19.3.2 Antibodies plus Vitamin D

Tuberculosis (TB) is a pandemic disease caused by *Mycobacterium tuberculosis* (MTb) responsible for millions of active lung TB cases worldwide associated with a high death rate. The prevalence of multiresistant TB and extensively drug-resistant TB converges with pandemics of HIV and diabetes, generating more problems due to the combination of diseases. Therefore, there is a need to develop new drug classes to reduce treatment duration for TB and to overcome infection from MDR. It has been shown in a series of *in vitro* studies that the active form of vitamin D, 1,25-di-hydroxyvitamin D3 or 1,25 (OH) 2D3, induces gene expression of β-defensin 2 and human cathelicidin LL-37. These peptides belong to two antimicrobial peptide classes produced in lung epithelial cells, monocytes/macrophages and neutrophils, which are able to suppress the increase of modular antimicrobial responses. Vitamin D 1,25 (OH) 2D3 also induces autophagy in macrophages/monocytes infected with MTb that may control the infection through an LL-37-dependent mechanism. Therefore, several studies showed an association between vitamin D deficiency and an increased risk of developing active TB. In total, these findings reinforced the interest in vitamin D as an adjuvant therapy for standard anti-TB treatment. Further, additional studies demonstrated a synergistic effect in the induction of LL-37 expression when vitamin D was used in combination with sodium 4-phenylbutyrate (PBA). These studies showed that a combination of PBA and vitamin D to healthy adults increased LL-37 expression and MTb intracellular death in macrophages.

19.3.3 Antibodies plus Clavanin

Clavanin A is a natural antimicrobial peptide that was isolated first from hemocytes of marine tunicate *Styela clava*. This peptide has an amino acid sequence rich in histidine, phenylalanine, and glycine residues, shown to be effective against Gram-negative and Gram-positive bacteria. Among other peptides, this peptide has the advantage of being active even at high salt concentrations and in acidic pH. To increase the potential, five nonpolar amino acids were incorporated to the N-terminal region, the hydrophobic part of clavanin A molecule, and the new engineered molecule was called clavanin-MO. Tests showed that the peptide effectively killed a panel of representative bacterial strains, including MDR clinical isolates. Its antimicrobial activity was shown in animal models, decreasing bacterial counts by six orders of magnitude and contributing to clearance of the infection. Moreover, clavanin-MO was able to modulate innate immunity through stimulating leukocyte recruitment to the site of infection site and the production of immune mediators GM-CSF, IFN-γ, and MCP-1, suppressing an excessive and potentially harmful inflammatory response by increasing anti-inflammatory cytokine