Editorial

Of Peptides and Peptidases: The Role of Cell Surface Peptidases in Cancer

David M. Nanus

Division of Hematology and Medical Oncology, Department of Medicine, and the Department of Urology, Weill Medical College of Cornell University, New York, New York

Introduction

The renin-angiotensin system has been studied for over three decades in relation to cardiovascular and renal physiology. Angiotensin II (Ang II), the central product of the renin-angiotensin system, functioning through the Ang II type 1 receptor has been shown to exert numerous effects, including stimulating cell growth, inducing gene expression of various growth factors (i.e., basic fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor) and extracellular matrix components, and activating a variety of intracellular signaling cascades including Janus-activated kinase/signal transducer and activator of transcription, mitogen-activated protein kinase, and epidermal growth factor receptor pathways (1). These downstream targets of Ang II are reminiscent of those implicated in the malignant phenotype; however, investigation into the potential role of the renin-angiotensin system in cancer has been extremely limited. Recent studies suggest that the Ang II type 1 receptor pathway is proangiogenic in tumors (2–4). In the current issue, Watanabe et al. (5) show that Ang II induces an increase in vascular endothelial growth factor expression in endometrial carcinoma cells resulting in increased vascular endothelial cell migration. The involvement of Ang II in the malignant phenotype is not surprising. Other small bioactive peptides (<30 amino acids) such as bombesin and endothelin together with their G protein-coupled receptors participate in autocrine/paracrine stimulation of tumor cell proliferation and migration in many epithelial cancers including breast, colon, lung, pancreatic, and prostate cancers. These peptides and their receptors not only stimulate the synthesis of conventional second messengers but also induce tyrosine phosphorylation signaling cascades (6–8).

The enzyme most commonly associated with degradation of Ang II is aminopeptidase A, a cell surface peptidase that removes the NH2-terminal amino acid aspartyl residue of Ang II to yield angiotensin III (9). Another angiotensinase, the cytosolic aminopeptidase adipocyte-derived leucine aminopeptidase, was first identified in human placenta and shown recently to be a final processing enzyme of the precursors of MHC class I-resented antigenic peptides (10). Watanabe et al. (5) report that overexpression of adipocyte-derived leucine aminopeptidase in human endometrial carcinoma cells attenuates the Ang II-mediated stimulation of endothelial cell migration in vitro and inhibits the vascular density of tumors grown in athymic mice, suggesting that adipocyte-derived leucine aminopeptidase in endometrial carcinoma cells regulates the local Ang II concentration, thereby regulating, in part, vascular endothelial growth factor-mediated angiogenesis. Although the role of both adipocyte-derived leucine aminopeptidase and aminopeptidase A in regulating Ang II effects on angiogenesis requires additional investigation, this study highlights the role of small peptides and peptidases in the malignant process.

Limited studies have explored the involvement of cell surface peptidases in the various stages of neoplasia such as tumor initiation and progression and the development of metastatic disease. Cell surface peptidases are the guardians of the cell against small peptides, functioning to control growth and differentiation in normal cells by regulating peptide access to their cell surface receptors. Over 25 cell surface peptidases have been identified in human cell types and tissues, most notably angiotensin-converting enzyme, aminopeptidase A, aminopeptidase N (CD13), dipetidyl-peptidase IV (CD26), meprin A, and neutral endopeptidase (CD10; Ref. 11). These peptidases are integral membrane proteins with their catalytic site exposed to the external cell surface, situated in the membrane with the NH3 terminus or the COOH-terminus facing extracellularly or through a glycol-phosphatidylinositol anchor. Many also exist as soluble isoforms found in extracellular fluids, although the mechanisms that regulate cell surface peptidase shedding are for the most part unknown. Some were originally identified as hematopoietic cluster of differentiation antigens and as kidney or melanoma differentiation antigens only later to be identified as cell surface enzymes.

