Int J Basic Sci Med. 2016;1(1):1-3 Editorial

http://ijbsm.zbmu.ac.ir/ doi 10.15171/ijbsm.2016.01

Autophagy, a Possible Future Approach for Tuberculosis Treatment

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Published online 22 June 2016

Please cite this article as follows: Mirzaei N, Sepehri Z, Ghavami S. Autophagy, a possible future approach for tuberculosis treatment Int J Basic Sci Med. 2016;1(1):1-3. doi:10.15171/ijbms.2016.01.

Mycobacterium tuberculosis (Mtb), the most important contributing factor for tuberculosis (TB), is approximately responsible for the dormant infection of around one-third population of the world and is still one of the most threatening bacterial pathogens for human communities, despite the fact that its treatment (streptomycin, isoniazid, and rifampin) has been available since 1944.[1] It is worth to mention that few latent infected individuals usually develop active disease, however it causes significant number of around eight million new TB cases and nearly 1.5 million deaths per year.[1] TB is a serious health issue in Sistan, an area located in the east of Iran near Afghanistan border with a population of about 0.4 million and belonging to the Sistan and Baloochestan province (31°1'43" N, 61°30'4"E).[2] It has been reported that TB is known as sad-disease with the incidence about 100 per year and 195 patients per 100 000 in Hirmand town, while TB incidence in Iran is 21 per 100 000.[3-5] In the past few years, multidrug-resistance (MDR) and extensively drug-resistance (XDR) have become serious problems in TB treatment (over 20% of new infections)[6] and currently many researches focus on finding a way against MDR and XDR for TB treatment.

Autophagy is a physiological intracellular mechanism which is responsible for degradation of damaged organelles, misfolded or unfolded protein aggregates, and some of intracellular pathogens.[7] Therefore, autophagy mechanisms play important roles in maintaining cellular homeostasis, organelle biogenesis, adjusting cellular energy, and as a specific protection and defense device in contradiction to microorganisms, a process specifically known as xenophagy.[8-11] Autophagy is considered an active flux which includes sequential steps initiating from formation of nucleation and isolation of cytoplasmic materials by an isolation membrane (phagophore formation), which later forms a double-membrane structure named autophagosome which finally moves toward and fuses with lysosomes to form autophagolysosomes for the degradation of its content.[12-15] In the autophagy process, several autophagy genes (Atg) are involved which tightly regulate the autophagy process.[16] In the first step (initiation), the Atg1-UNC-51-like kinase (ULK) complex initiates the autophagy, which later is followed by the PI3P (essential component of autophagosome) formation. Later Atg12–Atg5–Atg16L1 ubiquitin-like conjugation system which is the central complex in the elongation of the membrane and the liopidation of LC3 I (the mammalian orthologue of the yeast Atg8) to its phosphatidylethanolamine-conjugated LC3-II form, contributes in the formation of double membrane autophagosome[17] which in the final stage fuses to the lysosomes for degradation.[18]

Around three decades ago, the first scientific report highlighting the importance of autophagy in bacteria elimination was published. Rikihisa investigated Rickettsia conori infection in guinea pigs and showed that the infection induced the autophagosome formation in the polymorphonuclear cells of the infected animal.[19] Later inves-

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tigations have also confirmed that autophagy has a vital function in the elimination of pathogens including some types of bacteria.[20] Although many investigations have been done so far, the exact mechanism of bacterial recognition and elimination by autophagy (xenophagy) has not been clarified yet. Though, it has been recently reported that ubiquitination,[21] autophagy receptors, and LC3 interaction are involved in this process.[22]

It is of great importance to consider that autophagy activation can probably overwhelm the bacterial inhibition of xenophagy and could reestablish its bactericidal role in the host defending mechanisms. As an example, in the host phagocytic cells, Mbt can inhibit different steps of autophagy including phagosome maturation and phagosome-lysosome fusion. Interestingly, autophagy induction using the compounds like rapamycin stimulates the maturation of mycobacterial phagosomes in a Beclin-1-dependent pathway and alongside overpowers the mycobacterial subsistence in infected macrophages.[23] This finding was further confirmed using the autophagy induction with IFN-gamma (a cytokine with anti-TB action) in HeLa cell model.[24] In another recent investigation, it was shown that the classic anti-TB drugs (isoniazid and pyrazinamide) entail autophagy for their full effectiveness against Mbt in infected host macrophages, as mycobacterial survival is not significantly changed when autophagy genes like Beclin-1 or Atg5 gens are knocked down in this system.[25] Yet in another investigation, it was shown that several compounds that promote autophagy while lacking a direct effect on Mbt, also prevent mycobacterial growth or survival.[26]

In summary, considering autophagy mechanisms can represent beneficial application in developing new therapeutic strategies in the treatment of TB. As an example, targeting alveolar macrophages, particularly those cells sheltering Mtb, with drugs that can activate autophagy has the probable effect to deliver new approaches in clinical intervention of TB, where host-directed therapies are arranged. Inhaled particles represent an obviously practicable modality to achieve such a targeting. Drug discovery and intervention efforts targeting host signaling pathways which are in control for preventing autophagy could possibly add to the list of the drugs that can be tested for future use in TB treatment. It is of such an importance to test known and innovative molecules that prompt macrophage autophagy in TB model, alone and/or in combination with classical anti-TB medications. These include an approach of dosimetry and proper dose finding with reference to macrophage targeting on the one hand, and drug concentrations developed in systemic circulation on the other to deliver the best therapeutic strategies in TB treatment.

Ethical Approval

Not applicable.

Competing Interests

Authors declare that they have no competing interests.

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