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KERATINOCYTE & SKIN PHYSIOLOGY

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Properties and functions in the epidermis of two filaggrin-related proteins, filaggrin-2 and hornerin - Their pathophysiological implications.

On human chromosome 1q21, the “epidermal differentiation complex” comprises numerous genes that are of crucial importance for keratinocyte differentiation and stratum corneum properties. Seven of them encode members of the S100-fused type protein (SFTP) family: filaggrin, hornerin, filaggrin-2 (also known as ifapsoriasin), repetin, cornulin, trichohyalin and trichohyalin-like 1. Filaggrin is the best characterized and the most studied. The function and biochemical properties of the others are less known. The discovery that loss-of-function mutations in the filaggrin gene are the cause of ichtyosis vulgaris and a strong risk factor for atopic dermatitis turns the spotlights on SFTPs. The amino acid sequences of the SFTPs are not conserved; however they share the same structural organization at the gene and protein levels. They all comprise an N-terminal domain homologous to S100A proteins and containing two EF-hand calcium-binding sites. This domain is fused to a large central domain consisting of multiple tandem repeats, and to a specific C-terminal region. Another common feature of the SFTPs is their specific expression in the cornified epithelia and/or the hair follicles. Hornerin and filaggrin-2 are the closest relatives of filaggrin. In particular, the amino acid compositions of the three proteins are well conserved, with very high levels of serine, glycine, arginine, histidine and glutamine.
Human hornerin is a protein of 2850 amino-acids. Its central domain consists of six tandemrepeated basic subunits (468±2 amino-acids). Hornerin is produced by granular keratinocytes as a large precursor of 280-300 kDa which accumulates on keratohyalin granules. The precursor is then processed by proteolysis to smaller fragments down to 45 kDa. In the cornified layer, hornerin is located at the periphery of corneocytes. It is a component of cornified cell envelopes, transglutaminase 3 being responsible for its cross-linking. Hornerin function is probably to reinforce the envelopes and to contribute to the mechanical resistance of the stratum corneum. A role in antimicrobial defence has also been proposed for some hornerin-derived peptides.

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Human filaggrin-2 is a protein of 2391 amino-acids. Its central domain contains two types of tandem repeats, all of them being 75-77 amino-acids long. The nine A-type repeats are highly homologous to hornerin subunits, while the fourteen B-type repeats are closer to filaggrin monomers. The protein is located with profilaggrin in keratohyalin granules of the granular keratinocytes, and with filaggrin in the fibrous matrix of the lower corneocytes. Both proteins concomitantly disappear in the upper cornified layer. Filagrin-2 is synthesized as a large precursor of 250 kDa. Deimination promotes its processing by calpain 1 into numerous small peptides and probably into free amino-acids. The role of filaggrin-2 is still unclear. The filaggrin-2 B-type repeats could contribute to stratum corneum hydration and photo-protection. They may also aggregate intermediate filaments. The A-type repeats may serve as precursors of the cornified envelopes. Filaggrin-2 and hornerin are expressed at significantly lower levels in the non-lesional skin of atopic dermatitis patients, as compared to normal skin, and in the lesional as compared to non-lesional atopic skin. This decreased expression could contribute to the epidermal barrier defects associated with the disease.

Key words: filaggrin, cornified envelope, hydration, hornerin, atopic dermatitis