Therapeutic Modulation of Host Arginine-Associated Metabolic Pathways Disrupts Viral and Host Processes Required for Pathogen Replication and Manifestation of Disease

Awardee: Augusto C. Ochoa
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Awardee Institution: Louisiana State University Health Sciences Center
Co-authors: Timothy P. Foster, Maria Dulfary Sanchez
Co-authors institution: Louisiana State University Health Sciences Center

Since their inception five decades ago, most antivirals have been engineered to disrupt a single viral process or protein that is essential for viral replication. The nature of this approach has limited the overall therapeutic effectiveness and applicability of current antivirals due to restricted viral specificity, a propensity for development of drug resistance, and an inability to control deleterious host-mediated inflammatory responses. To overcome these limitations, we have developed a host-targeted antiviral, peg-ArginaseI (peg-ArgI), rather than pursuing traditional pathogen-targeted approaches. peg-ArgI modulates arginine-associated metabolic pathways that are essential for replication of most intracellular pathogens and for induction of inflammation-associated disease processes. RNASeq whole transcriptome analysis indicated that peg-ArgI treatment of primary epithelia induces a cellular environment that is not conducive for viral replication. peg-ArgI treatment down-regulated cellular processes required for efficient viral genomic replication and spread, while up-regulating transcription of cell-intrinsic antiviral processes. Consistent with these findings, unlike current antivirals that are specific for a given pathogen, peg-ArgI ablated productive replication of a diverse range of important human pathogens including, Chlamydia, HSV-1, HSV-2, Adenovirus, RSV, Parainfluenza, and Influenza. Whole viral transcriptome analysis, as well as subsequent biological and virological assays, indicated that unlike current drugs that target a single viral replicative process, peg-ArgI exerts multiple mechanisms that collectively inhibit HSV-1 replication and transmission. Indeed, other than viral entry, every aspect of the HSV-1 lifecyle was affected. peg-ArgI inhibited HSV-1 genomic replication, select viral protein expression, viral assembly, viral envelopment, intracellular transport, and cell-to-cell spread. In addition, host transcriptome analysis indicated that peg-ArgI could suppress some virus-induced host processes that are associated with development of disease (*e.g.* pathological inflammation and vascularization). In congruence with these results, in two rabbit eye models of virus-induced ocular keratitis, peg-ArgI treatment resolved deleterious inflammation and severe ocular disease processes initiated by either HSV-1 or Adenovirus infection. Collectively, this data demonstrates the viability of therapeutically targeting host metabolic pathways to broadly inhibit replication and transmission of a broad-range of viral pathogens, while simultaneously suppressing deleterious host-mediated inflammatory responses.