

# Innate Immune Response Triggers Lupus-like Autoimmune Disease

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Autoimmune disease is typically defined as an aberrant response of lymphocytes to self antigens that ultimately leads to tissue damage. Reporting in *Immunity*, Green et al. (2007) now show that mice lacking  $\alpha$ -mannosidase II develop an autoimmune disease similar to lupus. Remarkably, this illness is precipitated by an innate immune response to altered self glycans that mimic molecular patterns found on pathogens.

Autoimmune diseases, including systemic lupus erythematosus (SLE), juvenile (type 1) diabetes, rheumatoid arthritis, Crohn's disease, and over 80 others, are generally thought to be triggered by aggressive responses of the adaptive immune system to self antigens, resulting in tissue damage and pathological sequelae (Davidson and Diamond, 2001). Yet, the molecular and cellular mechanisms that underlie the initiation and progression of autoimmune diseases are still poorly understood. In work recently published in *Immunity*, Green et al. (2007) report on a mouse model of an autoimmune disease similar to lupus that does not require the adaptive immune system but is instead triggered by the innate immune response.

For many autoimmune diseases, the key roles of T cells and B cells are well documented and are evident in the success of T cell (anti-CD3) and B cell (anti-CD20) depletion strategies for the treatment of diabetes and rheumatoid arthritis, respectively. Research continues to reveal new insights into the respective roles of the humoral and cell-mediated arms of adaptive immunity and the distinct roles of T cell subsets, for example Th17 cells, in autoimmunity (Bettelli et al., 2007).

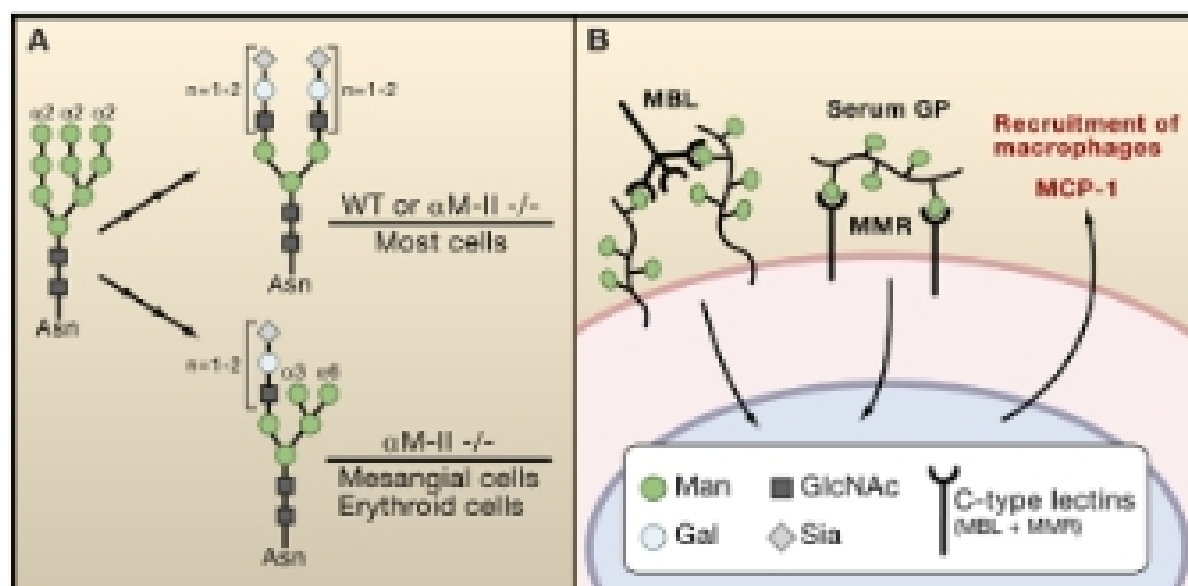
Dendritic cells, macrophages, and other myeloid cells also play important roles in autoimmune diseases, both as antigen presenting cells and