The following two basic mechanisms of cell surface peptidase involvement in the malignant process can be predicted: loss of function and gain of function (Fig. 1). Lost or decreased expression of a peptidase could result in the inability of a cell to inactivate a peptide substrate. This peptide (or peptides) may stimulate cell division, promote cell survival, or affect other processes that contribute to malignancy such as cell migration or invasion. If the cell surface peptidase regulates growth by converting a propeptide to a growth-inhibitory peptide, loss of expression would prevent activation of the growth-inhibitory pathway also resulting in unregulated proliferation. The second mechanism by which a cell surface peptidase could contribute to neoplastic processes, gain of function, would typically result from overexpression of a peptidase by a cell that normally expresses low levels, or peptidase expression in a cell type that normally does not express the enzyme. This resulting increase in catalytic activity could enhance growth by increased conversion of a propeptide to a biologically active form (i.e., endothelin-converting enzyme-1 catalyzes the conversion of the 39-amino acid basic fibroblast growth factor to the active form).
acid prohormone peptide big endothelin-1 to the 21-amino acid peptide endothelin-1; Ref. 12). Alternatively, overexpression of a cell surface peptidase could result in inactivation of a peptide that normally inhibits proliferation. Alteration in cell surface peptidases could theoretically occur at all stages of malignant transformation.

Most studies to date assessing the role of cell surface peptidases in cancer have examined the expression pattern of a specific enzyme in a malignant cell compared with its normal cellular counterpart (see Refs. 11 and 13 for review). Both loss and gain of expression have been reported for most peptidases, and it is clear that alterations in cell surface peptidase expression are tumor-type specific. Although these studies examining expression patterns provide circumstantial evidence for a role in neoplasia, they do not provide direct evidence that a specific peptidase is critical to the malignant processes, nor do they help define the molecular mechanisms of peptidase actions. A number of recent studies similar to Watanabe et al. have demonstrated that re-expression of specific cell surface peptidases in malignant cells are tumor suppressive and will inhibit cell migration, invasion, and tumorigenicity (i.e., neutral endopeptidase in prostate cancer, see Refs. 14 and 15; dipeptidyl-peptidase IV in melanoma and ovarian cancer, see Refs. 16–18), whereas other studies indicate re-expression is protective against apoptosis (i.e., aminopeptidase N in leukemia cells; Ref. 19).

In a review published in 1993, Shipp and Look suggested that “cutting is the key,” or that enzymatic inactivation of peptide substrates accounted for the biological activity of cell surface peptidases (20). Although this axiom remains true today, it is now clear that cell surface peptidases possess biological activity independent of their enzymatic function. Dipeptidyl-peptidase IV complexes with seprase/fibroblast-activating factor α resulting in enhanced negative effects on cell invasiveness (21), and neutral endopeptidase inhibits focal adhesion kinase phosphorylation and cell migration by a direct interaction of its cytoplasmic domain with Lyn kinase and phosphatidylinositol 3-kinase (22). It is probable that cell surface peptidases have much in common with integrins, where interactions with other proteins govern their function, and that these interactions result in a variety of properties, including intracellular signaling. Our understanding of the complexities of cell surface peptidases and their role in various cancers is still very limited. As our under-
standing increases, novel strategies will emerge for improving the diagnosis and treatment of individual malignancies.

References
Of Peptides and Peptidases: The Role of Cell Surface Peptidases in Cancer

David M. Nanus


Updated version  Access the most recent version of this article at: http://clincancerres.aacrjournals.org/content/9/17/6307

Cited articles  This article cites 20 articles, 7 of which you can access for free at: http://clincancerres.aacrjournals.org/content/9/17/6307.full#ref-list-1

Citing articles  This article has been cited by 8 HighWire-hosted articles. Access the articles at: http://clincancerres.aacrjournals.org/content/9/17/6307.full#related-urls

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, use this link http://clincancerres.aacrjournals.org/content/9/17/6307. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.