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Altered T Cell Differentiation and Notch Signaling Induced by the Ectopic Expression of Keratin K10 in the Epithelial Cells of the Thymus

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Abstract Transgenic mice expressing hK10 under the keratin K5 promoter display several alterations in the epidermis including decreased cell proliferation, and reduced susceptibility to tumor development. Given that K5 promoter is also active in the epithelial cells of the thymus, we explored the possible alterations of the thymus because of K10 transgene expression. We found severe thymic alterations, which affect not only the thymic epithelial cells (TEC), but also thymocytes. We observed altered architecture and premature thymus involution in the transgenic mice associated with increased apoptosis and reduced proliferation of the thymocytes. Interestingly, prior to the development of this detrimental phenotype, thymocytes of the transgenic mice also displayed altered differentiation, which is aggravated later on. Molecular characterization of this phenotype indicated that Akt activity is reduced in TEC, but not in thymocytes. In addition, we also observed altered expression of Notch family members and some of their ligands both in TEC and T cells. This produces reduced Notch activity in TEC but increased Notch activity in thymocytes, which is detectable prior to the disruption of the thymic architecture. In addition, we also detect altered Notch expression in the epidermis of bK5hK10 transgenic mice. Collectively the present data indicate that keratin K10 may induce severe alterations not only in a cell autonomous manner, but also in neighboring cells by the modulation of signals involved in cell–cell interactions. J. Cell. Biochem. 95: 543–558, 2005.

Key words: keratin; cell cycle; signal transduction; epidermis; transgenic mice; Akt; thymus; T lymphocytes; Notch

The issue of keratin protein function in epithelial cells and tissues is a matter of controversy. Keratin genes display a differential regulation in the various epithelia of the body and inherited mutations affecting keratin genes are responsible for a variety of epithelial fragility syndromes [Fuchs, 1995; Takahashi et al., 1999]. In addition to this shared family-wide functions, keratin filaments appear to carry out cell type- and context-dependent functions that include protection against metabolic stress, modulating apoptotic signals, cell cycle progression, and promotion of specific epithelial cytoarchitecture [Coulombe and Omary, 2002; Paramio and Jorcano, 2002; Herrmann et al., 2003; Kirfel et al., 2003]. Despite the recent progress in this field, our understanding of the relationship between keratin proteins and the differentiated epithelial cells remains poor. In particular, regarding functional explanation that may clearly justify the diversity and the tissue- and differentiation-specific expression patterns of these proteins.

Recently, we have investigated the possible existence of such specific keratin functions focusing on keratin K10. This protein is char-

Abbreviations used: SP, single positive T lymphocytes; DP, double positive T lymphocytes; FACS, fluorescence-activated cell sorter; TEC, thymic epithelial cells; NICD, Notch intracellular domain; PKC, protein kinase C.

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