European Journal of Cell Biology 93 (2014) 23–29

Contents lists available at ScienceDirect

European Journal of Cell Biology

journal homepage: www.elsevier.com/locate/ejcb

Mini Review

Metalloproteinases in melanoma

Nives Moro, Cornelia Mauch, Paola Zigrino*

Department of Dermatology and Venerology, University of Cologne, Germany

ARTICLE INFO

Article history:
Received 13 September 2013
Received in revised form 8 November 2013
Accepted 8 January 2014

Keywords:
ADAM
MMP
Proteases
Melanoma
Metastasis

ABSTRACT

Tumour cell adhesion, motility, proteolytic activities and cell receptors have important roles in cancer invasion. These processes are involved from early development of melanoma within the epidermis, to tumour cell invasion of the underlying tissue until intravasation of lymphatic or blood vessels, and thereafter, dissemination into distant organs occur. The activity of several proteolytic enzymes was shown to be pivotal in promoting melanoma cell invasion. These enzymes not only remodel the extracellular matrix, but also release active factors and shed cell surface receptors thereby mediating melanoma cross-communication with their microenvironment. This leads to the generation of a favourable environment for melanoma growth. Several proteases are involved in melanoma invasion and include serine, cysteine proteases, matrix metalloproteases (MMPs) and the disintegrin and metalloproteases (ADAMs).

This study summarises the current knowledge on the role of metalloproteinases, MMPs and ADAMs, in melanoma.

Introduction

Over the last years it has become obvious that the reciprocal interaction of tumour cells with their environment is a key step in cancer progression. Despite the progresses made to treat melanoma patients, the most reliable approach to prolong tumour-free life and reduce metastasis to distant organs remains early diagnosis and resection of the primary tumour. Once melanocytes transform to melanoma cells, the primary tumour initially grows horizontally within the epidermis and then starts to enlarge and invade the deeper levels of the dermis (vertical growth phase). In these processes a continuous cross-talk with the neighbouring epithelial, stromal and inflammatory cells occurs (Gaggioli and Sahai, 2007). Proteolysis in the pericellular and stromal compartments has been shown to largely contribute to altering the tumour microenvironment being pivotal in promoting melanoma invasion. Several protease families are involved in these processes including serine proteases, cysteine proteases, matrix metalloproteases (MMPs) and disintegrin and metalloproteases (ADAMs) (Egeblad and Werb, 2002; Mochizuki and Okada, 2007). Among these, enzymes containing a metalloproteinase domain (MMPs and ADAMs) have been shown to play an important role in tumour progression. Even though previously believed to be exclusively active as matrix degrading enzymes, their activity towards cell and growth factors receptors and many other important molecules has been described and shown to be of particular importance in the progression of several life-threatening disease including cancer. This review will focus on the roles and major functions of metalloproteinases, MMPs and ADAMs, in melanoma.

General characteristics

Metalloproteinases include the matrix metalloproteinases (MMPs), a disintegrin and metalloproteinases (ADAMs) and ADAMs with thrombospondin motifs (ADAMTS) enzymes which all present a conserved methionine residue in the active site and depend on the zinc ion for enzymatic reactions.

MMPs, 24 in man and 23 in mouse, were originally classified on the bases of their specificity for ECM components. They are now grouped in a way that also considers their structural features (Egeblad and Werb, 2002; Lopez-Otin et al., 2009). Activity of metalloproteases in tissues is tightly controlled ensuring that in steady-state conditions metalloproteases are mostly held inactive. Enzymatic activities or chemicals are required to remove the pro-domain, which by binding the Zn^{2+} ion of the active centre by a cysteine residue ensures enzyme latency. Activity is also regulated by endogenous inhibitors, the tissue inhibitors of metalloproteinase (TIMP) that in small amounts contribute to enzyme activation but, when their concentration is increased, contribute to inhibit enzymatic activity (Page-McCaw et al., 2007). MMPs are generally secreted proteases and function in the extracellular environment, though several MMPs are present as membrane bound (membrane-type matrix metalloproteinases; MMP-14, -15, -16) or anchored by GPI (MMP-17, -25) (Page-McCaw et al., 2007). MMP

* Corresponding author at: Department of Dermatology and Venerology, University Hospital of Cologne, Kerpener Strasse 62, 50937 Cologne, Germany.
Tel.: +49 221 478 97443; fax: +49 221 478 5949.
E-mail address: Paola.Zigrino@uni-koeln.de (P. Zigrino).

