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# In This Issue

## Unraveling Gastrin in Colon Cancer

For many years investigators have been attempting to determine the role of gastrin, a peptide hormone that controls gastric acid secretion, in the development of colon cancer. The first indications came from the observation that gastrin has the ability to stimulate gastrointestinal cell proliferation and differentiation. However, there have been several conflicting in vitro and in vivo reports of the ability of gastrin or pentagastrin to stimulate the growth of colon cancers. This scenario is confounded by conflicting reports of gastrin levels within human colon cancers. Two recent findings, however, have begun to turn the tide. First, a recent epidemiological study has found that prolonged hypergastrinemia correlates with an increased risk of some human colonic and gastric tumors. Also, recent investigations have shown that progastrin and progastrin processing intermediates, such as glycine-extended gastrin, which are not recognized by conventional anti-gastrin antibodies, are found in large amounts in colon cancers. This has led Stepan et al. to look into the proliferative effects of the progastrin processing intermediate glycine-extended gastrin (G-Gly) on colon cancer cells. On pages 147–159, these authors report the presence of a receptor for G-Gly on colon cancer cells. Incubation of these cells with the equivalent of plasma level concentrations of G-Gly led to an induction of cell proliferation through a JNK-mediated signalling pathway. Furthermore, incubating the colon cancer cells with both G-Gly and mature gastrin revealed a synergystic effect on cell proliferation. These observations lead the authors to suggest that human colon cancers may be capable of stimulating their growth in an autocrine fashion, through the use of gastrin processing intermediates.

## Potential Pathogenicity of the Presenilins

The development of familial Alzheimer's disease has been attributed to missense mutations in two highly homologous proteins, presenilin 1 (PS1) and 2 (PS2). These proteins are typically found in the endoplasmic reticulum and the Golgi apparatus, and undergo several post-transcriptional modifications. Among these modifications are endoproteolytic cleavages that lead to the formation of N-terminal and C-terminal fragments. However, the role of these fragments in the onset of Alzheimer's disease remains to be established. On pages 160–168, Alves da Costa et al. report finding that the C-terminal fragments of PS1 and PS2 lead to an increase in the secretion of A-$\beta$ and APP-$\alpha$, two products of $\beta$APP degradation that accumulate in brain and correlate with disease onset. Furthermore, this group demonstrates that both of these fragments are targets of the proteasome, and inhibiting proteasome activity exacerbates the production of A$\beta$ and APP$\alpha$. These observations led the authors to speculate that the C-terminal fragments of PS1 and PS2 have a biologically active role the maturation of $\beta$APP, a function that is modulated by the proteasome.

## The Shb Adaptor Protein and Apoptosis in Beta Cells

Type 1 diabetes mellitus is characterized in part by the loss of pancreatic beta cells. Because these cells appear to be limited in their ability to regenerate, much work has been devoted to the study of beta cell formation through the replication of existing beta cells, beta cell neoformation from precursor cells, and beta cell survival. In an effort to identify pathways involved in beta cell replication, Welsh et al. have recently cloned and partially characterized the serum-inducible gene Shb from a beta cell line. The physiological role of Shb has yet

to be elucidated, despite their finding that its Src homology 2 (SH2) and phosphotyrosine binding (PTB) domains, as well as its proline-rich motif, interact with various cellular proteins. To illuminate this subject, Welsh et al. created transgenic mice expressing Shb under the control of the rat insulin 2 promoter. On pages 169–178, they report that a modest level of overexpression of Shb results in an increased rate of glucose clearance and an increase in β-cell mass, detectable on day one neonatally. Trans-gene expression appeared to have no effect on β-cell replication in adult mice, suggesting that it may play a role in β-cell replication or neoformation from precursor cells during fetal development. However, it was also found that the β cells of these transgenic mice were more susceptible to the β-cell toxin streptozotocin, implicating Shb in an apoptotic pathway. The authors suggest that the balance of these two activities may be of extreme importance in the development of type 1 diabetes.

## A New Role for MIF

Macrophage migration inhibitory factor (MIF) was originally described as a factor, derived from T-cells, that prevented the random migration of macrophages. Since its cloning and molecular characterization several years ago, MIF has been found to have critical regulatory activities on the host immune and inflammatory responses. MIF plays a pivotal role in the host response to gram negative and gram positive shock and acts to regulate macrophage activation, and mitogen and antigen-driven T cell proliferation. MIF is unique among pro-inflammatory mediators in that its expression is induced by glucocorticoids, and in its ability to counter-regulate the immunosuppressive effects of glucocorticoids on macrophage and T cell cytokine production. On pages 179–189, Chesney et al. report finding a role for MIF in angiogenesis, complementing recent studies that have found MIF expressed in dermal capillaries and inflammatory lesions in vivo. The authors have found that MIF is expressed in tumor-associated endothelium, and is necessary for microvascular endothelial cell proliferation. Furthermore, it was shown that MIF is required for neovascularization in a mouse model of solid tumor formation. The authors suggest that unraveling the mechanism of action of MIF in the host angiogenic and immune response to tumor formation could lead to new insights into the regulatory pathways that control tumor growth.

## Exploring the Mechanisms of SIRS

Systemic Inflammatory Response Syndrome (SIRS) is a transient inflammatory response that, in about 10% of critical care patients, deteriorates into septic shock. Animal models have shown that the induction of septic shock involves a complex cascade of cytokines. However, disappointing clinical studies of several potential therapies have suggested that the underlying molecular mechanisms of SIRS may vary from one patient to another, and may be dependent upon the initial cause. If this were to be true, it would be unlikely that a single therapeutic could control SIRS and its progression to sepsis. In order to investigate this further, Wiegand et al. used differential display to examine gene expression in monocytes isolated from patients meeting the Consensus Conference definition of SIRS. On pages 190–200, the authors report finding seven differentially expressed sequences that correlate with SIRS, suggesting that there may be an underlying common mechanism of disease onset. While none of the sequences appear to be from known genes, the authors suggest that these moderately upregulated products could fit a model of progression of SIRS to shock, in which a series of small changes in gene expression leads to the loss of control of monocyte activation.