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Review Article

The Extracellular Matrix Metalloproteinase Inducer (EMMPRIN, CD147) - a potential novel target in atherothrombosis prevention?

Nader Joghetaei [a,1], Andreas Stein [a,1], Robert A. Byrne [a], Christian Schulz [b,c], Lamin King [a], Andreas E. May [d], Roland Schmidt [a,*]

[a] Deutsches Herzzentrum und I. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität München, Munich, Germany
[b] Cardiovascular Division, BHF Centre of Excellence, The James Black Centre, Denmark Hill Campus, King's College, London SE5 9NU, United Kingdom
[c] Division of Immunology, Infection and Inflammatory Diseases, Guy's Campus, King's College, London SE1 1UL, United Kingdom
[d] Medizinische Klinik III, Universitätsklinikum Tübingen, Tübingen, Germany

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ABSTRACT

The immunoglobulin superfamily member EMMPRIN (CD147) plays an important role in a number of organ systems, including the cardiovascular system. Here we review the contemporary understanding of EMMPRIN and EMMPRIN-associated sequelae in the course of atherosclerosis. A significant body of data documents the pivotal role of EMMPRIN in the complex processes of atherogenesis, atheroprogression, and acute atherosclerothrombosis, a role that goes beyond that of a mere marker of inflammation.

Contents

Introduction

EMMPRIN (CD147), a member of the immunoglobulin superfamily, was originally discovered on the surface of solid tumor cells [1] where it was shown to have the ability to induce the expression of various matrix metalloproteinases (MMPs) in adjacent fibroblasts [2] by virtue of homotypic interaction with other CD147 molecules. Based on these latter properties, CD147 – hitherto known as tumor cell-derived collagenase stimulatory factor (TCSF) – was renamed EMMPRIN [3] (extracellular matrix metalloproteinase inducer). EMMPRIN consists of two C2-like immunoglobulin like extracellular domains, a transmembrane and a short cytoplasmatic domain (Fig. 1) [4–6].

The extracellular domains include three glycosylation sites, which are variably glycosylated. Unglycosylated EMMPRIN was shown to be unable to stimulate MMP induction, moreover it was capable to block properties of the glycosylated EMMPRIN [7, 8].

Not only homophilic binding has been described, but also additional different EMMPRIN associations have been identified so far. EMMPRIN can interact with different integrins amplifying cell adhesion and cell spreading [9]. EMMPRIN can associate with caveolin-1 in lipid rafts,

Abbreviations: CyP-A, Cyclophilin A; EMMPRIN, Extracellular Matrix Metalloproteinase Inducer; ICAM-1, intercellular adhesion molecule-1; MMP, matrix metalloproteinase; PAI, plasminogen activator inhibitor; GP VI, platelet glycoprotein VI; SMC, smooth muscle cell; THP1, T helper cells type 1; TIMP, tissue inhibitor of metalloproteinase; t-PA, tissue plasminogen activator; ROS, reactive oxygen species; uPA, urokinase plasminogen activator; uPA-R, urokinase plasminogen activator receptor.

* Corresponding author at: Deutsches Herzzentrum und 1. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität München, Lazarettstr. 36, 80636 München, Germany. Tel.: +49 89 1218 0; fax: +49 89 1218 4013.
E-mail address: rolschmidt@yahoo.de (R. Schmidt).

[1] Both authors contr. equally.

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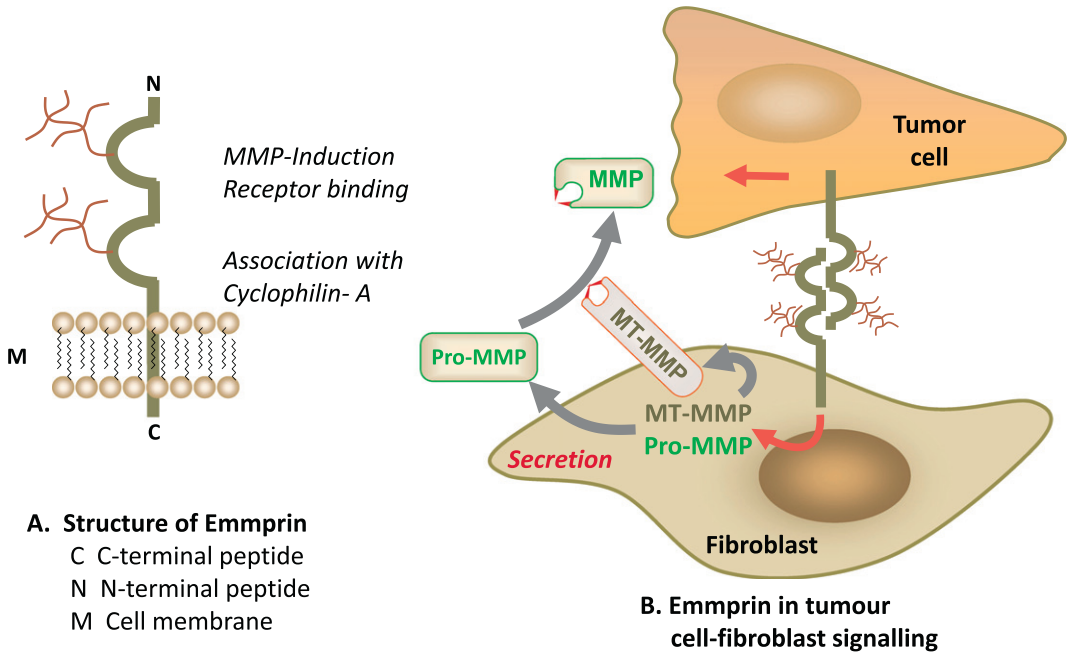

