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Autophagy as one of the most important strategies for the treatment of tuberculosis; Mini-review

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ABSTRACT

Cancer is defined as uncontrolled cell division, which could spread or invade various tissues. There are more than 200 types of cancer, including breast, skin, lung, colon, and prostate cancer, and lymphoma, the symptoms and indications of which vary depending on the type of tissues. Cancer has several treatments with different applications. For instance, chemotherapy, radiation therapy, surgery or their combination are common treatment modalities for cancer. However, a complete cure for cancer has not been achieved yet. On the other hand, novel drugs for cancer treatment are not efficient due to the ability of cancer cells to develop resistance against chemotherapeutic agents. Recently, natural compounds have been reported to improve the efficiency of cancer treatment. Polyunsaturated fatty acids (PUFAs) are natural compounds that could be used as dietary supplements in cancer patients. PUFAs are classified into two main categories, including n-3 and n-6 PUFAs. According to the literature, n-3 PUFAs exert protective effects against cancer through the induction of apoptotic pathways and suppressing cell proliferation, while n-6 PUFAs cause tumor formation by inducing cell growth and proliferation. Using PUFAs in combination with chemotherapeutic agents is considered to be an effective approach to the treatment of cancer patients through increasing cancer cell death. This review aimed to discuss the interactive effects of the structure and function of PUFAs on cancer and cell processes through various signaling pathways.

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Introduction

Mycobacterium tuberculosis (Mtb) is a common cause of death due to infectious diseases across the world. According to the report of the World Health Organization (WHO) in 2017, approximately 10 million new cases of Mtb infection have been recorded, including 5.8 million males, 3.2 million females, and one million children, among which 464,633 cases have been reported to be simultaneously infected with HIV-1.

The emergence and spread of drug-resistant tuberculosis (DR-TB) bacterial strains have increased the concerns regarding the treatment and control of TB, so that until 2017, 558,000 cases of resistance to rifampin were recorded, 82% of which were afflicted with multidrug-resistant TB (MDR-TB) (1-4). In addition, approximately a quarter of the world's population has been reported to be infected with latent TB, while only 5-10% are affected with active TB. Due to the inefficiency of the current TB vaccination, which is known as the Bacillus Calmette-Guérin (BCG) vaccine, in the prevention and complete immunization against active TB

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and TB re-activation in adults, it could be stated that the eradication of TB is not possible (1, 5-7).

Literature Review

Mtb effectively employs several strategies to escape the immune system. Therefore, the key to battling TB would be to consider and investigate the molecular mechanisms that may complicate the pathogenesis of Mtb (8).

Mtb is spread through the infected droplets that are generated by sneezing and coughing of TB-infected individuals. Upon arrival, the bacterium is detected by the alveolar macrophages and other innate immune cells. The final outcome of the disease varies depending on the interactions between Mtb and conditions of the host; the main outcomes could be classified as primary aborted TB infection, active TB, latent TB infection (LTBI), and re-activation of latent TB.

Cellular immune responses play a key role against TB. For instance, shift to the Th1 response and production of IFN-γ leads to the phagocytosis and degradation of TB bacilli (i.e., tubercle bacillus). On the other hand, switching to Th1/Th17 leads to LTBI. Moreover, shifts toward Th2/Th22 lead to the production of interleukin-10 (IL-10), IL-4, IL-13, and CTLA-4, thereby causing the impairment of the cellular immune system and TB re-activation (5-8). Co-infection with HIV and destruction of CD4+T cells (Th1) are also considered to be important risk factors for the re-activation of LTBI (9).

An elementary and effective Mtb mechanism for the prevention of degradation is the containment of the formation of intracellular phagosome-lysosome fusion. Additionally, tubercle bacillus remains hydrolyzed in phagocytosis cells by inhibiting the acidification of phagolysosomes through restraining the H+-ATPase pump, as well as the inhibition of phagosome maturation through blocking the phosphatidylinositol 3-kinase Vps34 pathway (10). Interestingly, many of these mechanisms are associated with the autophagy process, especially the phosphatidylinositol 3-phosphate (PI3P) and PI3K-hVps34 signaling pathways. Therefore, it seems that the autophagy process may be involved in the pathogenesis of Mtb (11).

