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Papillon-Lefèvre Syndrome and Malignant Melanoma

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Key Words

Cathepsin C · Malignant melanoma · Papillon-Lefèvre syndrome

Nakajima et al. [1] recently reported a case of malignant melanoma in a patient with Papillon-Lefèvre syndrome (PLS; OMIM 245000), a deficiency of the cysteine protease cathepsin C [2]. Nakajima et al. [1] raise the important issue of whether the defect in cathepsin C activity might contribute directly to the malignant phenotype or to the progression of the tumour. Remarkably, all of the known substrates of cathepsin C are serine proteases expressed in cells of the immune system.

Cathepsin C, also known as dipeptidyl peptidase I, removes the *N*-terminal dipeptide pro-domain from a number of serine proteases, activating their proteolytic function. The known cathepsin C substrates are the neutrophil serine proteases, cathepsin G, elastase and proteinase 3, mast cell chymase and members of the granzyme family of pro-apoptotic proteases expressed by natural killer (NK) cells and cytotoxic T lymphocytes (CTL). Amongst these cell types, NK cells and CTL are acknowledged to play an important role in the immune surveillance of tumour cells. NK or T cell activation by a tumour cell releases granzymes which, via the action of perforin, enter the tumour cell and cleave a number of proteins, including caspases. This results in the initiation of the apoptotic pathway and tumour cell death. In PLS, unstimulated NK cells have greatly reduced cytotoxic activity [3, 4] associated with a granzyme B processing defect and the inability to induce the caspase cascade in tumour cells [4].

These findings hint towards impaired cytotoxic lymphocyte activity in PLS, leading to immunodeficiency and the possibility that this might contribute to tumour progression. However, whilst there have been reports of liver abscesses in PLS [for example, see 5], these patients are generally not considered to suffer from a serious immunodeficiency. Instead, the common features of PLS are palmoplantar hyperkeratosis and severe periodontitis [2]. The lack of a severe immunodeficiency in PLS is probably due to the

presence of a cathepsin-C-independent pathway of granzyme activation that allows cathepsin-C-deficient NK cells and CTL to retain cytotoxic activity [4, 6]. It therefore appears unlikely that the cathepsin C deficiency found in PLS could contribute to melanoma progression via an NK cell or CTL immune surveillance defect. It is formally possible that the cathepsin-C-independent pathway is sufficient to retain normal cytotoxic lymphocyte activity in most PLS patients, but that certain alleles encoding the alternative granzyme-processing enzyme might be less efficient at substituting for cathepsin C. In this regard, it is interesting that 3 of the 4 PLS patients with melanoma reviewed by Nakajima et al. [1] were of Japanese descent, accounting for some 7.5% of known Japanese PLS patients [1]. However, severe immunodeficiency in this group of PLS patients has not been reported. Nakajima et al. [1] have demonstrated that melanomas can occur at sites of hyperkeratosis associated not just with PLS, but with a variety of disorders, and they suggest that the hyperkeratotic micro-environment itself plays an important role in the development and/or progression of the melanoma.

Cathepsin C also activates the neutrophil serine proteases, cathepsin G, elastase and proteinase 3, and these molecules are also defective in PLS [6]. The role that these proteases play in tumour progression is not clear. However, neutrophil serine proteases have been implicated in the proteolytic processing of cytokines, chemokines and receptors important in modulating immune responses [7]. Periodontitis is frequently associated with neutrophil deficiency, implicating defective neutrophil activity in this aspect of PLS. However, despite the importance of proteases in epidermal differentiation [8], our knowledge of the role of cathepsin C in the development of the dermatological manifestations of PLS remains very limited. Defining the role of cathepsin C in the skin may provide important clues to why the patients described by Nakajima et al. [1] developed melanoma.

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