A common origin for cornified envelope proteins?

Sir — Synthesis of the cornified cell envelope (CE) constitutes the ultimate step of keratinocyte differentiation in normal human epidermis. This highly insoluble structure, produced on the inside of the plasma membrane, protects against the loss of body fluids, the entrance of toxic agents or microorganisms and damage by physical forces. The extraordinary insolubility of the cornified envelope is likely due to the action of epidermal transglutaminase, resulting in the formation of N^{ε}–(γ-glutamyl)lysine crosslinks between the constituent proteins. The identification and characterization, however, of these constituent proteins has been hindered by the high insolubility of the CE, causing a large variability in the biochemical data obtained by various extraction methods[1].

The best characterized precursors of the CE are loricrin[2,3] and involucrin[4]. As both proteins are substrates for epidermal transglutaminase[2,5], one might expect that such a common property is reflected by the presence of at least some homologous domains. Both the N- and C-termini of these proteins show significant sequence homology (see figure), whereas internal domains are poorly conserved and are unique for each protein. The high proportion of conserved Gln (Q) and Lys (K) residues in the homologous areas suggests a direct involvement of these domains in the cross-linkage. Interestingly, a similar amino acid conservation is found in the N- and C-terminal domains of proteins belonging to the recently identified *spr* gene family. This multigene family codes for small proline rich (SPR) proteins, which are strongly induced during terminal differentiation of human keratinocytes *in vivo* and *in vitro*[6,7]. No function has been attributed to these genes, but the present comparison suggests that *spr* genes might belong to the same family as loricrin and involucrin and constitute a novel sub-class of CE precursor proteins. It is interesting to note that the CE has a high proline content which is not accounted for by the known CE precursor proteins such as loricrin, involucrin, keratolinin or CREP[1]. Furthermore, the homology between loricrin, involucrin and *spr* genes is also reflected in a similar genomic organization: short first exon, one single intron and a second exon which contains the entire open reading frame. The internal domains, specific for each of these genes, are characterized by the multiple reiteration of specific peptide motifs. Moreover loricrin, involucrin and all *spr* genes map to human chromosome 1 q21 (refs 8–10). This clustered organization might indicate that these genes were created by gene duplication of a common ancestor and have diverged by evolving internal domains specific for each protein. Such a view is in agreement with the phylogenic analysis of involucrins[11], which has shown that the N- and C-termini of the coding sequence encompass the ancestral segments whereas internal domains constitute the modern fragments of these genes.

It will now be interesting to analyse whether other potential precursors of the CE can be identified (possibly at 1q21) by using the sequence homologies described here, thereby supporting the biochemical identification of new potential precursor proteins of the epidermal CE envelope. This will be important for the molecular characterization of several inherited cutaneous diseases where an aberrant CE synthesis has been observed.

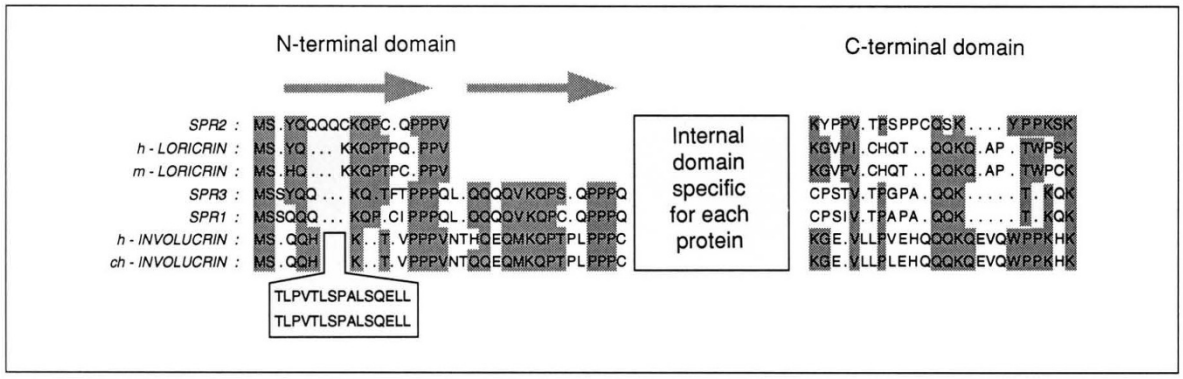

Fig. 1 Amino acid homologies in the N- and C-terminal domains of involucrin, loricrin and *spr* genes: Identical (or similar) amino acids are boxed. Arrows represent a duplication in *spr1* and *spr3*, which is partially conserved in involucrin but not in loricrin and *spr2*. An insertion of 15 amino acids present in involucrin but not in the other genes is indicated. h, human; m, mouse; ch, chimpanzee.

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