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Alopecia during chemotherapy: a hair-razing story

Hair loss is the most visible side effect of chemotherapy for malignant disease. Notorious among chemotherapeutic agents are the anthracyclines, of which doxorubicin is a key example. The hair follicle is a miniorgan richly supplied by blood flow, and is highly susceptible to the toxicity of chemotherapeutics. Previous studies have focused on induction of apoptosis in the proliferating epithelial compartment of the hair follicle. However, epithelial apoptosis is limited and does not adequately explain the severe hair loss of chemotherapy-induced alopecia. In this issue, **Selleri *et al***[1] (p. 1404) performed detailed light and microscopic studies of doxorubicin-induced damage to hair follicles in rats. Attention was given to both the epithelial and supporting mesenchymal compartments of the hair follicle. Rats 7 days old were studied, as their hair follicles are in the first postnatal anagen phase. Intraperitoneal injections of low-dose doxorubicin were given daily over 4 days; severe alopecia arose suddenly around 10 days after the first injection. The first morphologic sign of damage was at 5 days following the first injection: apoptosis of approximately 20% of fibroblasts in the perifollicular mesenchymal sheath, near the interface between connective tissue matrix and the follicular papilla. Remaining fibroblasts became randomized in orientation and showed features of a shift to a quiescent state, not unlike the catagen state of a normal hair follicle. This was in stark contrast to the expected aligned and robust proliferative state of fibroblasts in an anagen hair follicle. By 7 days, the epithelial cells of the hair follicle developed oncosis, a form of cell death characterized by cellular and organelle swelling owing to failure of ion transport pumps and increased membrane permeability. By 10 days, the hair follicles were extensively degenerated, with assumption of a collapsed, shrunken spiral shape. Remaining perifollicular fibroblasts were collapsed into a quiescent cluster, and the majority (75%) of residual follicular keratinocytes were oncotic. The degenerated hair shaft became separated from the sheath, although a connecting epithelial strand remained. (The preservation of this residual epithelial strand gives hope that the hair loss is readily reversible, as this epithelial strand normally plays a pivotal role in hair regrowth by guiding stem cells towards the nascent follicular papilla.)

These novel observations suggest a fundamental shift in the paradigm for chemotherapy-induced alopecia: early apoptotic degeneration in the perifollicular mesenchyme, followed by oncotic degeneration in the proliferative epithelium. These data implicate a causative role for apoptosis in the mesenchymal compartment of the hair follicle in alopecia. Likewise, for those who wish to prevent chemotherapy-induced alopecia, attention should be given to interruption of epithelial oncosis instead of epithelial apoptosis.

References

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VEGF-A overexpression: a common pathway of T-cell and vascular growth in angioimmunoblastic T-cell lymphoma?

Angioimmunoblastic T-cell lymphoma (AILT) is a systemic disorder that arises in middle-aged and elderly individuals, affecting men and women equally. It accounts for 15–20% of all peripheral T-cell lymphomas and 1–2% of all non-Hodgkin's lymphomas. Patients typically present at an advanced stage of disease with lymphadenopathy, hepatosplenomegaly, bone marrow involvement, and often, a skin rash. The median survival is less than 3 years with patients often developing infectious complications. A polymorphous population of medium-sized T lymphocytes are dispersed within a background of extensively arborizing venules and a mixed reactive inflammatory infiltrate including CD21-immunoreactive follicular dendritic-like cells. While T-cell receptor genes are rearranged in three-fourths of cases and Epstein–Barr virus has been detected in B and T cells, the pathogenesis of this disorder remains poorly understood. Specifically, molecular relationships between the neoplastic T-lymphoid population and proliferating endothelial venules are just beginning to be explored. In this issue, **Zhao *et al***[1] (p. 1512) examine the expression of vascular endothelial growth factor-A (VEGF-A) and its receptors in the cellular components of AILT. Affected lymph nodes from AILT patients were studied using laser microdissection, real-time quantitative PCR, and immunolocalization methods. The investigators show that, when compared to reactive hyperplasia, the VEGF-A gene and the two isoforms VEGF121 and VEGF 165 are overexpressed in microdissected lymphoma cells and endothelial

cells of AILT. VEGF-A and its receptor, VEGF-R1, were coexpressed in neoplastic T cells and endothelial cells of affected lymph nodes, bone marrow and especially in regions of lymphoma invasion. Furthermore, high levels of VEGF-A expression correlated with poor disease outcome, which may be related to increased tissue invasion. This study suggests that lymphoma cell growth and vascular endothelial proliferation in AILT share VEGF-mediated growth control and that the VEGF system could be targeted for treatment of this malignant lymphoma.

