Studies on the Molecular Pathogenesis of Psoriasis

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Psoriasis is a chronic skin disease of unknown pathogenesis characterized by keratinocyte hyperproliferation, neoangiogenesis, and inflammation. The disease is considered to be multifactorial requiring environmental trigger factors and genetic susceptibility to become manifested. The most important psoriasis susceptibility locus in human genome contains eight genes, of these the alpha-helix coiled coil rod homologue (HCR) has proven to be a good candidate gene based on its location, polymorphism, and a disease-associated allele, HCR* WWCC. Here we demonstrate HCR* WWCC to be strongly associated with psoriasis in different populations. Change in the secondary structure of the HCR possibly affects the antigenic properties of the protein. The HCR protein localized differently in psoriatic lesions than in normal skin or other hyperproliferative skin disorders. Its expression was opposite to the Ki67 and β-catenin, suggesting that HCR may have antiproliferative functions and that the adhesive properties of cells expressing HCR were abnormal. In regulation studies, interferon gamma (IFN-γ) downregulated HCR mRNA expression in primary keratinocytes.

The role of matrix metalloproteinases (MMPs) in wound healing is well established, but little is known about MMPs in psoriasis although these conditions share many common features. We demonstrated MMP-12 to be upregulated in psoriatic lesions in macrophages, possibly aiding macrophage migration through the basement membrane. The keratinocytes of hyperproliferative areas of psoriatic lesions expressed MMP-19. The upregulation was verified with quantitative TaqMan PCR. Neutrophils expressed MMP-9 and MMP-8, while MMP-9 was also expressed in macrophages. MMP-3 was expressed in basal psoriatic keratinocytes in a few samples, associating with areas of basement membrane disruption. Expression of TIMP-1 (tissue inhibitor of matrix metalloproteinase-1) mRNA and TIMP-3 mRNA was upregulated in psoriatic lesions, possibly reflecting the anti-angiogenic properties of TIMPs.

IFN-γ and IFI27, an interferon inducible gene, are upregulated in psoriasis. IFI27 mRNA was expressed in the psoriatic epidermis, other hyperproliferative skin disorders, healing wounds, and squamous cell carcinomas in a spatially and temporally regulated manner. IFN-γ, TNF-α, and TGF-β1 upregulated IFI27 mRNA expression in primary cultured keratinocytes, possibly affecting their proliferation. Thus, IFI27 may be a novel marker of epithelial proliferation and cancer.

This thesis is based on the following papers

Asumalahti K, Veal C, Laitinen T, Suomela S, Allen M, Elomaa O, et al. Coding haplotype analysis supports HCR as the putative susceptibility gene for psoriasis at the MHC PSORS1 locus. Hum Mol Genet 2002: 11: 589–597.

Suomela S, Elomaa O, Asumalahti K, Kariniemi A-L, Karvonen S-L, Peltonen J, et al. HCR, a candidate gene for psoriasis, is expressed differently in psoriasis and other hyperproliferative skin disorders and is downregulated by interferon-gamma in keratinocytes. J Invest Dermatol, 2003: 121: 1360–1364.

Suomela S, Kariniemi A-L, Snellman E, Saarialho-Kere U. Metalloelastase (MMP-12) and 92-kDa gelatinase (MMP-9) as well as their inhibitors, TIMP-1 and -3, are expressed in psoriatic lesions. Exp Dermatol 2001: 10: 175–183.

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Suomela S, Cao L, Bowcock A, Saarialho-Kere U: Interferon alpha-inducible protein 27 (IFI27) is up-regulated in psoriatic skin and certain epithelial cancers. J Invest Dermatol 2004: 122: 717–721.