Taking advantage of this occasion 100 years after Darier’s initial description, it is interesting to highlight the possibility that some common pathophysiological mechanisms must underlie the elicitation of dermographism and this relatively common clinical sign. Due to the urtication of previously “normal” skin upon mechanical friction characterizing dermographism, the potential of Darier’s sign as a model for better understanding of the clinically more significant dermographism can be advocated.

Physical (mechanical) mast cell activation seems to be the crucial event in the pathophysiological cascade leading to both conditions, i.e., positive Darier’s sign and dermographism. However, increased histamine release in susceptible skin does not always rely on increased numbers of mast cells.[2] The exact mechanism of mechanical degranulation of tissue mast cells is still obscure. Possible mechanisms that can explain how friction forces (such as those used to elicit Darier’s sign) may lead to mast cell degranulation include:

(a) Minor tissue traumatization, probably mediated by local complement or plasminogen activation.

(b) Irritation of neuronal structures of the skin resulting in degranulation of adjacent/connected/dependent mast cells. Mechanical nerve stimulation may result either “specifically” via ‘professional mechanoreceptor’ activation or “nonspecifically,” e.g., via local activation of nociceptive nerve endings. It can be further speculated that abnormal neuronal stimulation may result from pathological function of mechanoreceptors directly on nerve endings or indirectly on other interconnected cells, including epidermal keratinocytes. Alternatively, local pathologic neuronal-mast cell connections may mediate mast cell degranulation and confined urtication.

(c) Finally, mechanical forces via tissue deformation may directly induce mast cells degranulation, probably via mechanoreceptors located on the mast cells themselves. In different species, mechano-sensitive ion channels seem to play a central role in the physiology of a wide spectrum of mammalian cell types, including mast cells.[3-5] According to this assumption, Darier’s sign might reflect abnormal mechanosensitivity of mast cells within certain skin lesions. In analogy, constitutional generalized vulnerability of skin mast cells could underlie dermographism in some individuals.

In conclusion, we propose that comparative studies of skin lesions characterized by either positive or negative Darier’s sign with respect to the physiology of the contained mast cells, could not only contribute to the delineation of the pathomechanism of this peculiar clinical sign, but they may also serve as a vehicle to better understand dermographism.

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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

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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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