New molecular insights into the old tuberculin skin test and type VII secretion system

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Tuberculosis is a critical infectious disease that is caused by *Mycobacterium tuberculosis*, a very successful human pathogen. About 1/3 of the total world population is a carrier of tuberculosis pathogens. Several species of the mycobacterial genomes were sequenced and a comparative analysis identified 16 regions of difference (RD1 - RD16). Of these regions, RD1 is deleted in all non-virulent species, e.g. the vaccine strain BCG. This region encompasses approximately 9000 base pairs encoding for 16 genes; their gene products assemble a new secretion system, the Type-VII secretion system. In the centre of this region two genes are located, ESAT-6 and CFP-10, encoded in an operon. The two proteins belong to the family of WXG100 proteins. It has been reported that the ESAT-6/CFP-10 complex plays an important role in the pathogenicity of the bacteria. Interestingly, they are the molecular basis of the "tuberculin skin test" (TST) and the newly developed interferon-γ releasing assay (IGRA). We have determined the atomic structure of this complex and a similar complex of another pathogen, *S. agalactiae*. To investigate the origin of these molecules we had to develop a novel approach of knowledge based bioinformatics study, since the proteins share less than 15% sequence identity. This revealed that there are two groups of WXG-100 protein complexes, hetero-dimers and homo-dimers.