References

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Chemokines and T-cell trafficking in encephalomyelitis

T-lymphocyte migration into peripheral tissues in response to antigenic stimuli is a complex, multistep process involving selectins, integrins, cell adhesion molecules and members of the chemokine superfamily. The latter include over 40 secreted proteins that are produced by a variety of cell types and regulate migration and activation of leukocytes *in vivo*. Chemokines are divided into two subfamilies, based on predicted primary structures that feature distinctive cysteine-containing motifs: either the first two cysteines are juxtaposed without (C–C) or with (C–X–C) an intervening amino acid. Chemokine receptors (CCRs and CXCRs) and their ligands (CCLs and CXCLs) have been implicated as major mediators of infectious and autoimmune processes. In AIDS, for example, HIV-1 uses CCR5 and CXCR4 as coreceptors for viral entry into target cells.

Experimental allergic encephalomyelitis (EAE) is a well-characterized autoimmune disease that can be induced in various experimental animals by the injection of homogenized brain or spinal cord in Freund's adjuvant. The resulting inflammatory demyelinating disorder is mediated by Th1 lymphocytes, which recognize antigens presented by macrophages and stimulate the cell-mediated immune response that is directed against CNS myelin. Although the chemokine receptor CXCR3 is believed to play a major role in trafficking of activated Th1 lymphocytes, possible roles of this receptor and its cognate ligands have not been adequately studied in EAE.

In this issue, **McColl *et al***[1] (p. 1418) report the cloning of rat CXCL11, which is the least well-characterized of three known CXCR3 ligands. Based on the predicted primary amino-acid sequence, this group synthesized a functional form of CXCL11, which induced chemotaxis of activated T lymphocytes *in vitro* and migration *in vivo*. Expression was increased in lymph nodes and spinal cord from rats with EAE and the astrocyte was implicated as the major cellular source of CXCL11 by immunohistochemistry. The data suggest a functional role for this chemokine and its receptor in inflammatory demyelination. Further work in this area is required in order to better define this role.

References

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Breaking the inflammatory cycle of Crohn's disease: the role of IL-12

Idiopathic inflammatory bowel diseases (IBD), namely Crohn's disease and ulcerative colitis, are debilitating chronic inflammatory conditions of the intestine. Crohn's disease primarily affects the small intestine and colon, can cause stricture, ulceration, and fissure formation, and places the patient at risk for dysplasia and adenocarcinoma. The inciting causes of IBD remain unclear, but Th1 cytokines are thought to play a pivotal role in the development of Crohn's disease. IL-12 is a 70 kDa heterodimeric cytokine comprised of p40 and p35 subunits, that drives naïve T cells to Th1 differentiation. Excessive production of IL-12 by macrophages and dendritic cells is reported to promote the Th1 response in tissues affected by Crohn's disease. IL-12 induction of IFN-γ production promotes the chronic inflammation of Crohn's disease, as IFN-γ stimulates further IL-12 production. Prevention of this self-stimulatory loop might therefore have benefit in diminishing the chronic inflammation of Crohn's disease.

