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Gal-3 regulates the capacity of dendritic cells to promote NKT-cell-induced liver injury

Vladislav Volarevic[1], Bojana Simovic Markovic[1], Sanja Bojic[1], Maja Stojanovic[1], Ulf Nilsson[2], Hakon Leffler[3], Gurdyal S. Besra[4], Nebojsa Arsenijevic[1], Verica Paunovic[5], Vladimir Trajkovic[5] and Miodrag L. Lukic[1]

[1] Centre for Molecular Medicine and Stem Cell Research, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia
[2] Centre for Analysis and Synthesis, Department of Chemistry, Lund University, Lund, Sweden
[3] Section MIG, Department of Laboratory Medicine, Lund University, Lund, Sweden
[4] School of Biosciences, University of Birmingham, Birmingham, UK
[5] Institute for Microbiology and Immunology, School of Medicine, University of Belgrade, Belgrade, Serbia

Galectin-3 (Gal-3), an endogenous lectin, exhibits pro- and anti-inflammatory effects in various disease conditions. In order to explore the role of Gal-3 in NKT-cell-dependent pathology, we induced hepatitis in C57BL/6 WT and Gal-3-deficient mice by using specific ligand for NKT cells: α-galactosylceramide, glycolipid Ag presented by CD1d. The injection of α-galactosylceramide significantly enhanced expression of Gal-3 in liver NKT and dendritic cells (DCs). Genetic deletion or selective inhibition of Gal-3 (induced by Gal-3-inhibitor TD139) abrogated the susceptibility to NKT-cell-dependent hepatitis. Blood levels of pro-inflammatory cytokines (TNF-α, IFN-γ, IL-12) and their production by liver DCs and NKT cells were also downregulated. Genetic deletion or selective inhibition of Gal-3 alleviated influx of inflammatory $CD11c^+CD11b^+$ DCs in the liver and favored tolerogenic phenotype and IL-10 production of liver NKT and DCs. Deletion of Gal-3 attenuated the capacity of DCs to support liver damage in the passive transfer experiments and to produce pro-inflammatory cytokines in vitro. Gal-3-deficient DCs failed to optimally stimulate production of pro-inflammatory cytokines in NKT cells, in vitro and in vivo. In conclusion, Gal-3 regulates the capacity of DCs to support NKT-cell-mediated liver injury, playing an important pro-inflammatory role in acute liver injury.

Keywords: Dendritic cells · Gal-3 · Hepatitis · NKT cells · Regulatory T (Treg) cells

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Introduction

Galectin-3 (Gal-3) is involved in several biological processes including regeneration, cell migration, as well as inflammatory and immune responses [1]. In the liver, Gal-3 was recently found to regulate hepatic progenitor cell expansion during liver injury [2]. It is also established that Gal-3 plays an important role in metabolic and inflammatory responses of this organ to various environmental challenges [3, 4]. Although it is well known that Gal-3, which is highly expressed in activated $CD4^+$ and $CD8^+$ T cells, macrophages, DCs, and natural killer (NK) cells, functions

Correspondence: Dr. Vladislav Volarevic
e-mail: drvolarevic@yahoo.com