Fig. 1. Illustration of the molecular structure of EMMPRIN (A). Tumor-cell induced activation of adjacent fibroblasts by homophilic EMMPRIN signaling (B).

leading to a reduced cell surface expression and subsequent diminished EMMPRIN mediated protease induction [10].

EMMPRIN on tumour cells was first described to induce MMP-1 in adjacent fibroblasts by mitogen activated protein kinase (MAPK) p38 signalling leading to enhanced gene expression [11]. However EMMPRIN induced MMP-2 induction was shown to mediated by a phospholipase A(2) and 5-lipoxygenase catalyzed pathway [12].

In subsequent years, EMMPRIN was demonstrated to have pleiotropic [13] roles in various organs required for both normal development and homeostasis. In human atherosclerotic plaques, proteolytic activity and thus plaque instability have been attributed to the activity of MMP. Based on this finding, and the similarities evident between atheroprogression and metastatic tumor growth – mainly matrix degradation and macrophage and smooth muscle cell (SMC) transmigration – evidence has mounted in support of a central role for EMMPRIN in the process of atherosclerosis. In the current review, crucial steps in the development of atherosclerosis are first briefly mentioned followed by evidence available on the role of EMMPRIN within the context given.

Atherogenesis

An important initial step in the process of early atherogenesis consists of the accumulation and aggregation of small lipoprotein particles within the proteoglycan matrix of the intima [14]. Lipoprotein particles bound to intimal proteoglycan have increased susceptibility to oxidative modifications [15]. May et al. demonstrated that enzymatically modified low density lipoproteins directly activate MMP as well as EMMPRIN expression in monocytes and vascular SMCs [16]. Based upon this mechanism enzymatically modified low density lipoprotein may directly contribute to atherogenesis.

Another pivotal step in the beginning of atherogenesis is the recruitment of leukocytes – namely monocytes and T lymphocytes – early after the onset of hypercholesterolemia. These cells then adhere to the endothelium and enter the intima through endothelial cell junctions where they take up lipids and differentiate into foam cells. Foam cells origin not only from mature leukocytes, but also differentiate from CD34(+) progenitor cells. During this process EMMPRIN is upregulated and its ligand, CyPA, is released [17]. There also is evidence supporting involvement of CD147 in the recruitment of leukocytes. Zhou et al. demonstrated upregulation of CD147 during the differentiation of monocyte THP-1 cells to macrophage cells, and furthermore that CD147 induces the secretion and activation of MMP-2 and MMP-9 and enhances the invasive ability of THP-1 cells [18].

In addition, MMP also serves as a regulator of leukocyte migration by virtue of its interaction with cyclophilins. Damsker et al. recently demonstrated that proinflammatory leukocytes, including monocytes, lose their ability to migrate in response to cyclophilin A *in vitro* when treated with anti-CD147 monoclonal antibody. Furthermore, *in vivo* treatment with anti-CD147 monoclonal antibody reduced the development of collagen-induced arthritis in mice by over 75% [19]. Similarly, Gwinn et al. examined the role of extracellular cyclophilin-CD147 interactions in recruitment of leukocytes from the periphery into tissues during inflammatory responses. In a mouse model of asthmatic inflammation, they found that *in vivo* treatment with anti-CD147 mAb significantly reduces the accumulation of leukocytes in lung tissues [20]. Seizer et al. investigated the role of EMMPRIN and its ligand Cyclophilin A (CyP-A) in inflammatory cardiomyopathy in a series of 102 human endomyocardial biopsies where the expression of EMMPRIN and CyP-A were correlated with histological and immunohistological findings. EMMPRIN was enhanced in both inflammatory and non inflammatory cardiomyopathies and thus may serve as a marker of myocardial remodelling [21].

A distinct subset of leukocyte adhesion molecules on endothelial cells regulates the adherence of monocytes and T cells to the endothelium. The intercellular adhesion molecule-1 (ICAM-1) is a typical example of molecules within this group. Kasinrek et al. demonstrated that CD147 mAb, by binding to the CD147 molecule, activated the LFA-1/ICAM-1 intercellular adhesion pathway [22].

After entry to the intima, monocytes take up lipids – in a process mediated by scavenger receptors – and eventually become foam cells. Zhang et al. recently showed that the expression of both EMMPRIN mRNA and protein was significantly increased during phorbol 12-myristate 13-acetate (PMA)-induced monocyte differentiation into macrophages. However, the same results were not observed when macrophages were further induced to become foam cells in the presence of oxidized low-density lipoproteins (LDL). Furthermore both the PPARalpha agonist clofibrate and PPARgamma agonist pioglitazone potently and specifically inhibited EMMPRIN expression in macrophages and foam cells.