Serbian Biochemical Society
Ninth Conference

"Diversity in Biochemistry"

Proceedings

Serbian Biochemical Society

Proceedings

Editor: Ivan Spasojević
Cover design: Zoran Beloševac
Publisher: Faculty of Chemistry, Serbian Biochemical Society
Printed by: Colorgrafx, Belgrade

Serbian Biochemical Society
Ninth Conference

with international participation

University of Belgrade – Kolarac Endowment
14-16.11.2019. Belgrade, Serbia

"Diversity in Biochemistry"

Suppresion of type 1 diabetes in mice by oral treatment with ATRA- and TGF-β-loaded microparticles

Ivan Koprivica[1*], Dragica Gajić[1], Tamara Saksida[1], Eugenio Cavalli[2], Dominick Auci[3], Sanja Despotović[4], Nada Pejnović[1], Stanislava Stošić-Grujičić[1], Ferdinando Nicoletti[5], Ivana Stojanović[1]

[1]Department of Immunology, Institute for Biological Research "Sinisa Stankovic", University of Belgrade, Belgrade, Serbia
[2]IRCCS Bonino Pulejo, Messina, Italy
[3]TherapyX, Buffalo, USA
[4]Institute of Histology and Embryology, School of Medicine, University of Belgrade
[5]Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy

[*]e-mail: ivan.koprivica@yahoo.com

Type 1 diabetes (T1D) is an autoimmune disease in which a strong inflammatory response causes the death of pancreatic β-cells. Attempts to induce anti-inflammatory/regulatory immune mechanisms that would attenuate disease progression have shown little or no beneficial effects. We introduced microparticles (MPs) loaded with Transforming Growth Factor β (TGF-β) and All-Trans Retinoic Acid (ATRA), both well-known stimulators of T regulatory cell (Treg) differentiation and stabilization. Male C57BL/6 mice were treated with multiple low doses of streptozotocin for T1D induction, and with vehicle, empty MPs, or ATRA- and TGF-β-loaded MPs for 10 days (every other day). Both T1D incidence and immune cell infiltration into the pancreatic islets was lower in ATRA/TGF-β-treated mice. In Peyer's patches (PP), ATRA/TGF-β up-regulated tolerogenic dendritic cells (tolDC). Additionally, IL-1β expression was reduced in PP, as was the ratio of iNOS/Arginase expression, reflecting a less inflammatory environment. This was accompanied by a reduced proportion of Th1 and Th17 cells and up-regulation of Treg. IL-17 expression within $CD4^+$ T cells from PP was also lower, and was accompanied by down-regulation in RORγt expression (key transcription factor of IL-17). The situation in the pancreatic lymph nodes (PLN) was similar to PP regarding the down-regulation of Th1 cells. Additionally, in response to ATRA/TGF-β treatment, the proliferation of T effector cells was reduced in PLN, while Treg proliferated more, and several crucial markers of Treg suppressive activity were increased. In conclusion, ATRA and TGF-β released from MPs successfully ameliorated T1D by potentiating tolDC and Treg responses and inhibition of Th1 cell differentiation in the draining lymph nodes, thus blocking the entrance of immune cells into the pancreatic islets and protecting β-cells from further destruction.

Acknowledgements

Supported by Ministry of Education, Science and Technological Development, Republic of Serbia (grant #173013).