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Breaking up the tie: Disintegrin-like metalloproteinases as regulators of cell migration in inflammation and invasion

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Abstract

Cell adhesion and cell migration are essential for a variety of important events in both embryonic development and in the adult organism. Cell adhesion molecules (CAM) like selectins, immunoglobulin superfamily members, integrins, and cadherins undergo diverse mechanisms of regulation. Dysregulation of adhesion can lead to pathological processes, including inflammatory diseases or tumor metastasis either by disrupting the normal anchorage, thereby altering cell movement and regulatory signalling, or by promoting inappropriate temporal and spatial adhesion. An increasing body of evidence has emerged showing that members of the a disintegrin and metalloproteinase (ADAM) family critically contribute to the regulation of CAM functions. While the disintegrin domain can interact with integrins and mediate adhesion, the metalloproteinase domain can mediate anti-adhesive functions by cleaving the membrane bound adhesion molecules. This "shedding" process leads to the release of often still functional soluble ectodomains and can additionally influence intracellular cell signalling pathways. Several soluble CAMs have been detected in vitro and in vivo. Some of them are strongly increased in inflammatory diseases or in the serum of cancer patients. Therefore the level of soluble CAMs but also the expression of the metalloproteinases responsible for their release might provide prognostic information. It could also be useful for monitoring malignant disease stages and for evaluating the effectiveness of various therapeutic approaches. Moreover, metalloproteases of the ADAM family are emerging as promising targets for new therapeutic options.

Keywords: ADAM; Cell adhesion; Signalling; Inflammation; Cancer

Abbreviations: ADAM, a disintegrin and metalloproteinase; APP, amyloid precursor protein; CAM, cell adhesion molecule; CHL1, close homologue of L1; ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; GPCR, G protein-coupled receptor; HB-EGF, heparin-binding epidermal growth factor; ICAM, intercellular adhesion molecule; IgCAM, immunoglobulin superfamily cell adhesion molecules; MMP, matrix metalloproteinase; MT1-MMP, membrane type-1 matrix metalloproteinase; NCAM, neural cell adhesion molecule; NrCAM, NgCAM related cell adhesion molecule; PECAM, platelet endothelial cell adhesion molecule; PMA, phorbol 12-myristate 13-acetate; PSGL-1, P-selectin glycoprotein ligand-1; RA, rheumatoid arthritis; TIMP, tissue inhibitor of metalloproteinases; VCAM, vascular cell adhesion molecule.

Contents

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1. Introduction

The regulation of cell adhesion and cell migration is a critical process throughout life. During development, complex interaction processes such as fertilization, implantation, embryogenesis, and morphogenesis have to be regulated. Some cells need to migrate long distances before they reach their final destination where they assemble into tissues and organs. But also in the adult organism dynamic regulation of physiological changes like the turnover of epithelia in mature tissue, the maintenance of synaptic plasticity in the nervous system, or the permanent recirculation of leukocytes in the bloodstream and immune organs remain important.

In particular, adhesion molecules do not only mediate the contact of cells with each other and with the extracellular matrix (ECM). They also convey information about the environment to the cell by interacting with a complex network of cytoskeletal and signalling molecules. Cell–cell and cell–martix contacts can protect cells against apoptosis and can stimulate cell proliferation or differentiation (Buckley et al., 1998). On the other hand, non-physiological alterations in cell adhesion and cell migration can result in pathological processes, including tumor invasion and metastasis or inflammatory diseases (Lauffenburger & Horwitz, 1996; Gonzalez-Amaro et al., 1998; Harlozinska, 2005). While the recruitment of leukocytes to the site of infection is an essential process in innate immunity, dysregulation of this process can cause tissue damage such as ischemia and infarction or several autoimmune disorders like systemic lupus erythematosus, multiple sclerosis or rheumatoid arthritis (RA). Therefore, cell adhesion molecule (CAM) function is regulated by a variety of mechanisms. For example, cadherins show a very distinct spatio-temporal transcriptional regulation during embryonic development. Protein function and localisation can also be modulated through post-translational changes that include phosphorylation, glycosylation or endocytosis. These modifications do not only allow the fine tuning of cell interaction but also rapid responses to signals like growth factors or cytokines.

In particular, proteolytic ectodomain release, a process known as “shedding”, has emerged as a key mechanism for regulating the function of cell surface proteins (Hooper et al., 1997). In physiological situations the ability to refashion the cell surface and its surroundings by selective proteolysis is of major importance for cell–cell communication. Shedding of integral membrane proteins is usually limited to type I and type II transmembrane proteins or GPI-anchored molecules in which the cleavage site is generally located close to the membrane surface. The proteolytic down-regulation of cell surface expression can not only abrogate cell adhesion but additionally activate intracellular signalling processes. Moreover, in several cases the soluble ectodomain can still be functionally active. It has the capacity to bind to its receptors and stimulate cell migration or it might act as a competitor for the cell bound protein and inhibit attachment (Schleiffenbaum et al., 1992; Mechtersheimer et al., 2001). The number of CAMs that are described to exist as both transmembrane proteins and soluble circulating forms is still increasing. Soluble forms of several CAM can be found in the serum under non-pathological conditions, but increased levels of such proteins like the vascular cell adhesion molecule (VCAM)-1 and the epithelial (E)-cadherin have also been correlated with a variety of diseases like inflammatory diseases and tumor metastasis, respectively and may be of prognostic value (Gearing & Newman, 1993; Syrigos et al., 2004a; Kato et al., 2005). Even though several members of the superfamily of zinc-dependent metalloproteinases have been implicated in the process of protein cleavage, ADAMs have emerged as the major proteinase family which can mediate ectodomain shedding.

2. A disintegrin and metalloproteinase superfamily

ADAMs belong to the metzincin family of metalloproteinases which also includes astacins and matrix metalloproteinases (MMP). Together with snake venom metalloproteinases (SVMP) and ADAMs containing thrombospondin motifs (ADAMTS), they form the adamalysin subfamily. ADAMs possess a characteristic domain structure that is responsible for their proteolytic, adhesive, and putative signalling activities (Huovila et al., 2005). They are characterized by an N-terminal signal peptide followed by a prodomain, a metalloproteinase