tumor growth is an important observation, since selection for certain clones that are most 'fit' for primary growth might simultaneously result in selection for metastatic clones because of overlapping growth requirements between primary and secondary sites.

On a clinical level, an obvious question is whether these 54 lung-metastasis genes represent a 'magic' set that is responsible for all breast-cancer metastasis to the lung? This seems unlikely since only a small subset of primary human tumors expressed the signature in this study, while the lung is a common site of breast cancer metastasis. Thus it is possible that other similar signatures exist. From a therapeutic standpoint, most patients with metastatic breast cancer develop disease in multiple sites during the course of their disease. Do individual primary tumors express multiple signatures that are predictive of metastasis to different sites? Overall, these findings suggest that complex strategies, which account for genetic heterogeneity among metastatic cells both within and between patients with metastatic cancer, may be required eventually to treat and prevent breast cancer metastasis■

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Mouse Models

Psoriasis: an epidermal disease after all?

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In the September 15th issue of *Nature*, a research group from Austria reported a novel mouse model with epidermal specific double-knockout of the c-Jun and JunB genes with subsequent development of psoriasis-like skin phenotype and arthritic lesions.[1] In this interesting model, the authors show that epidermal changes precede and are independent of recruitment or function of T cells.

Psoriasis is a common chronic inflammatory and hyperproliferative skin disease characterized by complex alterations in epidermal growth and differentiation, as well as multiple inflammatory, immunological and vascular abnormalities.[2] A significant proportion of psoriasis patients also develop seronegative inflammatory arthritis.[3] Many lines of evidence indicate that the disease is genetic, although its mode of inheritance is usually multifactorial.[4] To date, no causative gene has been definitively identified.[5]

While the most prominent features of psoriasis are abnormal proliferation of epidermal cells (hyperplasia), and increased cutaneous blood flow, multiple lines of evidence indicate that infiltrating immunocytes initiate and maintain these changes.[6] For example, bone marrow transplantation from psoriatic donors has previously triggered psoriasis in donor recipients.[7] Moreover T-cell-specific immunosuppressants exert dramatic therapeutic effects on psoriatic patients.[2] Xenograft experiments in which uninvolved skin of psoriatic patients is grafted onto immunodeficient mice have shown a clear role for T-cells, as transformation into a psoriatic plaque is blocked when T-cell function is inhibited.[8]

Given these lines of evidence that implicate T-cell involvement in psoriasis these new data are surprising. The Jun proteins (c-Jun, JunB and JunD), together with the Fos proteins (Fos, FosB, Fra1 and Fra2) and some members of the ATF and CREB protein families, are the principal components of the activator protein 1 (AP-1) transcription factor.[9] C-jun plays an essential role in cell proliferation by regulation of cell cycle regulators such as p53 and cyclin D1, whereas JunB negatively regulates cell growth by activating the $p16^{INK4a}$ inhibitor and decreasing cyclin D1 expression.[10] It has been proposed that the

balance of Jun proteins with opposing effects determines whether cells progress through the cell cycle or die.[10] Not surprisingly, both c-jun$^{-/-}$ and junB$^{-/-}$ mice have embryonic lethal phenotypes.[11]

In their paper, the authors knocked out JunB and c-Jun in the epidermis of postnatal mice. Single knockout mice had no observable changes but JunB/c-Jun double-knockouts developed psoriasis-like features associated with destructive arthritis. Furthermore, the authors showed that JunB is downregulated in human psoriatic lesions, whereas c-Jun was slightly upregulated. Histologically, the mouse knockout skin lesions showed infiltration of neutrophils and lymphocytes, with upregulation of several cytokines and chemokines known to be increased in psoriatic lesions: interleukin-1α (IL-1α), IL-1β, interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α).

Notably, the S100A8 and S100A9 genes were upregulated shortly after epidermal knockout of c-Jun and JunB, before any of the other cytokine and chemokine genes were detectably induced. The genes encoding S100A8 and A9 are localized to the epidermal differentiation complex (EDC) on human chromosome 1q21.3, together with at least 58 genes involved in keratinocyte terminal differentiation.[12] Along with several other EDC genes, S100A8 and S100A9 are strongly overexpressed in psoriasis.[13] While both linkage and association to the EDC have been reported in psoriasis,[14] these results remain to be widely confirmed.

Knocking out the same genes against a background of T- and B-cell deficiency (Rag2 knockout mice) or tumour necrosis factor receptor 1 (TNFR1) deficiency resulted in a slight reduction of the epidermal inflammation and hyperproliferation but near complete resolution of the arthritis. Thus, the authors viewed their results as being consistent with epidermal initiation of an inflammatory and hyperproliferative cascade with minimal contribution of T-cells.

Despite the similarities of this model to psoriasis, there are several important differences. No expression of IL-12 (IL-12p35) or IL-18 was seen in lesional skin, but these cytokines are characteristically upregulated in psoriasis and their levels decrease with clinical improvement.[15] Likewise, interferon-γ (IFN-γ) was only slightly upregulated and in a delayed manner, whereas it is markedly upregulated in psoriasis. Furthermore, the histopathological images presented showed intercellular edema (spongiosis) between keratinocytes, a finding characteristic of eczema, but not of psoriasis. The apparent lack of remission when the model was established on the background of immunosuppressed animals (Rag2 knockout and TNFR1) goes against most of the data on the pathogenesis of psoriasis accumulated over the past 15 years, including the fact that TNF antagonists are highly effective against psoriasis.[2]

These discrepancies indicate that the argument that T cells are unlikely to initiate psoriasis in humans must be viewed with caution. Various other transgenic and knockout mice developed over the past decade mirror many of the aspects of the psoriatic phenotype and pathogenesis. Although these models have been valuable for studying the effects of these specific factors, their utility in psoriasis research has been limited as each of them only reproduce certain aspects of the psoriatic pathomechanism.

One way of viewing the histologic and molecular changes seen in psoriasis is as a regenerative phenotype, comparable to what is seen in wound healing.[16] Interestingly, S100A8 and S100A9 are rapidly upregulated following epidermal injury.[17] The intracellular cascades driving these changes are unknown but these new results[1] might indicate that the epidermal change in psoriasis are driven, at least in part, by changes in the expression of the c-Jun and JunB proteins. Other studies that show decreased AP-1 DNA binding activity in lesional psoriatic skin support this idea.[18] Although the double knockout results in a psoriasis-like phenotype in mice, this model does not establish whether the changes in the expression of c-Jun and JunB in human psoriatic lesions are secondary to the release of inflammatory mediators from activated T cells or are due to a primary defect in keratinocytes. It is possible that alterations in c-Jun and JunB expression and/or activity represent a common final pathway involved in the regenerative phenotype that is characteristic of psoriasis. Clearly further experiments are necessary to determine the utility of this new model. Given that the JunB gene is localized to the psoriasis susceptibility locus PSORS6,[2] a search for allelic association between psoriasis and variants of c-Jun and/or JunB certainly seems warranted■

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