ErbB2: Nonimmune genetic key to leprosy

Sir,

I read with interest, the article titled "Ligand-binding prediction for ErbB2, a key molecule in the pathogenesis of leprosy" in the January 2008 issue of IJDVL.[1] It illustrates the growing importance of structural bioinformatics in clinical medicine and drug discovery. However, the use of the term 'ligand' in place of 'ligand-binding site' in the article could be misleading. A ligand is a molecule that is able to bind to and form a complex with a biomolecule to serve a biological purpose. Bioinformatics tools like Q-Site finder[2] predict putative binding sites within biomolecular structures after excluding bound ligands. ErbB2 has no known ligands[3] (unlike other ErbB receptors) and signalling is mediated through heterodimerization with ErbB3 or homodimerization with another ErbB2 (proposed mechanism of signalling in leprosy).[4] Docking studies and

virtual high-throughput screening techniques are needed to identify unknown ligands (potential drug candidates) for ErbB2.[5]

Only extracellular *Mycobacterium Leprae* utilizes ErbB2 for downstream extracellular signal-regulated kinase (ERK) activation.[6] In contrast, lymphoid cell kinase (p56Lck) has been found to activate ERK 1/2 directly through a PKC ε-dependent (Protein Kinase C ε), MEK-independent (MEK = MAPK/Erk kinase; MAPK = Mitogen-activated protein kinase) pathway in intracellular *Mycobacterium leprae*.[7] Hence, ErbB2 inhibitors are unlikely to have a huge impact on leprosy therapeutics.

ErbB2 is a membrane protein with an extracellular region comprised of four domains, a single transmembrane helix and an intracellular region with a tyrosine kinase domain.[8] The structure (PDB: 2A91) used in the study, is a truncated one with three domains and 510 residues.[9] The structure of the entire extracellular region of ErbB2 bound to herceptin is available in PDB: 1N8Z.[10]

There is strong epidemiological evidence that genetic factors influence susceptibility to leprosy *per se* and to the leprosy type. Majority of the genes implicated in susceptibility to leprosy are immunity-related such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-10.[11] A recent study of the spatial structure of the transmembrane domains of dimerized ErbB2 identified certain single-nucleotide polymorphisms (SNPs) which can excessively stabilize dimeric ErbB2 leading to spontaneous signalling.[12] Although the obvious relevance is its oncogenic potential, the possibility of a similar nonimmune mechanism that increases the susceptibility to leprosy, cannot be overlooked.

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