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Opinion

Therapeutic Potential of Anti-Tubercular Peptides: A Million Dollar Question

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No doubt, Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), is a leading cause of death and remains one of the most serious threats worldwide. According to the current report of World Health Organization (WHO), there are increased total counts for new TB cases globally than in last few years [1]. The DOTS (direct observed therapy strategy) developed by WHO in the mid-1990s, caused the emergence of multidrug resistant (MDR) Mtb and surprisingly 13% of patients were found to be co-infected with human immunodeficiency virus (HIV) due to the impairment of the immune system of the patient, leading to the delayed diagnosis and treatment of TB [2]. Likewise, extensively drug resistant tuberculosis (XDR-TB), a subset of MDR-TB emerged, which is resistant to the second line anti-TB drugs.

At present, the total counts of MDR-TB and XDR-TB are continuously emerging and few countries reported at least one case of XDR-TB. Generally, despite the digestive characteristics of macrophages, Mtb has potentiality to develop multiple adaptive strategies in order to destruct the phagosomal pathways and survive intracellularly in the host macrophages. Bacillus Calmette Guerin (BCG) is the only available TB vaccine that prevents us from primary TB but it failed to show its effectiveness in pulmonary patients. Currently, in the drug developmental pipeline, there are 20 new diagnostic test platforms, 14 TB vaccine candidates in clinical trials and over 35 candidates in preclinical development. Additionally, 4 anti-TB agents are in Phase III trials, 7 anti-TB agents are in Phase II, 5 anti-TB agents are in preclinical development and 3 anti-TB agents are in Good Laboratory Practice toxicity evaluation. Recently US FDA has approved only one drug namely TMC207 as a part of combination therapy to treat adults with MDR pulmonary TB in the absence of other alternatives [3].

It is surprising that several drugs and anti-tubercular agents are currently under different phases of preclinical and clinical evaluation, indicating lack of potent anti-tubercular drugs developed in the last four decades. There is an urgent necessity for the quick diagnosis and the development of newer anti-tubercular agents from diversiform sources in order to achieve END-TB strategy due to the emergence of MDR-, XDR- and total drug resistant (TDR)-TB.

Anti-tubercular peptides are gene-encoded peptides produced by genera from specific domains, showing direct mycobactericidal activity and playing significant roles in host defense. It can be a leading alternative to existing antimycobacterial agents of various trial phases. Anti-tubercular peptides have advantages over other mycobactericidal agents due to low immunogenicity, affinity to prokaryotic negatively charged cell envelopes, and diverse mechanisms of action. These peptides have unique properties not only by creating transmembrane pores but also showing second non-membrane targets within mycobacteria. The direct killing of Mtb and immune-modulators in infectious conditions makes these anti-tubercular peptides promising candidates for the development of newer and efficacious drugs [4]. Comprehensive literatures on the anti-tubercular activities of peptides from varied origins emerged as an idealistic approach towards the TB treatment. Peptides derived from human immune cells, human non-immune cells, bacteria, fungi, venoms and other sources have been successfully investigated as emphatic anti-tubercular agents. These peptides can contribute to mycobactericidal innate immunity through direct as well as indirect (immune modulation) action. Few of them are produced in different types of innate immune cells, such as macrophages, keratinocytes, neutrophils and epithelial cells. Figure 1 enlists the various potent anti-tubercular peptides identified from diverse sources.

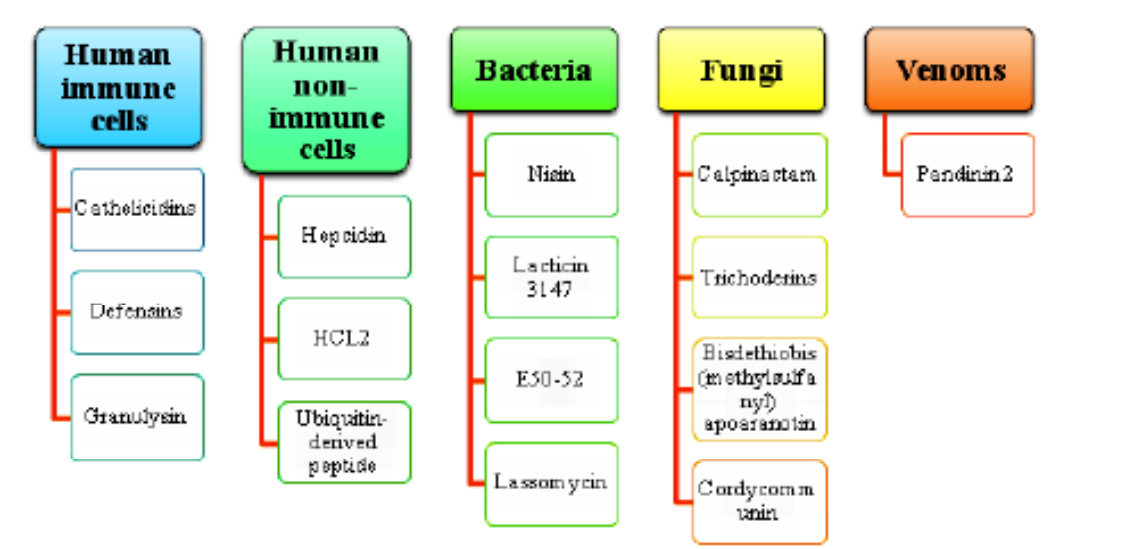

Figure 1: *Anti-tubercular peptides from diversiform sources.*

The anti-tubercular peptides may be exploited substantially to inhibit Mtb in a relatively shorter time period due to their conceivable mycobactericidal properties and undoubtedly it can be considered auspicious candidates for the development of efficacious drugs in future due to their specific mode of action. An insight into the correlation between peptide structure and molecular mode of action will lead to design novel anti-tubercular drugs that might overcome the complications of existing drugs. Understanding the mechanism of action, immunogenicity and non-toxicity of the newly discovered peptides from distinct sources in future will act as therapeutic weapon and it will pave a way for us in order to develop puissant anti-tubercular drugs. In spite of the significant anti-tubercular activity of peptides from diverse sources, the development of efficient drugs without the emergence of MDR-, XDR-, TDR-TB and overcoming the obstacles in the line of drugs preparation is a million-dollar question at present. A major obstacle is the short half-life of peptides *in vivo* that may lose activity under different physiological conditions. On the other hand, its delivery to combat intracellular infections is another challenge due to larger size in comparison with the commercially available antibiotics. Additionally, the hydrophobicity, charge and biocompatibility of peptides may also be a hurdle towards the development of efficacious anti-tubercular drugs [4]. But at present we are desperately looking into the eradication of TB using anti-tubercular peptides in order to overcome the existing era of drug resistant Mtb.

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