

A possible pivotal role for transglutaminase 2 in the pathophysiology of cutaneous amyloidosis

Sir,

Amyloidosis is a generic term that signifies the abnormal extracellular tissue deposition of one of a family of biochemically unrelated proteins that share certain characteristic staining properties, including apple-green birefringence of Congo red–stained preparations viewed under polarizing light.^[1,2]

As a term, ‘amyloid’ was used historically to define proteins that shared similar microscopic characteristics and affinity for certain stains. The various diseases characterized by deposition of ‘amyloid’ proteins are similarly heterogeneous but have in common the deposits of fibrillar proteins characterized as ‘amyloid’ in the dermis. In nodular localized cutaneous amyloidosis, the amyloid is believed to be derived from local plasma cells; in contrast to lichenoid or macular amyloidosis, which have keratinocyte-derived amyloid.^[1,2] Amyloid deposits in macular and lichen amyloidosis bind to anti-keratin antibodies and contain sulfhydryl groups, pointing to altered keratin as a source for these deposits. There is no difference in staining characteristics

of cytokeratins between macular amyloidosis and lichen amyloidosis.^[3] Some argue that the deposition of amyloid in macular and lichen amyloidosis may be the result of frequent itching and scratching.^[4] The concept has arisen of focal epidermal damage and filamentous degeneration of keratinocytes, followed by apoptosis and conversion of filamentous masses (colloid bodies) into amyloid material in the papillary dermis, perhaps with a contribution from the dermal-epidermal junction.^[5]

It has been proposed that in lichenoid and macular amyloidosis, specific immunologic tolerance to the presence of keratinocyte-derived apoptotic bodies in the papillary dermis favors their transformation into amyloid by macrophages or fibroblasts; whereas in lichen planus, an autoimmune disorder, a brisk inflammatory response ensures their removal.^[6]

Transglutaminase 2 (TG2) is a unique member of an enzyme family (EC 2.3.3.13) because in addition to its primary enzymatic activity of Ca²⁺–dependent transamidation of polypeptide chains through their glutamine and lysine residues (or through polyamines), it also binds GTP (which blocks transamidation) and may act as a G protein. It is often up-regulated in cells undergoing apoptosis. In addition, another important role is attributed to TG2: the prevention of tissue injury, inflammation, and autoimmunity once the apoptosis has already been initiated. This function of TG2 is partially achieved by being expressed and activated also in macrophages digesting apoptotic cells and mediating a crosstalk between dying and phagocytic cells. Generally from the *in vivo* results obtained in some laboratories, it has been proposed that the most important role of TG2 *in vivo* is to ensure that apoptosis is finished without causing inflammation necrosis and apparent tissue injury. Besides facilitating apoptosis, induction of TG2, and enhancing phagocytosis, TGFβ was shown to be required for the proper down-regulation of pro-inflammatory cytokine production in macrophages as well. If, however, necrosis still occurs, TG2 promotes both tissue stability and repair. In TG2–/– animals, all these anti-inflammatory actions are compromised, which results in the appearance of inflammatory cells at the apoptotic sites in the short term and autoimmunity in the long term.^[7,8]

Moreover, it merits noting that transglutaminase is suggested to play a role in the pathogenesis of Dutch-type hereditary amyloidosis and Alzheimer’s disease by cross-linking proteins into insoluble polymers.^[9]

Given the above facts altogether, couldn't TG2 be involved in the pathogenesis of macular and lichen amyloidosis through promotion of keratinocyte apoptosis, facilitating the ingestion of apoptotic cells by macrophages, inhibiting inflammation, and cross-linking keratinocytic proteins to produce amyloid?

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