Synergistic modulation of AhR of Arid5a: A new therapeutic strategy at transcriptional and post-transcriptional levels for multiple sclerosis

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Background: Problem Statement: Multiple sclerosis (MS) is a neurodegenerative disease affecting millions globally, causing varying disabilities. While studies at transcriptional level have identified therapeutic targets for MS, recent post-transcriptional studies highlight the role of RNA-binding proteins (RBPs) in MS pathogenesis by modifying the pro-inflammatory transcriptome. However, linking proteins from these two regulatory levels as a therapeutic strategy for MS is rarely explored. Activation of the Aryl hydrocarbon receptor (AhR) has been shown to ameliorate MS, and AT-rich interactive domain-containing protein 5a (Arid5a) is essential for MS pathogenesis by stabilizing Il6, Stat3, and OX40 mRNAs. This study aims to identify a small molecule that differentially modulates these proteins. Methodology & Theoretical Orientation: In silico methods created a 3D model of mouse Arid5a to screen for modulatory molecules. These molecules were tested for association with Arid5a and AhR using RNA-protein interaction and luciferase assays to assess promoter and 3'UTR activity. mRNA and protein were measured by real-time PCR, immunoblotting, and ELISA. Cell populations were analyzed via flow cytometry and sorting. The anti-inflammatory potential of the candidate molecule was tested in a mouse model of MS (EAE) and confirmed in an LPS-induced septic shock model. Findings: An in silico and in vitro approach identified the synthetic pyrazole compound 3-DFP as an AhR agonist that induces its downstream gene expression while reducing that of Arid5a target genes in Th1, Th17, and macrophages. Interestingly, 3-DFP inhibited Arid5a stabilizing function on the 3'UTR of target mRNAs. In EAE, 3-DFP reduced disease severity, CD4+IL-17+ cells, IL-6, and TNF-α, while increasing CD4+FoxP3+ cells. Additionally, EAE amelioration was linked to reduced CD4+OX40+ and CD4+CD45+ cells in the CNS. 3-DFP also reduced mortality, alleviated severity, lowered pro-inflammatory cytokines, and alleviated tissue injury. In conclusion, our findings suggest that differential modulation of AhR and Arid5a is a promising therapeutic strategy for MS.

Biography

He completed his postgraduate studies and worked as a senior researcher at some of the world's leading universities in Japan. Throughout his career as a Research Center Director, Associate Professor, Consultant, and Researcher, he has conducted several studies in the field of immunology, focusing on inflammation and immune regulation. Additionally, he has carried out a series of studies in oncology. These research efforts have resulted in highly ranked publications and the registration of international patents. Notably, some of these patents were the first to introduce specific Arid5a inhibitors, providing evidence for the feasibility of blocking this protein as a therapeutic strategy at the post-transcriptional level.