Autophagy protects against active tuberculosis by suppressing bacterial burden and inflammation


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AUTHOR SUMMARY

Degradation of cellular components by autophagy is required for maintaining homeostasis in diverse organisms, and knowledge of its participation in immunity is expanding rapidly (1). Autophagy acts as a cell-autonomous defense system against Mycobacterium tuberculosis in cultured macrophages (2), but its role in vivo is unknown. Here, we tested whether autophagy protects against M. tuberculosis infection by using a transgenic mouse with autophagy selectively disabled in myeloid cells. We challenged these mice with an aerosol of virulent M. tuberculosis. A dose-dependent increase in bacterial burden in the lungs and increased lung pathology were observed (Fig. P1A). These findings demonstrate that autophagy is important for control of M. tuberculosis in vivo: By controlling the bacterial burden and by suppressing inflammation, autophagy prevents progression to active tuberculosis. These findings provide fundamental insight into the immunological function of autophagy and reveal its potential to suppress transmission of tuberculosis, which depends on the development of active disease in infected individuals.

The autophagy-defective mice were deficient in the Atg5 protein, a product of one of the many autophagy genes present in mammals. We noticed that the differences in bacterial burden between Atg5-proficient and Atg5-deficient mice were relatively small. This finding prompted us to look beyond the established role of autophagy in vitro in the direct elimination of mycobacteria within macrophages (2). Mice deficient for autophagy in the myeloid lineage showed elements of endogenous inflammation in the lung. Moreover, we found that lungs of infected autophagy-deficient animals displayed higher levels of IL-17 and IL-1α (Fig. P1A). We also observed that the level of IL-1α was elevated even in the uninfected lungs and that IL-1α was secreted at higher levels from cultured Atg5-deficient macrophages (Fig. P1B). Importantly, IL-1α promoted a Th17 response in vitro. Further, mixed immune cells isolated from Atg-deficient mice polarized T cells to produce IL-17 after restimulation with specific M. tuberculosis antigens. This result provides evidence that autophagy acts as a negative regulator of Th17 inflammation (3) and suggests that autophagy suppresses the Th17 response and neutrophilia as potentiators of pathogenesis in tuberculosis.

We could not address the pathology-inducing role of IL-1α in vivo inferred from the above experiments, because IL-1α also confers a key protective role against M. tuberculosis in mice (4). We determined, nevertheless, that the cell-autonomous mechanism of its elevated secretion by Atg-deficient macrophages differed from the mechanisms of increased IL-1β production by autophagy-deficient macrophages reported by others (5). It turned out that the mechanism of IL-1α hypersecretion was independent of constituents of the inflammasome and caspase 1 and instead involved a reactive oxygen species (ROS) and calpain-dependent pathway (Fig. P1C). The process is initiated by accumulation of depolarized mitochondria in autophagy-deficient macrophages (autophagy normally removes defunct mitochondria), resulting in the production of reactive oxygen intermediates that lead to increased IL-1α secretion in a calpain-dependent fashion.

In conclusion, we unveiled a role for autophagy in vivo that protects against tuberculosis and revealed that autophagy...
acts beyond its known role as a cellular antimycobacterial effector mechanism. Autophagy prevents excessive inflammation with features of a Th17 response and neutrophilic infiltration, tissue necrosis, and organ damage, the main features of active tuberculosis and contagious state of the host. The dual roles of autophagy in controlling the bacterial burden and in suppressing the inflammation that leads to active tuberculosis, the latter being a sine qua non for transmission in human populations, make autophagy an attractive target for development of therapeutics.