http://dx.doi.org/10.1016/j.ejcb.2014.01.002
0171-9335/

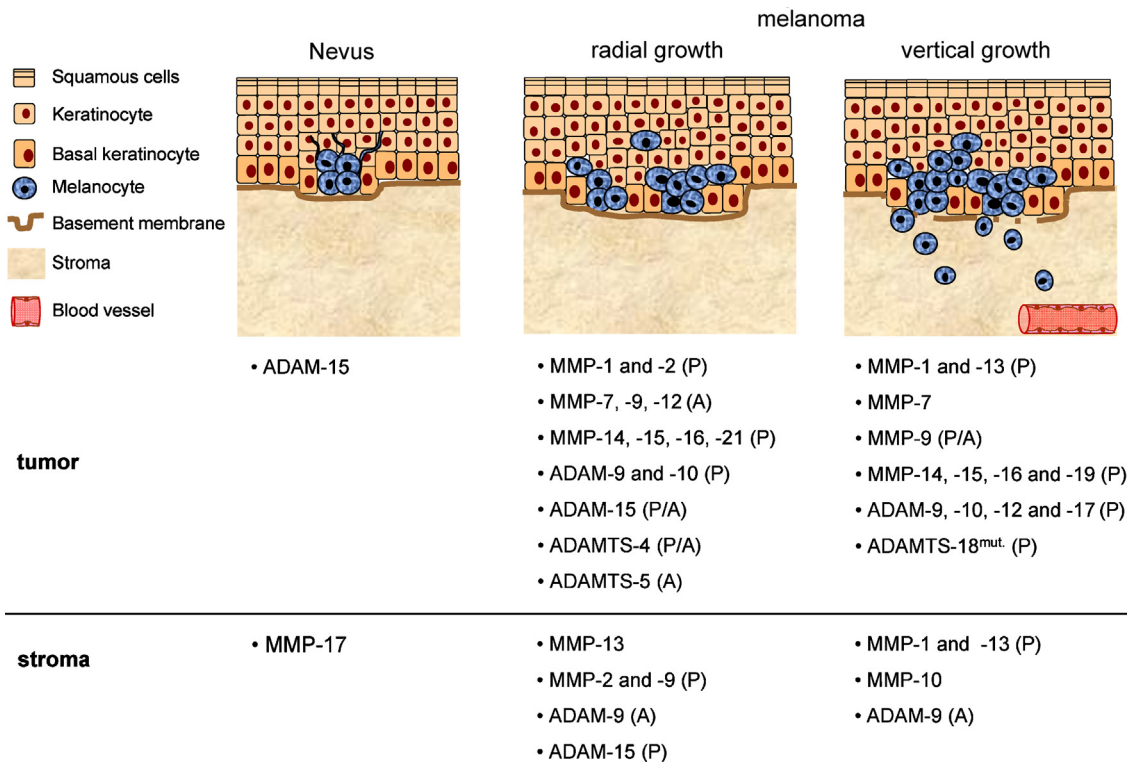

Fig. 1. Topographical distribution of metalloproteinases expression in nevi and melanoma. Known pro- (P) and anti-tumour (A) function of metalloproteinases during tumour progression has been indicated.

expression is regulated mostly at the transcriptional level by a variety of growth factors, cytokines, and chemokines (Clark et al., 2008). Based on their structural diversity, MMPs play multiple functions and influence cell behaviour, cell death and survival. Accordingly in cancer MMPs play diverse roles in all stages of tumour development targeting growth factors and their receptors, cytokines, chemokines and adhesion components (Lopez-Otin et al., 2009). Structurally, ADAMs are type I transmembrane proteins which consist of a pro-domain, a zinc metalloprotease domain, a disintegrin domain, a cysteine-rich region, an EGF-like sequence, a transmembrane region and a cytoplasmic tail. The cytoplasmic tail interacts with Src homology 3 domain-containing proteins, but a clear role for ADAMs in signal transduction is not yet been characterised (Klein and Bischoff, 2011). ADAMs, 21 in man and 37 in mouse, have similar regulation of proteolytic activity as described above for MMPs. However, about half of human ADAMs are proteolytically active and can interact with integrin receptors (Bridges and Bowditch, 2005). This function was shown to be mediated by the cysteine-rich and disintegrin domains. ADAMs lack the classical RGD motif (ADAM-15 excluded) but have an ECD motif that influences adhesive capability (Edwards et al., 2008). After activation ADAMs cleave other membrane associated proteins as shown for the activation of different growth factors (TNF-alpha, IL-6), shedding of growth factor receptors (EGFR) and cell adhesion molecules (Edwards et al., 2008). Another proteolytic process in which ADAMs are involved is regulated intramembrane proteolysis (RIP). This process has been well described for example in the shedding of the Notch receptor and amyloid precursor protein (APP). After an initial shedding by ADAMs at a site outside the membrane, a second proteolytic cleavage within the cell membrane performed by the γ-secretases leads to release of an intracellular domain which translocate to the nucleus and modulates gene expression (Edwards et al., 2008; Lichtenthaler et al., 2011).

ADAMTS are related to the ADAMs, they all preserve both the metalloprotease and a disintegrin-like domain. In contrast to ADAMs, ADAMTS contain thrombospondin repeats and lack transmembrane domain and are primarily found as secreted enzymes (Kuno et al., 1997). Like ADAMs, ADAMTSs are activated intracellularly and secreted as active forms. The precise function of the disintegrin domain remains unclear (Porter et al., 2005).

Matrix metalloproteinases (MMPs)

In physiological conditions, skin matrix remodelling occurs by a continuous process of synthesis and degradation of matrix components and among others, MMPs are strongly involved in perpetuating skin integrity. During skin ageing, changes in ECM deposition and degradation are frequently leading to malignancies (Reed et al., 2000). In melanoma, both tumour cells and tumour-associated stromal cells show increased expression of several MMPs as well as of tissue inhibitors, TIMPs (Hofmann et al., 2000).

The major findings about the roles and expression of some metalloproteinases in melanoma progression and metastasis (Fig. 1) are summarised according to their subgroup.

Collagenases

MMP-1 is an interstitial collagenase cleaving collagen types I, II, and III. Initially MMP-1 was detected in a highly invasive vertical growth phase of malignant melanoma together with MMP-13 (Airola et al., 1999). Following studies provided evidence that these two collagenases are released predominantly by peritumoural fibroblasts (Uria et al., 1997; Wandel et al., 2000). MMP-1 expression by stromal fibroblasts has also been implicated in the processing of PAR1, a thrombin receptor, thereby promoting the metastatic potential of cancer cells (Boire et al., 2005). Furthermore, MMP-1-mediated activation of PAR1 in endothelial cells induces acute endothelial cell activation (ECA) generating a proinflammatory environment associated with increased tumour