as effector cells that mediate tissue damage (Davidson and Diamond, 2001; Geijtenbeek et al., 2004; Mensah-Brown et al., 2006; Ohtsubo and Marth, 2006). Because these cells are also major mediators of innate immunity, interest has surfaced in the potential for innate immune responses to contribute to disease pathology. Receptors that mediate innate immune responses such as Toll-like receptors (TLRs) and glycan-specific C-type lectin receptors (CLRs) that recognize pathogen-associated molecular patterns (PAMPs) have been implicated in autoimmune disease mechanisms, both directly through recognition of self ligands and indirectly through the regulation of immune homeostasis (Geijtenbeek et al., 2004; Marshak-Rothstein and Rifkin, 2007; Robinson et al., 2006).

In light of the roles of myeloid cells as effector cells in disease progression, can "autoimmune" disease occur in the absence of adaptive immunity? The case of the *moth-eaten* mouse mutant suggests that it can (Yu et al., 1996). *Moth-eaten* mice are deficient in hematopoietic cell phosphatase. They exhibit a severe autoimmune-like disease characterized by alopecia (hence the "moth-eaten" appearance) inflamed paws, high titers of autoimmune antibodies, deposition of immune complexes in kidney and other tissues, and shortened lifespan resulting from pneu-

monia associated with accumulation of leukocytes in the lungs. Although this mouse was considered a model of classic autoimmune disease, Yu et al. (1996) crossed the mice deficient in the hematopoietic cell phosphatase with mice lacking recombinase-activating gene-1 (RAG-1) that are deficient in production of T and B cells. They found that the disease progressed normally in the absence of an adaptive immune response (Yu et al., 1996). Although the mice lacked the high titers of antibodies and deposition of immune complexes in tissues, they exhibited all of the other symptoms of the disease, including shortened lifespan. Although the detailed mechanism of the initiation and progression of the disease was not defined, it was concluded that the autoimmune disease of *moth-eaten* mice was mediated by an aggressive response of macrophages and other myeloid cells.

Now, Green et al. (2007) describe an SLE-like disease in mice deficient in the enzyme  $\alpha$ -mannosidase II ( $\alpha$ M-II) that appears to be driven solely by a mechanism involving an innate immune response (Green et al., 2007). Aging  $\alpha$ M-II null mice acquire symptoms characteristic of SLE and lupus nephritis including high titers of anti-DNA antibody, immunoglobulin deposition in the kidney and other tissues, glomerulonephritis, renal dysfunction, and kidney failure. To assess the



**Figure 1. Self Glycans Trigger an Innate Immune Response in Mice Lacking  $\alpha$ M-II**

(A)  $\alpha$ -mannosidase II ( $\alpha$ M-II) participates in the normal processing of N-linked glycans from the high-mannose type (left) to complex type (top right). In  $\alpha$ M-II null mice, most cell types process glycans normally due to a compensating enzyme,  $\alpha$ M-IX. However,  $\alpha$ M-IX is not expressed by erythroid cells or kidney mesangial cells, resulting in "hybrid" type glycans with terminal mannose residues (bottom right).

(B) Recognition of hybrid type glycans by macrophage mannose receptor (MMR) on mesangial cells, and binding of mannose binding lectins (MBL) to hybrid type glycans on membrane glycoproteins, is proposed to induce expression of monocyte chemoattractant protein-1 (MCP-1). This results in recruitment of activated macrophage effector cells, which then mediate tissue damage that leads to an autoimmune-like disease with features similar to systemic lupus erythematosus.

role of antibodies and the adaptive immune system in the pathology of the disease, mice lacking  $\alpha$ M-II were crossed with RAG-1-deficient mice, which are incapable of producing T and B lymphocytes. Surprisingly, the absence of an adaptive immune system exacerbated and accelerated the onset of the SLE-like disease, demonstrating that the initiation and propagation of the disease was independent of an immune response to self antigen. High dose intravenous immunoglobulin actually reduced the disease pathology, suggesting that the adaptive immune system had a moderating effect. These and supporting results led to the conclusion that the disease is mediated by an innate immune response resulting from  $\alpha$ M-II deficiency.

