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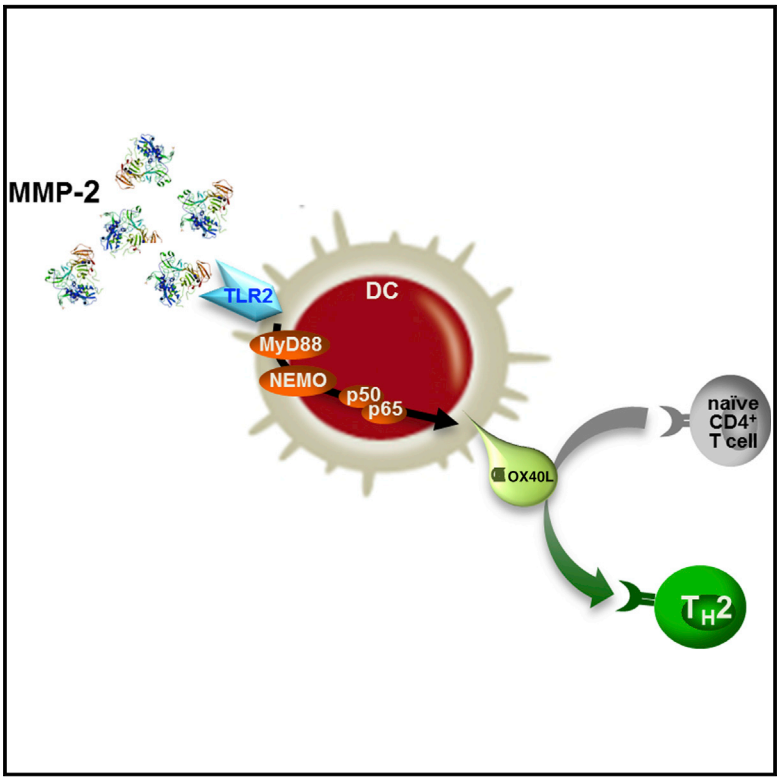
Activation of Toll-like Receptor-2 by Endogenous Matrix Metalloproteinase-2 Modulates Dendritic-Cell-Mediated Inflammatory Responses

Graphical Abstract



Authors

Emmanuelle Godefroy, Anne Gallois, ..., Sergio Trombetta, Nina Bhardwaj

Correspondence

nina.bhardwaj@mssm.edu

In Brief

Godefroy et al. now demonstrate that matrix metalloproteinase-2 (MMP-2) directly interacts with and activates dendritic cells (DCs) via Toll-like receptor-2. MMP-2-exposed DCs upregulate OX40L, promoting type 2 polarization both in vitro and in vivo. This may represent a key immune regulatory mechanism involved in a variety of inflammatory disorders.

Highlights

MMP-2 is shown to be a ligand for the Toll-like receptor 2

MMP-2-dependent TLR2 triggering induces type 2 polarization via OX40L upregulation

MMP-2 triggers TLR2 independently of its usual coreceptors, i.e., TLR1, 6, and 4

MMP-2 polarizes T_H2 immune responses in vivo in a TLR2-dependent manner

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Activation of Toll-like Receptor-2 by Endogenous Matrix Metalloproteinase-2 Modulates Dendritic-Cell-Mediated Inflammatory Responses

Emmanuelle Godefroy,[1,7] Anne Gallois,[1,7] Juliana Idoyaga,[1,2,3] Miriam Merad,[1] Navpreet Tung,[1] Ngozi Monu,[4] Yvonne Saenger,[1] Yichun Fu,[1] Rajesh Ravindran,[5] Bali Pulendran,[5] Francine Jotereau,[6] Sergio Trombetta,[4] and Nina Bhardwaj[1,*]