The study of idiopathic inflammatory bowel disease (IBD) took a major step forward with the advent of murine models of chronic intestinal inflammation. A growing number molecular manipulations engender enterocolitis, including generation of mice deficient in IL-2, IL-10, or Stat3; mice transgenically over expressing IL-7; chemically treated mice; and other models. IL-10-deficient mice, in particular, develop a chronic colitis resembling human Crohn's disease. In this issue, **Shiraki *et al***[1] (p. 1491) hypothesized that the IL-12 stimulatory loop would be an effective target for disruption of the chronic inflammation of IBD. Taking advantage of the fact that soluble IL-12 p40 can inhibit the binding of intact IL-12 to its cognate receptor, the authors generated transgenic mice overexpressing IL-12 p40 behind a $T3^b$ promoter. The $T3^b$ gene encodes a nonclassical major histo-

compatibility complex class I molecule, which is expressed exclusively in the intestinal epithelium of C57BL/6 mice. These mice were then crossed with IL-10-deficient (IL-$10^{-/-}$) mice, to generate IL-$10^{-/-}$/^{T3b} IL-12 p40^{+} double-mutant mice. As measured by animal weight gain, colon length, and colon histology, the presence of secreted IL-12 p40 substantially ameliorated the chronic colitis of IL-$10^{-/-}$ mice. In *in vitro* culture, there was substantially less production of IFN-γ from mesenteric lymph nodes and colon tissue of IL-$10^{-/-}$/IL-12 p40^{+} mice *vs* IL-$10^{-/-}$/IL-12 p40^{-} mice. There also was substantially less secretion of intact IL-12 from colon tissue of IL-$10^{-/-}$/IL-12 p40^{+} mice. Fewer $CD4^{+}$ T cells could be isolated from mesenteric lymph nodes of IL-$10^{-/-}$/IL-12 p40^{+} mice. In contrast, generation of IL-4 and TNF-α by these same cultures was comparable. These findings clearly demonstrate the key role of local IL-12 production and signaling in generation of the colitis in IL-$10^{-/-}$ mice. Just as important is the demonstration of the proof-of-principle that overexpression of IL-12 p40 in intestinal epithelia can prevent colitis in the appropriate setting. Indeed, localized gene transduction of the intestinal epithelium becomes a potential option for treatment of Crohn's disease.

References

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Antimuscarinic acetylcholine receptor (M3R) antibodies are directly linked to salivary dysfunction in Sjögren's syndrome patients

Sjögren's syndrome (SS) is an autoimmune disease characterized by functional impairment of the salivary and lacrimal glands, featuring extensive lymphocytic infiltrations and high levels of circulating autoantibodies. The mechanism of salivary dysfunction in SS patients has been hotly debated in the research community. Anti-M3R IgG immunoglobulins have been identified among the autoreactive antibodies. Since M3R is expressed by acinar tissue, it has been hypothesized that anti-M3R antibodies cause a loss of signaling of this receptor through the IP3 pathway. This would lead to decreased Ca^{2+} release and the lack of transposition of the water-channel protein aquaporin from the apical to the basolateral plasma membrane of the secretory epithelial cells. In this issue, **Li *et al***[1] (p. 1430) demonstrate the veracity of this hypothesis. They showed that purified serum IgG from SS patients, but not from controls, significantly inhibited Ca^{2+} flux in a carbachol-stimulated human salivary gland cell line. This effect was specific as it was blocked by the addition of competing M3R peptides, and ATP-induced Ca^{2+} levels were not changed by SS IgG preincubation. Furthermore, they showed that incubation of rat parotid acinar cells with SS IgG prevented pilocarpine-induced trafficking of the aquaporin AQP-5 to the apical membrane, the target site for aquaporin regulation of primary salivary flow. These results suggest that Sjögren's syndrome can be added to the list of autoimmune diseases in which autoantibodies specific for a receptor are the primary cause for the functional impairment that affect patients. Specifically, for Sjögren's syndrome autoantibodies target the M3R acetylcholine receptor; for myasthenia gravis the target is the nicotinic acetylcholine receptor; and for Graves' disease it is the TSH receptor. This paper thus constitutes a major step forward in understanding Sjögren's syndrome pathogenesis, and should provide venues for therapeutic intervention. The question remains whether the production of anti-M3R antibodies by SS patients results from abnormal M3R expression or processing, or from an abnormal immunological environment in their salivary gland that allows the loss of tolerance to this specific antigen.

References

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