MOSPD2 regulates the activation state of αLβ2 integrin to control monocyte migration

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Abstract

Monocytes are innate immune cells that drive the chronicity of various inflammatory diseases, making them an attractive target for therapeutic intervention. Monocyte migration to inflamed tissues involves multiple steps of interaction with the vascular endothelium and the extra-cellular matrix (ECM), a process mainly mediated through conformational transitions in cell surface integrins. We previously described Motile sperm domain-containing protein 2 (MOSPD2) as a surface protein expressed on myeloid cells that is essential for the migration of monocytes and a key regulator of inflammatory disease pathogenesis. Therefore, a possible role for MOSPD2 in regulating adhesion and integrin activation in monocytes was assessed.

Silencing of MOSPD2 expression in THP-1 monocyctic cell line significantly increased the adhesion of monocytes to various ECM ligands of integrins. Employing VB-601, a humanized anti-human MOSPD2 monoclonal antibody, on wild-type THP-1 cells or primary human CD14 monocytes similarly increased cell adhesion to ECM ligands as well as to adhesion molecules. At the molecular level, silencing of MOSPD2 or blocking MOSPD2 using VB-601 led to a transition in integrin αLβ2 conformation into active high affinity binding-form and to the phosphorylation of adhesion-associated pathways. Co-precipitation experiments show that MOSPD2 binds integrin-β2, but not integrin-β1.

Our results reveal a novel regulatory mechanism on monocyte migration in which MOSPD2 governs the balance between monocyte adhesion and release from adhesion molecules and ECM. Targeting MOSPD2 has the potential to treat inflammatory diseases by inhibiting monocyte infiltration into inflamed tissues.

Introduction

Monocyte migration into inflamed tissues perpetuates chronicity in inflammatory diseases

- MOSPD2-deficient mice were protected from the development of CNS inflammation in the EAE model of multiple sclerosis⁴
- Treatment with a mouse anti-MOSPD2 mAb inhibited disease progression in autoimmune inflammatory models for multiple sclerosis, rheumatoid arthritis and colitis
- We have developed VB-601, a humanized mAb that targets human MOSPD2, as a potential therapy for the treatment of autoimmune diseases

Results

Silencing MOSPD2 increases adhesion of monocytes to ECM molecules (THP-1 cell line)

Anti-MOSPD2 mAb VB-601 inhibits migration and increases adhesion of human primary monocytes in a dose-dependent manner

VB-601 increases adhesion of human primary monocytes to diverse ECM and adhesion molecules

Silencing or blocking MOSPD2 in monocytes induces αLβ2 integrin transition to high affinity conformation

Co-Immunoprecipitation discovers binding interaction between MOSPD2 and Integrin-β2

Conclusions

MOSPD2 - “the Mono-walk Protein”, regulates the activation state of β2 integrins - (A) MOSPD2 enables the monocyte to adhere and migrate (B) Treatment with anti-MOSPD2 mAb - VB-601, blocks monocyte ability to detach from the tissue and migrate.

- MOSPD2 - “the Mono-walk Protein”, is a surface protein expressed on myeloid cells
- At the molecular level, MOSPD2 binds integrin β2 to regulate the activation state of αLβ2, thus controlling the dynamic process of adhesion and release from endothelial adhesion molecules and ECM components, which is required for monocyte ‘walking’
- Targeting MOSPD2 via knockout or with the humanized anti-MOSPD2 mAb VB-601 increases adhesion and therefore inhibits migration of monocytes
- Targeting MOSPD2 is a novel and differentiated approach to regulating inflammation:
  - Current agents are mainly directed against lymphocytes, while MOSPD2 regulates monocytes
  - MOSPD2 mAb arrests monocyte from ‘walking’ to inflamed tissues through a distinct mechanism of chemokines and their cognate receptors, thereby overcoming the broad redundancy of these pathways
- Proof of concept demonstrated:
  - Promising results in preclinical models of MS, RA, IBD, NASH
  - VB-601 was found to inhibit ex-vivo the migration of monocytes isolated from patients with MS, RA, PsA, Ulcerative Colitis and Crohn’s disease
- VBL’s lead candidate VB-601 is a humanized IgG1 mAb developed as subcutaneous formulation for treatment of people with chronic immune-inflammatory diseases. VB-601 is being advanced toward first-in-human study, expected 2H 2022