

The PE/PPE Multigene Family of Mycobacteria and TB Vaccines

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Mycobacteria including *Mycobacteria tuberculosis* (Mtb) contain a multi-gene family, named the PE/PPE family. Mycobacterial strains contain about 165 genes, consisting of two major subfamilies the PE (containing the PE_PGRS group) and PPE, of which many of the constituents are very homologous (>50%). Since their discovery, scientists speculated about the role the members in this family might play in Mtb pathogenesis, immunity, evolution, and antigenic variation. Brennan et al. [1] in Issue 6 of Infection and Immunity, summarizes what is known about PE/PPEs with a particular focus on how they could be used in new TB vaccines. In fact, two TB vaccines presently being studied in clinical trials, GSK's M72 and IDRI's ID93, each contain a PPE protein. Another TB vaccine, the live Mtb mutant strain Mtb Δ PE/PE25-PE19 developed by the laboratories at the University of Pisa and Institute Pasteur, is a mutant which is missing two PEs and three PPEs, is under preclinical development. Evidence indicates that this vaccine is safe and is protective due to cross reactivity among the PE and PPEs in animal models for TB.

Numerous investigations over the past decade have demonstrated that certain representatives of this family display a variety of characteristics. They are found at the bacterial cell surface, can act as chaperones carrying proteins to the surface, interact with mitochondria leading to necrosis of cells and bind to immunologically active receptors like TLR2. The multiple PE/PPE genes have evolved along with the ESX regions of mycobacteria and are often associated with ESX regions including ESX5 of Mtb.

Very recently, Camassa et al. [2], have shown that Mtb knock-out mutant of PE_PGRS33 (in Mtb strain H37Rv) acts like a persister mutant, being more virulent over time than the parental/wildtype in the murine model. It is very unusual for an attenuated mutant to be more virulent in an animal model of the disease and the studies indicate that (1) the Mtb is mostly extracellular in the lung and (2) the mutant is associated with chronic TB disease, not early infection. Together with the additional evidence that truncations of PE_PGRS33 may be associated with the absence of caseous necrosis and with the amplified transmission of Mtb, this points to the significance of PE_PGRS33 and other representatives of this multigene family.

In summary, the variety of important functions assigned to PE/PPEs suggests that they should be included in a new TB vaccine. The PE/PPEs can elicit strong TH1 and also humoral immune responses and some have already been shown to be protective in preclinical studies. Immunological cross reactivity is an important feature of the numerous PE/PPEs. Success in the future rests with scientists, who are fearless enough to investigate and explore the PE/PPEs of mycobacteria.

References

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