Design and Synthesis of Immune Signaling Modulators

by

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Thesis Directed by Professor Hang Yin

Abstract

The immune system is comprised of tissue, cells, and chemicals that have been evolutionarily developed to protect ourselves from simple pathogenic components such as viruses and allergens, and more complex invading organisms such as bacteria, fungi, and parasites. This network of tissue, cells, and chemicals can even identify and remove compromised host cells, such as cancer cells. The components of the immune system can be organized into two categories: the innate immune system and adaptive immune system. Components of the innate immune system can be further organized into two categories: physical barriers and leukocytes. Physical barriers, such as skin, hair, epithelial cells, stomach acid, gut flora, and mucus membranes are the body's first line of defense against invading pathogens. If the physical barriers of the innate immune system are breached, leukocytes are freely patrolling the body, ready to coordinate an immune response to any newfound pathogens. This is often achieved by phagocytic cells capable of antigen presentation, which in short, is how the innate immune system engages the adaptive immune system to generate immunological memory. Toll-like receptors (TLRs) exist at this interface between the innate and adaptive immune system. These receptors exist on either the cell surface or within endosomal compartments of monocytes, macrophages, dendritic cells, mast cells, B cells, and T cells. Activation of TLRs triggers a signaling cascade that results in the activation of several transcription factors. Depending on the transcription factor, either proinflammatory cytokines or type-1 interferons (IFNs) are produced.

Proinflammatory cytokines are important in the recruitment and activation of immune cells, further amplifying the immune response. IFNs can go on to bind IFN receptors, activating the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. One key outcome of this activation is the upregulation of inducible nitric oxide synthase (iNOS) and the subsequent production of nitric oxide, a key molecule involved in the recruitment of immune cells with additional microbicidal properties. Within this thesis is described the design and synthesis of small molecules capable of 1) inhibiting the JAK/STAT1 signaling pathway and 2) synergistic agonism of TLR8 signaling in the presence of single-stranded ribonucleic acids (ssRNA).