So, what is the link between  $\alpha$ M-II deficiency and induction of an autoimmune-like disease? The  $\alpha$ M-II enzyme carries out a key step in the biosynthesis of N-linked glycans of glycoproteins and is constitutively expressed in most cell types. Its function is to complete the trimming of mannose residues from the high-mannose type N-linked glycans of newly synthesized glycoproteins, prior to addition of terminal "com-

plex" sugars to the three mannose core structure (Figure 1A). Without this step, the cell makes "hybrid" structures that contain two additional mannose residues on one branch of the N-linked glycans. The deficiency of  $\alpha$ M-II has a minimal effect on glycan biosynthesis in most cell types because another mannosidase,  $\alpha$ M-IX, can compensate for the absence of  $\alpha$ M-II. In cells deficient in both  $\alpha$ M-II and  $\alpha$ M-IX, glycoproteins are produced with the aberrant hybrid type structures. In  $\alpha$ M-II null mice, hybrid structures are increased in serum glycoproteins and are abundantly expressed on kidney cells and cells of the erythroid lineage.

Green et al. provide evidence that the abnormal presence of hybrid glycoprotein structures acts as a trigger for the induction of an innate immune response mediated by members of the C-type lectin family that are specific for mannose. The serum mannose binding lectins (MBL-A and MBL-B) are soluble lectins that mediate innate immunity to pathogenic bacteria and fungi that express mannose-containing glycans. The cell surface macrophage mannose receptor (MMR) is similarly thought to participate in

innate immune responses, and its expression has been documented on kidney mesangial cells (Linehan et al., 1999; Robinson et al., 2006). In  $\alpha$ M-II null mice, MBL lectins are deposited on kidney glomeruli that express high levels of mannose-containing glycans. Mesangial cells also express increased levels of MMR, which can bind mannose-containing ligands in the serum. Elevated levels of monocyte chemoattractant protein-1 (MCP-1), produced by activated mesangial cells, account for the influx of activated macrophages. From these findings, Green et al. propose that the aberrantly expressed mannose-containing glycans in  $\alpha$ M-II null mice act as a trigger for an innate immune response mediated by mannose-specific C-type lectins programmed to recognize high mannose glycans as a PAMP. This results in production of MCP-1 and recruitment and activation of macrophages. The macrophages then serve as the primary effector cells that cause tissue damage and loss of kidney function.

Which came first, the chicken or the egg? Or, in this case, the adaptive or innate immune response? The demonstration of anti-DNA antibodies in serum of  $\alpha$ M-II null mice led the investigators to initially conclude that the SLE-like disease was caused by an aberrant adaptive immune response to self antigens. In fact, this now appears secondary to the primary disease mechanism. The surprisingly minor roles of autoantibodies in the disease mechanisms of the *motheaten* mice and  $\alpha$ M-II null mice are strikingly similar. The take-home lesson may be to keep an open mind with respect to the roles of the adaptive and innate immune responses in mechanisms of autoimmune disease.

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## The VEGF Family, the Inside Story