[1]Mount Sinai School of Medicine, Tisch Cancer Institute, New York, NY 10029, USA
[2]Laboratory of Cellular Physiology and Immunology and Chris Browne Center for Immunology and Immune Diseases, The Rockefeller University, New York, NY 10065, USA
[3]Department of Microbiology and Immunology, Stanford University School of Medicine, Stanford, CA 94305, USA
[4]New York University Langone Medical Center, Cancer Institute, New York, NY 10016, USA
[5]Emory Vaccine Center, Department of Pathology, Emory University, Atlanta, GA 30322, USA
[6]INSERM U892, 44093 Nantes, France
[7]Co-first author
*Correspondence: nina.bhardwaj@mssm.edu
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SUMMARY

Matrix metalloproteinase-2 (MMP-2) is involved in several physiological mechanisms, including wound healing and tumor progression. We show that MMP-2 directly stimulates dendritic cells (DCs) to both upregulate OX40L on the cell surface and secrete inflammatory cytokines. The mechanism underlying DC activation includes physical association with Toll-like receptor-2 (TLR2), leading to NF-κB activation, OX40L upregulation on DCs, and ensuing T_H2 differentiation. Significantly, MMP-2 polarizes T cells toward type 2 responses in vivo, in a TLR2-dependent manner. MMP-2-dependent type 2 polarization may represent a key immune regulatory mechanism for protection against a broad array of disorders, such as inflammatory, infectious, and autoimmune diseases, which can be hijacked by tumors to evade immunity.

INTRODUCTION

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases. They can degrade extracellular matrix proteins, participate in the cleavage of cell-surface receptors and chemokines or cytokines, and modulate cell proliferation, migration, differentiation, and angiogenesis. MMP-2, a member of the gelatinase subfamily of MMPs, participates in the remodeling and resolution of tissue injury (Bian and Sun, 1997; Brooks et al., 1998), embryonic development and morphogenesis (Seshagiri et al., 2003), infection clearance (Atarashi et al., 2011; D'Angelo et al., 2001; Lima et al., 2012), and tumorigenesis (Coussens and Werb, 2002; Egeblad and Werb, 2002; Hanahan and Weinberg, 2000; Liotta et al., 1980; Westermarck and Kähäri, 1999).

We recently identified an unexpected role for MMP-2 in the modulation of innate immune function and in the differentiation of inflammatory T_H2 responses. MMP-2 pre-exposure inhibits interleukin-12 (IL-12) function and upregulates OX40L expression by human dendritic cells (DCs) (Godefroy et al., 2011). Enzymatically active MMP-2 causes degradation of the IFNAR1 chain of the type 1 interferon (IFN) receptor, reducing the ability of IFN-β to enhance transcription of the IL-12p35 subunit through STAT1 phosphorylation (Godefroy et al., 2011). In the absence of IL-12, OX40L now functions as a key costimulatory molecule for the priming of T_H2 cells (Ito et al., 2005; Soumelis et al., 2002). However, the mechanism by which MMP-2 upregulates OX40L is not known, and the role of MMP-2-driven T_H2 cells in vivo has not been determined.

MMP-2 overexpression is observed in certain infections where eradication and control of immunopathogenesis rely on the development of protective type 2 responses (Oakley et al., 2013; Sauer et al., 2013). For instance, various parasites including plasmodium (Lima et al., 2012) and toxoplasma (Lu and Lai, 2013) species can trigger MMP-2 overexpression. As another example, MMP-2 plays a central role during wound healing and repair (Bian and Sun, 1997; Brooks et al., 1998). Inflammatory T_H2 cytokines (tumor necrosis factor alpha [TNF-α], IL-4, and IL-13) have been described as essential components in this process (Chen et al., 2012). Last, MMP-2, which is overexpressed in tumors, promotes cancer progression (Egeblad and Werb, 2002; Hofmann et al., 2000), and our prior studies suggest that this may in part be due to its ability to skew type 2 polarization (Godefroy et al., 2011). These observations suggest that MMP-2, through its ability to drive T_H2 cells, plays a unique role in modulating effector T cell responses.

In this study, we specifically investigated mechanisms by which MMP-2 upregulates OX40L on DCs to drive type 2 polarization. We identified a physiological receptor for MMP-2 on DCs that, upon activation, leads to T_H2 polarization. Therefore, extracellular MMP-2 has the potential to locally affect DCs leading to