Autophagy is considered to be an important intracellular mechanism for the degradation and reprocessing of macromolecules, as well as damaged and worn-out organelles. During the process, part of the cell cytoplasm is enclosed within an exclusive vacuole, which is known as autophagosome, and is ultimately fused with a lysosome to be decomposed. Approximately 30 genes regulate the autophagy process in yeasts,

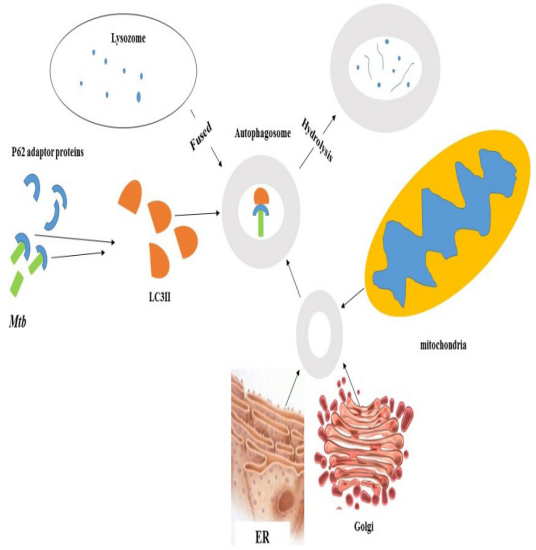

Figure 1. World Health Organization. Global tuberculosis .report 2018: World Health Organization; 20198

among which 16 homologous genes have been identified in the human genome as well (12, 13).

Autophagy is one of the mechanisms of programmed cell death, which occurs in order to maintain normal homeostasis, cellular starvation, adenosine triphosphate (ATP) supply, aging, stress response, and cancer and infectious particles in eukaryotic cells (14). In general, three elements are involved in the autophagy process, including autophagy-related genes (Atgs), autophagosome vesicles interacting with organelles (e.g., mitochondria and endoplasmic reticulum/Golgi apparatus), and lysosomes (15). The most prominent ATGs include ULK1 (Atg1), Beclin-1 (Atg6), PI3PK, hvP34, p62, NBR1, NDP52, LC3 (Atg8; containing the LC3I solution and LC3II lipid form and expressed in three isoforms of LC3A, LC3B, and LC3C), GABARAP, GABARAPL1, and GABARAPL2. LC3II is considered to be the most important autophagy marker, which is produced through the action of Atg3 from LC3I (12, 16). In addition, Beclin-1 and Atg5 play a key role in the regulation of signaling pathways and formation of autophagosomes, while p62 and NDP52 are often expressed as autophagy receptors in the cell cytoplasm (16).

Several factors affect the regulation of the autophagy pathway, including the mammalian target of rapamycin (mTOR), reactive oxygen species (ROS) response, microbial antigens, cytokines, TAB2/3-TAK1-IKK signaling pathway, and pattern recognition receptors (PRRs), such as toll-like receptors, RIG-l-like receptors, NOD-like receptors, and microRNAs (14, 17).

As a defensive strategy in innate immunity, autophagy deals with various intracellular

pathogens, such as Mtb. During infections, bacterial antigens are identified by a specific group of PRRs known as sequestosome-like receptors, which are introduced and bound to the LC3 proteins after ubiquitin tagging through adapter proteins, such as NRB1, p62, and NDP52. Afterwards, LC3 acts as a carrier, integrating autophagosomes into lysosomes (fusion). As a result, the TB bacilli are degraded by lysozyme hydrolyzes (Figure 1) (18).

According to the literature, the autophagy process is induced and enhanced owing to the degradation of latent TB bacilli in macrophages after isoniazid and pyrazinamide treatment, leading to the release of Mtb antigens and response to ROS and NADPH oxidase (19). In a study in this regard, Gutier et al. demonstrated that the starvation of Mtb-infected macrophages and simultaneous rapamycin treatment increased the interactions between Mtb, Beclin-1, and LC3, thereby inducing autophagy. Furthermore, the mentioned study indicated that IFN-γ could improve the clearance of Mtb from the body via the immunity-related GTPase family M protein 1 signaling pathway through stimulating autophagy (20). Moreover, ATP, damage-associated molecular patterns, vitamin D, and ROS could stimulate and increase autophagy, while IL-1β, IL-10, mycobacterial cell wall compounds (especially phosphatidylinositol ManLAM, ESAT-6, and CFP-10) could restrain and dysregulate autophagy (21).

