the current literature on the expression of MMPs by human tumors is shown in Table 1. Many of the studies in which MMP levels have been measured in human tumors demonstrate a positive correlation between MMP levels and tumor grade (2-4). Concomitantly, a number of researchers also examined endogenous levels of inhibitors produced by tumors and found that tumor aggressiveness tends to be related not only to an overall increase in MMP levels but also a decrease in TIMP levels (5,6). This leads to the theory that the aggressive, invasive, and ultimately metastatic nature of a tumor is due, at least in part, to an imbalance between proteases and their inhibitors resulting in excessive proteolytic degradation (7-10).

Although studies in which multiple MMP family members have been examined in a single cohort of specimens are relatively rare, the coexpression of several members of the family appears to be a common occurrence in many cancer