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Editorial

Toll-like Receptor Agonists Induce Anti-Viral Responses that Inhibit HIV-1 Replication

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Innate immune responses represent the first line of defense against invading microbes including viruses, bacteria and fungi. These responses are mediated by several immune cell populations following activation of specific receptors called "pattern recognition receptors" (PRR) [1-3]. These PRR bind distinct "pathogen-associated molecular patterns" (PAMPs) present on microbes, triggering a rapid signaling cascade in the cell that leads to the production of inflammatory mediators and anti-viral molecules [4,5]. Each PRR binds a specific ligand such as double- or single-stranded RNA or DNA, or bacterial lipopolysaccharide, allowing specificity of the response according to the type of invading pathogen. Some of the best studied PRR are the toll-like receptors (TLR) that are present on myeloid and lymphoid cells, and are located either on the cell membrane or within endosomal vesicles [3,4,6]. TLR, of which there are more than a dozen well-characterized receptors, become activated once bound to ligand. Activation of the TLR leads to down-stream signaling events designed to rapidly induce expression of inflammatory mediators and innate immune molecules designed to thwart an infection [7-10]. In addition, TLR activation leads to the up-regulation of surface receptors that promote interactions among immune cells leading to induction of acquired immune responses [11-13]. These responses likely enhance the adaptive immune responses mediated by the T and B cell compartments of the immune system, thus ensuring a long-lasting, durable, and memory immune response to the pathogen.

The use of agonists to endosomal TLR have been studied for the potential to mediate anti-viral responses in general, and anti-human immunodeficiency virus type 1 (HIV-1) responses in particular. Endosomal TLR respond primarily to viral nucleic acids at the time of initial infection [14]. Activation of these TLR induces expression of type I interferons and interferon-stimulated genes (ISG) along with additional anti-viral factors [4,5]. Some of these factors include interferon (IFN) -alpha, IFN-beta, IFN-gamma, as well as the interferon-induced proteins such as myxovirus resistance gene (MxA) [15], 2'-5' oligoadenylate synthase (OAS) [16], double-stranded RNA-dependent protein kinase R (PKR) [17,18], ribonuclease L (RNAL) [16] and its endogenously-expressed and HIV-induced suppressor protein termed ribonuclease L inhibitor (RLI) [19]. Two additional HIV-1-specific restriction factors that impart potent HIV inhibitory activity include apolipoprotein B mRNA-editing catalytic 3G (Apobec3G) [20], and SAM-domain and HD-domain containing protein 1 (SAMHD1) [21]. All of these proteins have been shown to be critically important to the antiviral innate immune response.

We studied the anti-HIV-1 activity of several TLR agonists and have found that these compounds can potently inhibit HIV-1 replication in primary cultures of peripheral blood mononuclear cells (PBMC). Our initial studies focused on a TLR7 agonist, gardiquimod, that was shown to effectively inhibit HIV-1 replication even when added to PBMC 48 hours after HIV-1 infection [7]. We determined that gardiquimod, an imidiazoquinoline compound, functioned to inhibit HIV-1 replication by two distinct mechanisms. This compound activated TLR7 and induced high levels of IFN-alpha in PBMC. By blocking the MyD88 adaptor protein with a peptide inhibitor, we showed that IFN-alpha production was blocked, and some, but not all, of the anti-HIV activity was reversed. However, because of its molecular structure, gardiquimod also functioned as a reverse transcriptase inhibitor, blocking HIV-1 reverse transcriptase in newly infected cells, and effectively stopping the spread of infection. Our current studies focus on defining the intracellular signaling pathways induced by agonists to other endosomal TLR, including TLR3, TLR8 and TLR9. It is likely that these agonists, similar to gardiquimod, can function to inhibit HIV-1 replication by both TLR-mediated and non-TLR-mediated mechanisms. For example, because these agonists mimic both single- and double-stranded nucleic acids, it is likely that they can activate non-TLR nucleic acid sensors in the cytoplasm, and activate anti-viral mechanisms by bypassing TLR activation. Such agonists would have greater utility in therapeutic applications if they could prevent the inflammatory cytokine and chemokine responses that also recruit additional immune cells to the site of infection.

Moreover, because TLR agonists have been shown to augment vaccine responses to HIV-1 peptides in both mice [22,23] and non-human primates [24,25], it is possible that these compounds could have a combined therapeutic use to enhance T and B cell responses to HIV-1 vaccines, while at the same time, induce

protective innate immune responses in HIV-exposed individuals. If designed appropriately, TLR agonists, or other compounds that would be capable of triggering anti-viral immune responses, could function to induce anti-viral responses while avoiding the induction of potentially harmful inflammatory responses.

In sum, the use of TLR agonists and other small molecules that mimic viral genomes, may hold great promise as novel anti-viral therapeutics to inhibit HIV-1 infection and replication. Whether these compounds could be developed as microbicides to prevent HIV transmission across mucosal tissues at the initial point of entry, or as post-exposure therapeutic agents, is not clear at this point. However, harnessing innate immune responses against viral infection is one area that deserves to be developed further in the fight against HIV-1 infection.

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