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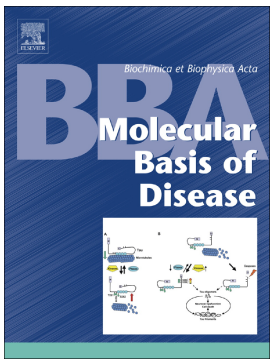

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Protective C allele of the single-nucleotide polymorphism rs1335532 is associated with strong binding of Ascl2 transcription factor and elevated CD58 expression in B-cells

Nikita A. Mitkin[1], Alisa M. Muratova[1,2], Kirill V. Korneev[1,2], Vsevolod V. Pavshintsev[2], Konstantin A. Rumyantsev[3], Murad S. Vagida[4], Aksinya N. Uvarova[1,2], Marina A. Afanasyeva[1], Anton M. Schwartz[1], Dmitry V. Kuprash[1,2,*]

[1] Laboratory of Intracellular Signaling in Health and Disease, Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, Russia

[2] Biological Faculty, Lomonosov Moscow State University, Moscow, Russia

[3] Laboratory of Fundamental Research, Moscow Clinical Scientific Center, Moscow, Russia

[4] National Research Center for Hematology, Moscow, Russia

* Corresponding author. Laboratory of Intracellular Signaling in Health and Disease, Engelhardt Institute of Molecular Biology Russian Academy of Sciences, Vavilov str. 32, 119991 Moscow, Russia. Phone: +7-499-135-9770; E-mail: kuprash@eimb.ru

Abstract

CD58 is expressed on the surface of antigen-presenting cells, including B-cells, and provides co-stimulation to regulatory T-cells (Treg) through CD2 receptor binding. Tregs appear to be essential suppressors of tissue-specific autoimmune responses. Thereby, CD58 plays protective role in multiple sclerosis (MS) and *CD58* was identified among several loci associated with MS susceptibility. Minor (C) variant of the single-nucleotide polymorphism (SNP) rs1335532 is associated with lower MS risk according to genome-wide association studies (GWAS) and its presence correlates with higher *CD58* mRNA levels in MS patients. We found that genomic region containing rs1335532 has enhancer properties and can significantly boost the *CD58* promoter activity in lymphoblast cells. Using bioinformatics and pull-down assay we found that the protective (C) rs1335532 allele created functional binding site for ASCL2 transcription factor, a target of the Wnt signaling pathway. Both in B-lymphoblastoid cell lines and in primary B-cells, as well as in a monocytic cell line, activation of Wnt signaling resulted in an increased CD58 promoter activity in the presence of the protective but not the risk allele of rs1335532, whereas ASCL2 knockdown abrogated this effect. In summary, our results suggest that ASCL2 mediates the protective function of rs1335532 minor (C) allele in MS.

Keywords: Antigen-presenting cells, costimulation, CD2, monocytes, Treg cells, Wnt signaling pathway

1. Introduction

CD58, also known as lymphocyte function-associated antigen 3 (LFA-3), is expressed on the surface of professional antigen-presenting cells (APC), including B-cells [1], and facilitates their adhesion to most types of T-cells through binding to their counterreceptor CD2 [2]. This interaction strengthens immune recognition and facilitates direct transmission of co-stimulatory signals [3]. CD2 expression is required