Therapeutic Effects of Benzoylacetonitrile on Microglia Activation in Multiple Sclerosis

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Background: Multiple Sclerosis (MS) is an autoimmune disease of the central nervous system (CNS). Pathogenic T cells, such as Th1 and Th17, infiltrate the CNS, resulting in neuroinflammation, demyelination and axonal damage. Th1 activates microglia (MG) in the CNS and Th17 acts as a chemokine to recruit immune cells into the CNS. MG is a resident immune cell in the CNS and its activation is associated with destruction of myelin and secretion of inflammatory cytokines such as IL-12, IL-23 and IL-1β. IL-12 and IL-23 are important for Th1 and Th17 differentiation and reactivation, respectively. IL-1β is a key mediator of the inflammatory response. Benzoylacetonitrile (BTN) has been shown to reduce disease severity in mouse model of MS and reduce Th1 and Th17 differentiation in vitro. However, the effects of BTN on MG are unknown, and this study was aimed to investigate the effects of BTN on MG activation in vitro. We hypothesize that BTN can suppress MG activation and decrease the production of inflammatory cytokines.

Methods: Primary MG were pretreated with BTN at concentration of 200μM or 300μM for 2 hours or with DMSO (vehicle), followed by lipopolysaccharide (LPS) 100ng/ml stimulation for 1.5 or 3 hours. RNA was isolated from MG and mRNA expression levels of IL-12, IL-23, IL-1β were measured using Q-PCR.

Results: Our results showed that BTN suppressed MG activation and reduced inflammatory cytokine production. The mRNA expression levels of IL-12, IL-23, and IL-1β in LPS and BTN-treated MG were significantly lower than LPS-treated MG.

Conclusion: This study demonstrated that BTN was able to suppress MG expression of inflammatory cytokines in vitro, suggesting that BTN exhibits immunomodulatory effects on MG activation in vitro. BTN has a potential to attenuate neuroinflammation in MS through the reduction of inflammatory cytokines.

General Excellence Award

Angela Zhao is a third-year medical student, who is currently interested in neurology and family medicine.

"Research has been a valuable experience during which I was able to gain more knowledge about the immune system and how modulation of the inflammatory response can affect disease progression. This experience emphasized the integral role research plays in advancing medicine and patient care. I am looking forward to continuing research during medical school and incorporating research in my future medical career."

EPHA2 is a Potential Target for the Treatment of NF2-/- Vestibular Schwannoma

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Neurofibromatosis type 2 (NF2) is an autosomal dominant cancer predisposition syndrome characterized by the development of bilateral vestibular (VS) and spinal schwannomas secondary to loss of heterozygosity of NF2 in Schwann cells or their precursors. While these tumors are largely benign, they can cause considerable morbidity due to compromised auditory, vestibular, facial, and vertebral nerve function. This may result in deafness, vertigo, facial muscle weakness, chronic neuropathic pain, and even death. There are currently no pharmacotherapies for VS, and surgical resection remains the standard of care, which is associated with significant morbidity. Thus, there is an urgent need to develop pharmaceutical approaches to halt or reverse the progression of tumor growth in NF2 patients who develop VS. Our lab previously identified the receptor tyrosine kinase inhibitors brigatinib and dasatinib as potentially efficacious agents for the treatment of VS and demonstrated that both agents targeted the Ephrin A2 receptor (EPHA2). EPHA2 is a transmembrane receptor tyrosine kinase that is involved in cell contact-mediated motility, adhesion, and migration. Additionally, EPHA2 modulates axon guidance, and synaptogenesis in developing brain. Here we demonstrate that EPHA2 expression is increased in NF2-/- Schwann cells and NF2-/- cancers. We identify ponatinib, a receptor tyrosine kinase inhibitor targeting ABL1 that is FDA-approved for CML, as an additional agent that targets EPHA2. We demonstrate that ponatinib treatment impairs the viability of both human and murine NF2-/- Schwann cells in vitro and decreases EPHA2 protein expression. Accordingly, pharmacologic, and siRNA-mediated inhibition of EPHA2 also impaired the growth of human NF2-/- Schwann cells in vitro. Lastly, we demonstrate that both ponatinib and EPHA2 inhibition induce morphological changes in NF2-/- Schwann cells. Our findings suggest that ponatinib or the direct targeting of EPHA2 may be efficacious for the treatment of NF2-associated vestibular schwannoma. Future in vivo efficacy studies are warranted.

Marvella Bayh Memorial Scholarship

Kéyana A. Foster is a third-year medical student, who is currently interested in otolaryngology. She attributes her interest to her love for head/neck anatomy and oncology.

"I want to be a physician who can treat a patient in all aspects of their care. To me, that means translating groundbreaking research from the lab to the clinic/OR space. That was my most important takeaway from my summer research experience. We were doing the work to find new methods of treating a patient's vestibular schwannomas by targeting cancer cells with currently FDA approved chemotherapies. In addition to that, the numerous skills I gained as a researcher is something I will take with me throughout my entire career. I am tremendously grateful for the opportunity to learn from my mentors during this project".