
In This Issue

Breast Carcinomas and Cell Cycle Regulators

Atypical nevi, which are the precursor stages of malignant melanoma, are defined by their size (≥ 5 mm in diameter), irregular borders, and irregular brown color. In patients with a history of familial or sporadic melanoma, atypical nevi have to be persistently monitored to detect the earliest signs indicative of progression to melanoma. Surgical excision is currently the only way to prevent this progression. For patients who are at high risk for melanoma relapse, systemic interferon- α (IFN- α) treatment has been shown to benefit relapse-free and overall survival. Data in the literature demonstrated that IFN- α induces the activation of a family of proteins called Stats, which represent transcription factors that acti-

vate a number of different genes. To determine whether IFN- α can modulate these transcription factors in melanoma precursor lesions, patients who had a prior melanoma and displayed multiple atypical nevi on their skin, were treated for three months with low-dose IFN- α . Using novel imaging technology and biochemical assays, the data presented in the study by Kirkwood et al. (pp. 11–20) document that this clinical treatment leads to inactivation of the transcription factors, Stat1 and Stat3, in melanoma precursor lesions. This finding suggests that inhibiting these factors may open one possible avenue to preventing progression of atypical nevi to melanoma.

The Role of MDM2 in p53 Inhibition

The tumor suppressor p53 can cause growth arrest or apoptosis in response to various signals, including stress and genomic damage, and roughly 50% of tumors carry mutations in p53. The MDM2 oncogene has recently been shown to bind to and inhibit p53, and is able to promote p53 degradation by acting in the ubiquitin proteolytic pathway. On pages 21–34, Chen et al. report the development of an improved antisense-MDM2 oligonucleotide that specifically inhibits MDM2 production. Surveying a panel of over 25 tumor cell lines revealed that MDM2 inhibition led to an increased level of nuclear p53

accumulation and activity. Most importantly, the increased activity of p53 was also seen in tumor cell lines that have low endogenous levels of MDM2 and p53. The authors suggest that inhibition of MDM2 expression may serve as an important therapeutic avenue for augmenting drugs that are poor p53 activators, or complementing those drugs that do not activate p53 at all. They caution, however, that systemic p53 activation may be deleterious in normal cells that rapidly proliferate, such as the cells of the hematopoietic system, and that the specificity and toxicity of MDM2 inhibitors require further study.

Production of Human Anti-RSV Antibodies

The use of human monoclonal antibodies remains the sole immunotherapy available for the treatment of many infectious diseases, including respiratory syncytial virus (RSV). However, since there is no general way to activate human B cells against a particular antigen, the production of fully human antibodies is inefficient or, in many cases, impossible. Although B cells have been cloned from immune donors by Epstein-Barr virus (EBV)-transformation and subsequent pas-

sage through severe combined immunodeficiency disorder (SCID) mice, extensive viral removal procedures would be necessary before using the antibodies therapeutically. Furthermore, descriptions of cloned VH2 genes, which may often be a source for high affinity antibodies, are noticeably absent from the literature. On pages 35–45, Heard et al. report the development of a new step in the cloning of VH2 genes. After passage through SCID mice, the VH2

mRNAs were isolated from the immortalized B cells and cloned. To overcome the difficulties encountered in polymerase chain reaction amplification, most likely due to secondary structures in the mRNA, thermostable reverse transcriptase was employed, yielding two related,

high affinity anti-RSV antibodies. The authors suggest that the use of this system in the development of an immunotherapy for this disease will be more economically feasible than the current use of non-specific, anti-RSV immunoglobulins given by intravenous injection.

***Borrelia burgdorferi*: Potential Cargo of the Fibrocyte**

One of the most debilitating results of chronic infection of *Borrelia burgdorferi*, the causative agent of Lyme disease, is the onset of Lyme arthritis. The spirochete is known to bind host plasminogen, which can be activated to form the potent serine protease plasmin. Additionally, it has been shown that *B. burgdorferi* carries endogenous collagenase and proteoglycanase activities that may play an important role in the development of the associated arthritis. Although the blood stream may passively carry the spirochetes to the joints, other more specific mechanisms may be involved. A recently described novel circulating lymphocyte, the fibrocyte, has the potential to be involved in such a mechanism, since it expresses on its surface collagen type I, colla-

gen type III, vimentin, and fibronectin, and is present in connective tissue scars. On pages 46–54, Grab et al. report finding light- and electron microscopic evidence that the *B. burgdorferi* spirochete can react directly with fibrocytes. This interaction appears to promote changes in the membrane of the fibrocyte, and the spirochete becomes imbedded within deep invaginations of the fibrocyte's cell membrane. The authors suggest that the crevices formed by these invaginations help to shelter *B. burgdorferi* from the immune system as well as the fibrocyte's lysosomal-digestive system, and that the fibrocyte may play an important role in spirochete targeting to the joint tissue.

The Potential Role of P210bcrabl on Chemokine Expression in a Myeloid Cell Line

One of the predominant genetic markers of chronic myelogenous leukemia (CML) is a translocation event between chromosomes 9 and 22. This creates a fusion gene product between the normal cellular proteins bcr and cabl, a protein kinase. Because this misregulated product, called P210bcrabl, has been associated with several post-receptor kinases and transcriptional regulatory proteins, Lane et al. tested its ability to alter the expression levels of mRNAs in a transfection assay using differen-

tial display-PCR. On pages 55–61, they report finding that the transfected P210bcrabl cDNA led to a decrease in expression of the beta-chemokine C10. From this, the authors hypothesize that a decrease in the expression of beta-chemokine C10 may be one of the many changes generated in myeloid cells by P210bcrabl, and this change in beta-chemokine C10 expression partially contributes to the unregulated growth of myeloid progenitor cells in CML.