Based on the mentioned molecular mechanisms, autophagy is considered to be one of the most basic and principal mechanism to eliminate TB bacilli. Recent studies have shown that autophagy enhances the presentation of Mtb antigens by the MHCI and MHC II molecules, further stimulating cellular immunity against TB. Therefore, rapid elimination of TB bacilli through the autophagy mechanism could inhibit overactive cell-mediated immune responses, ultimately preventing tissue destruction, formation, and expansion (22).

Table 1. Different types of biological molecules and their effects on autophagy

Type of molecules	Production sources of molecules	Effect on autophagy	Effect on tuberculosis
IFN-Ɣ	Macrophages and Th1	Influenced the STAT-1 pathway	Bacterial clearance
Rapamycin	drug	Repression of mTOR	Bacterial clearance
PAMPs	Mtb	Induction STING cytosolic pathway	Bacterial clearance
Parkin	Dysfunctional mitochondria	Induce ATGs	Bacterial clearance
P62	Human genomics	Promote E3 ligase expression	Bacterial clearance
NF-kB	Human genomics	Expression of IRGM, LC3 and ATG16L1	Bacterial clearance
Cathelicidin	Human genomics	Pro-inflammatory cytokines production	Bacterial clearance
25-dihydroxyvitamin D3	Nutrition	Co-factors and provoke phagocytosis	Bacterial clearance
anti-protozoal drug	others	Ca2+ influx and PLC-Ɣ pathway impressed	Bacterial clearance
Toll-like receptor 4	Human genomics	MyD88 signaling pathway	Bacterial clearance
Extracellular ATP	others	$P2x_7$ receptor impressing	Bacterial clearance
microRNA-155	Human genomics	Ras and Reb inhibitor	Bacterial clearance
Reactive oxygen response	Human genomics		Bacterial clearance
Metformin	others	AMPK signaling pathway	Bacterial clearance
Anti-tuberculosis drugs	others	Destruction of TB bacilli	Bacterial clearance
Eis	Mtb	Inhibition of JNK-pathway	Bacterial survival
Rab-GTPase	Mtb	Inhibition ca2+ flux	Bacterial survival
ESAT-6/CFP-10	Mtb	Dysregulation of ATG8	Bacterial survival
IL-1β	Th2	Inhibitor of ATG16L1 and beclin 1	Bacterial survival
miR-30A	Human genomics	Phagosomal evasion	Bacterial survival
env	HIV	Dysregulation of Beclin 1	Bacterial survival

It is speculated that provoking autophagy pathways is an effective anti-TB strategy, which may lead to the development of anti-TB drugs with a new mode of action. In this regard, findings have demonstrated that rapamycin and pyrazinamide treatment could enhance the autophagy pathway (22, 23). In addition, the administration of the antipsychotic drugs that increase and stimulate calcium pumps and metformin through the activation of AMPKs (mTOR inhibitors) could ultimately stimulate and increase autophagy, thereby improving TB control (Table 1) (23, 24). Some of the proteins belonging to the autophagy pathway (especially p62) are also known as neo-antimicrobial peptides owing to their central role against TB and could be synthesized and commercialized as pharmaceutical compounds (25).

Conclusion

Considering the emergence of high-resistance bacterial strains against common antibiotics and ineffectiveness of TB vaccines (e.g., BCG) in the prevention and treatment of the disease, eradication of TB does not seem to be possible. Therefore, the emphasis lays on the prevention of TB, and the use of immunity-based methods has been highlighted in this regard. Cellular immune responses play a pivotal role against TB, such as the shift to the Th1 response and production of IFN-γ, which leads to the phagocytosis and degradation of Mtb or switching to Th1/Th17, which results in LTBI. Furthermore, the shifts toward Th2/Th22 lead to the production of IL-10, IL-4, IL-13, and CTLA-4, causing the impairment of the cellular immune system and TB re-activation. Interestingly, several of these mechanisms (particularly the signaling pathways of PI3P and PI3K-hVps34) are associated with autophagy development.

Autophagy is an innate immune defense mechanism, which deals with intracellular pathogens such as Mtb. At some stage during infections, bacterial antigens are identified by a specific group of PRRs, and after ubiquitin tagging, they are bound to LC3 proteins through adapter proteins such as NRB1, p62, and NDP52. Therefore, it could be hypothesized that provoking the autophagy pathways is a prominent anti-TB strategy, which may enhance anti-TB drugs with a novel mode of action.

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Conflict of Interest

The authors declare no conflict of interest.

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