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Inhibitory binders derived from ABD-domain scaffold targeting human IL-17RA receptor as a non-immunoglobulin alternative for modulation of Th17-mediated pro-inflammatory axis

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Interleukin 17 (IL-17) and its cognate receptor (IL-17RA) play a crucial role in Th17 cells-mediated pro-inflammatory pathway and pathogenesis of several autoimmune disorders including psoriasis. Psoriasis is a chronic inflammatory skin disease with prevalence up to 3% worldwide, it is characterized by hyperplasia of the epidermis, infiltration of leukocytes into both dermis and epidermis and dilation and growth of blood vessels. IL-17 is mainly produced by Th-17 helper cells and via binding to its receptor, mediates IL-17-driven cell signaling in keratinocytes. This work was aimed to generate novel protein binders of IL-17RA that will prevent from binding of IL-17A cytokine to this receptor expressed on the surface of keratinocytes. To this goal, we used a high-complex combinatorial library derived from scaffold of albumin-binding domain (ABD) of streptococcal protein G and ribosome display selection, to yield a collection of ABD-derived high-affinity ligands of human IL-17RA called ARS binders. From 67 analysed ABD variants, 7 different sequence families were identified. Representatives of these groups competed with human IL-17A for binding to recombinant IL-17RA receptor as well as with IL-17RA-IgG chimera as tested in ELISA. Five ARS variants bind to IL-17RA-expressing THP-1 and Raji cells, as tested by flow cytometry. The four variants exhibited high-affinity binding in nanomolar range to human keratinocyte HaCAT cells, as measured using Ligand Tracer Green Line system. Thus, we identified several ARS inhibitory variants with a blocking potential that will be further tested for their immunomodulatory function.

Biography

Marie Hlavnickova is a PhD candidate at the 1st Faculty of Medicine, Charles University in Prague, Czech Republic. She is a Member of the Laboratory of Ligand Engineering at the Institute of Biotechnology CAS, v.v.i., Czech Republic. Her research topic is focused on the development of inhibitory protein binders derived from scaffold of albumin-binding domain and suppressing function of cytokine receptors modulating IL-23/Th17 pro-inflammatory axis.

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