Molecular Medicine 5: 285-286, 1999

Molecular Medicine

In This Issue

Of Mice and Monkeys: DNA Vaccines and the Immune Response

According to studies performed in animal models, DNA vaccines carry the potential to overcome many of the limitations of antigen-based immunization techniques, by eliciting major histocompatibility complex (MHC) presentation and prolonging antigen production. This led to great expectations for the use of DNA-based immunizations in humans. However, recent clinical trials have been disappointing. The poor immune responses that were found could arise for a number of reasons, including morphological differences of the cells and dosage differences. Another likely reason, vaguely suggested by a number of studies, may be the route and method of vaccine delivery. Despite the effort to develop DNA-based vaccines, few studies in mice, and fewer in non-human primates, have been published that directly compare the immune responses generated by different methods of vaccine delivery. On pages 287–300, McCluskie et al. present the results of an extensive study of vaccine delivery routes, and the immune responses that they generate, in both mice and rhesus monkeys. This group found a wide range of immune responses between delivery routes. Furthermore, they found that success in the mouse model was not necessarily predictive of the findings in the primates. The authors suggest that this observation is not necessarily surprising, since vaccine efficacy is dictated not only by the immune response, but also by factors that may vary more greatly between species, including successful cell transfection and subsequent antigen presentation.

T Cell Subsets in Tuberculous Meningitis

The advent of antibiotics led developed countries such as the U.S. into a false sense of security in regard to infectious diseases. Among those on the temporary decline was tuberculosis (TB). Today, in Europe and the US, the incidence rate of TB is rising; in underdeveloped countries, TB remains a leading infectious disease. Acquired immunity against TB is dependent upon $\alpha\beta$ T cells, and their interaction with macrophages. A few reports, however, have raised the possibility that $\gamma\delta$ T cells may also be involved in producing an immune response to TB. Because there have been conflicting reports on the numbers of $\gamma\delta$ T cells in response to TB infection, the role of this type of T cell remains unclear. Dieli et al. have recently conducted a series of studies on the cerebrospinal fluid (CSF) of children affected by TB meningitis. On pages 301–312, the authors report finding that more than 80% of the $\gamma\delta$ T cells in the CSF of infected children were of the Vγ9/Vδ 2 subtype, while this population made up less than 30% of the $\gamma\delta$ T cells in normal children. In vitro analyses revealed that this subset of $\gamma\delta$ T cells proliferated in response to several phosphoantigens, and produced discrete amounts of IFN-γ and TNF-α. Interestingly, the authors report that four months after treatment with antituberculosis chemotherapy, the levels of Vγ9/Vδ2 T cells returned to normal. IFN-γ has known protective roles in raising the immune response to TB infection. TNF-α, while crucial for the induction of IFN-γ production, can have pathogenic effects when overproduced. The decline of Vγ9/Vδ2 cells during recovery, coupled with their ability to produce TNF-α, suggests that these cells may actually contribute to the pathology of this disease, while their type 1 phenotype also suggests a protective role.

Finding Markers of Metastasis in Circulating Tumor Cells

Although treatments for primary tumors are becoming more efficacious, cancer recurrence and metastasis continue to threaten the health of patients. A widely held belief is that detecting

cancer during its early stages, when the tumor cell burden is lower and presumably more treatable, will enhance the prognosis of patients experiencing secondary tumors. However, relatively little is known about the molecular mechanisms that enhance circulating tumor cell survival and metastasis. In the bloodstream, circulating tumor cells are potentially eliminated by many factors, including blood turbulence, natural killer cells, macrophages, nitric oxide, and the induction of apoptosis. On the other hand, tumor cells are subject to fibrin deposits and platelet aggregation, which may help protect them from immune system attacks and trauma. This suggests that circulating tumor cells may have molecules on their surfaces that allow these processes to occur. In an effort to identify novel molecular markers, Fournier et al. used differential display to compare the RNA isolated from the blood of tumor-free subjects with the RNA from the blood of lung, breast, and colon cancer patients. On pages 313–319, they report finding more than 20 up-regulated genes in the cancer patients. Among these was a gene the authors refer to as AB-1, which is 95% homologous to Bcl-2, an apoptosis suppressor. The authors suggest that the use of differential display to identify misregulated genes in the blood of cancer patients may prove to be a useful tool in identifying novel genetic markers in metastasis.

The Role of Cathepsin S in Regulating ECM Interactions

A key player in cell-mediated immune responses against infection is the macrophage. These highly phagocytic cells are activated by a number of external stimuli, resulting in the secretion of well over 100 products. Although the macrophage is thought to be able to influence the structure of the extracellular matrix (ECM) and the basement membrane, the mechanism by which it exerts its effects is uncertain. The family of cysteine lysosomal proteases are among the products that are upregulated upon macrophage activation. Of these, only cathepsin S remains active in neutral pH, making it a strong candidate in the remodeling of ECM in the extracellular environment. In the study presented on pages 320–333, Liuzzo et al. demonstrate that the mRNA levels of cathepsins S, B, and L, as well as the activity of cathepsin S, are regulated by lipopolysaccharide and cytokines. These studies also revealed that cathepsin S can degrade a basement membrane heparan sulfate proteoglycan (HSPG). HSPGs are known to function in adhesion, protease binding, and the regulation of growth factors including bFGF. These observations suggest that cathepsin S might be involved in the regulation of basement membrane signalling and ECM remodeling.

A Potential Role for Cathepsin S in Degenerative Neuropathies

While the secretion of the cysteine protease cathepsin S from macrophages is upregulated in response to various proinflammatory mediators, its intracellular activity and its mRNA levels are decreased as a result of the same stimuli. In a rodent model of neurodegeneration and microglial activation, the mRNA levels of several members of the cathepsin family, and especially cathepsin S, are markedly upregulated; however, the factors that are responsible for this activation have yet to be identified. These observations led Liuzzo et al. to investigate the role of two well characterized growth factors, basic fibroblast growth factor (bFGF) and nerve growth factor (NGF) in cathepsin S regulation. On pages 334–343, the authors report that both bFGF and NGF have the ability to increase mRNA levels, intracellular activity, and secretion of cathepsin S in macrophage and microglial cell lines. They suggest that during injury, bFGF and NGF are released, increasing the activity of the cathepsin proteases. Because they also find that cathepsin S has the ability to degrade myelin basic protein and amyloid β peptide the authors indicate that abberant upregulation of this protease may contribute to the development of neurodegenerative diseases such as multiple sclerosis and Alzheimer's disease. It is of note that dysregulation of NGF is characteristic of both neuropathies. The authors suggest that under normal conditions there is a fine balance between the growth factors and proinflammatory mediators, which are able to down-regulate the mRNAs for several cysteine lysosomal proteases, and that a disruption of this balance can facilitate the onset of disease processes.