Utilizing Autophagy to Control HIV and Tuberculosis

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In San Diego County, the *Mycobacterium tuberculosis* (Mtb) case rate is more than twice as high as the rest of the US and the annual incidence of HIV-Mtb co-infection has remained stable despite the decline of both Mtb and HIV cases. Furthermore, the prevalence of multi-drug resistant (MDR)-Mtb and the extensively-drug resistant (XDR) Mtb is likely to increase. This, combined with the unwanted pharmacologic interactions between the drugs used to treat Mtb and HIV complicate therapy for persons co-infected, demonstrates a necessity to develop new drugs to combat HIV-Mtb co-infection. One mechanism by which Mtb and HIV subvert the immune system to establish a persistent and latent infection is through the inhibition of macroautophagy (hereafter referred to as autophagy). Autophagy is a natural degradation pathway that occurs in cells whereby compartments termed autophagosomes engulf cytoplasmic constituents such as sub-cellular organelles and microbial pathogens, including viruses and bacteria, and targets them for degradation using lysosomes. Both HIV and Mtb block autophago/lysosome biogenesis, enabling their intracellular survival and persistence in macrophages.

In the proposed study, we will examine the regulation of autophagy by HIV and Mtb, and on the survival and persistence of both pathogens within primary macrophages and ask whether it is possible to subvert autophagy to control HIV and Mtb infection? We will also identify the molecular processes by which the active metabolite of vitamin D, interferon-gamma and interleukin-1-beta induce autophagy and inhibit HIV and Mtb infection of macrophages while developing our understanding of how the endo/lysosomal system of macrophages is converted into providing a niche environment for controlled replication by Mtb and HIV. We will also identify pharmacological agents that both induce autophagic flux and inhibit both HIV and Mtb in macrophages.

The methodology that we will employ will involve the isolation and infection of macrophages with HIV and/or Mtb followed by treatment with the pharmacological agent being studied. HIV and Mtb replication will be monitored using conventional methods and the role of autophagy in altering HIV and Mtb infection will be assessed as part of each specific aim using techniques that will analyze the formation and turnover of autophagosomes and thus autophagic flux. We will also address the specific roles of autophagy proteins and immune modulators such as cathelicidin as well as monitoring downstream phosphorylation events. The role of HIV proteins in modulating autophagy will be assessed using deletion mutants and recombinant proteins.

We expect to elucidate how HIV modulates autophagy and, using this information, demonstrate that autophagy-inducing drugs inhibit both HIV and Mtb during co-infection and remain active against strains of MDR-Mtb and XDR-Mtb. Therefore, results from this research will not only significantly contribute to the understanding of HIV-Mtb co-infection, but also have the potential to develop a novel approach to improve significantly the treatment of persons dually infected with HIV and Mtb.