5TH SCIENTIFIC MEETING

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BENCH TO BEDSIDE TRANSITION FOR PHARMACOLOGICAL REGULATION OF NRF2 IN NON-COMMUNICABLE DISEASES (BENBEDPHAR)

TRANSLATING NRF2 RESEARCH INTO CLINICAL PRACTICE

University of Graz | Austria

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Venue
Meerscheinschlössl
Mozartgasse 3 | 8010 Graz | Austria

Local Organizers

Christina Morgenstern | Brigitte Winklhofer-Roob | University of Graz

Christina Unteregger | Harald Sourij | Medical University of Graz

P-04: Nrf2 down-regulation mediates pro-inflammatory effects of novel synthetic AhR ligands

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Aryl hydrocarbon receptor (AhR) and nuclear factor erythroid 2-related factor 2 (Nrf2) are transcription factors involved in the regulation of drug-metabolizing enzymes. Moreover, both of them can modulate the immune response. AhR activation can lead to the activation or inhibition of specific immune cells, especially at barrier tissues such as skin, lungs, gut-associated lymphoid tissue, etc. Nrf2 was also shown to play a role in the anti-inflammatory process by inhibiting the recruitment of inflammatory cells and regulating anti-inflammatory gene expression. Nrf2 gene transcription can be directly modulated by AhR activation, as the Nrf2 promoter possesses three xenobiotic response element-like elements that were shown to be able to bind AhR in response to a known Ahr agonist TCDD.
In this study, we explored the effect of newly synthetized AhR agonists (indole-based derivatives) termed C46 and B19 on mouse macrophage differentiation. Peritoneal cells were incubated with 1.5 μM of AhR ligands for 24 h, after which the proinflammatory M1 ($F4/80^+CD40^+$) and anti-inflammatory M2 ($F4/80^+CD206^+$) macrophage phenotype was determined by flow cytometry. The results indicate that both compounds push macrophages towards a more inflammatory state, as C46 tripled the M1/M2 ratio in culture, while B19 doubled it, compared to the DMSO (0.005% v/v) control. Additionally, both mRNA and protein expression of cytochrome P450 1A1 (CYP1A1), commonly used as an indicator of AhR activation, were also increased by C46 and B19. Finally, western blot analysis showed that both of the tested AhR ligands downregulated the protein expression of Nrf2 within the treated cells.
These results suggest that AhR activation and subsequent Nrf2 down-regulation by the newly synthesized AhR agonists C46 and B19 boosted the proinflammatory phenotype of mouse peritoneal macrophages.

Ivan Koprivica is a Research Associate at the Department of Immunology, Institute for Biological Research “Siniša Stanković” – National Institute of the Republic of Serbia, University of Belgrade, Serbia, where he has been a part of the Diabetology Research Laboratory since 2016. His main research interest is focused on identifying cellular and molecular mechanisms responsible for Type 1 Diabetes (T1D) development in mice, as well as pharmacological modulation of experimental T1D, using a range of bioactive compounds in order to treat T1D autoimmunity. Recently, his research interests have also included investigating the role of gut immune cells in T1D development, as well as exploring the immunomodulatory potential of several novel synthesized AhR ligands.