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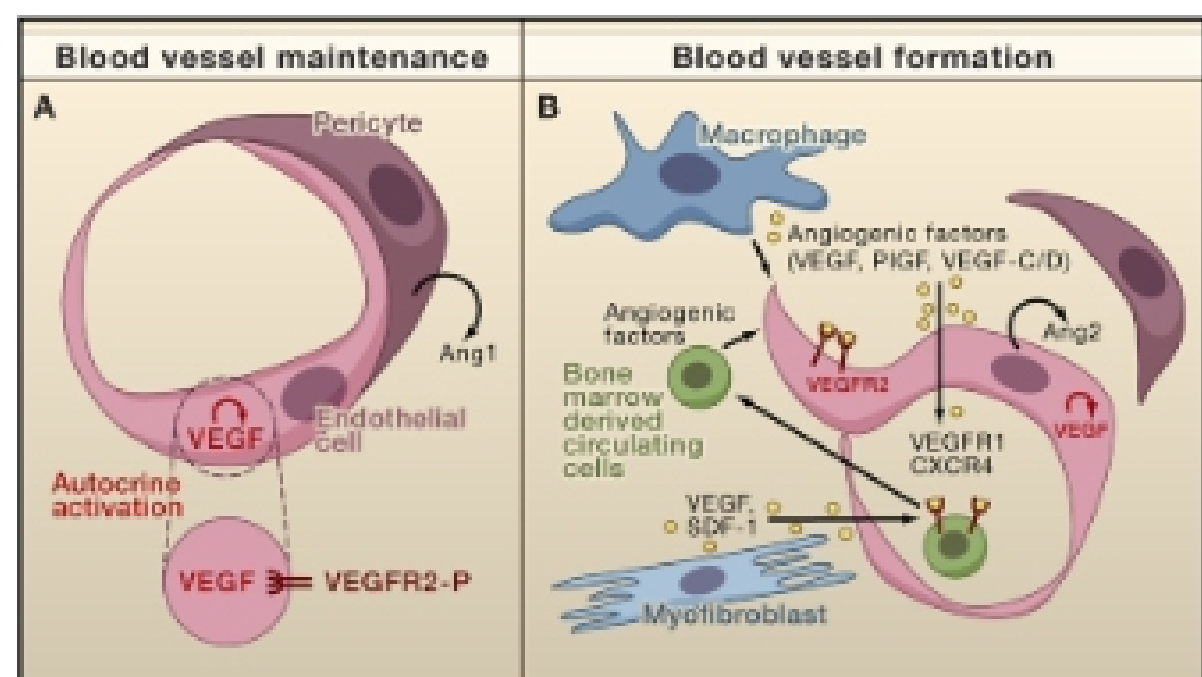
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The role of paracrine signaling by vascular endothelial growth factor (VEGF) in the formation and maintenance of blood vessels has been studied extensively. In this issue, Lee et al. (2007) report unexpected results showing that endogenous VEGF produced by endothelial cells is also crucial for vascular homeostasis.

The function of vascular endothelial growth factors (VEGFs) in the formation and growth of blood vessels has been well characterized. In addition to VEGFs, vascular growth also depends on a bilateral paracrine signaling of factors including platelet-derived growth factor (PDGF) and angiopoietins (Ang), which are involved in stabilizing the vasculature and protecting the endothelium by providing survival signals (Figure 1). The prevailing view is that an endothelial cell protects itself by secreting PDGF-B that acts on pericytes (which cover blood vessels) that in turn secrete Ang1, resulting in the stabilization of blood vessels (von Tell et al., 2006). Endothelial cells were not thought to produce VEGF until recently (Maharaj et al., 2006), but in this issue, Lee et al. (2007) now reveal the surprising result that endogenous VEGF produced by endothelial cells is crucial for vascular homeostasis. These authors demonstrate that in the absence of their own autocrine VEGF, endothelial cells commit suicide causing collateral damage by



**Figure 1. Paracrine and Autocrine Effects of Growth Factors in Capillaries**

(A) During steady-state conditions paracrine angiopoietin-1 (Ang1) and low levels of paracrine vascular endothelial growth factor (VEGF) are produced by pericytes and other cell types associated with the endothelium. Lee et al. (2007) show that VEGF produced by endothelial cells promotes intracellular autocrine stimulation of VEGFR2 that supports endothelial cell survival. (VEGFR-2-P, phosphorylated VEGFR2.)

(B) Several pathways are activated during the formation of new blood vessels (angiogenesis). VEGF production increases in response to ischemia/tissue hypoxia that is in part responsible also for autocrine production of Ang2 involved in pericyte detachment (Yancopoulos et al., 2000). VEGF and placental growth factor (PlGF) as well as stroma-derived factor-1 (SDF-1)—produced by perivascular myofibroblasts—recruit mononuclear cells into the perivascular space by binding to the receptors VEGFR1 and CXCR4, respectively (Grunewald et al., 2006; Luttun et al., 2002). These cells and related macrophages produce additional angiogenic factors including VEGF, VEGF-C, and VEGF-D, and they may in some cases be responsible for why tumors are refractory to continued anti-VEGF treatment (Shojaei et al., 2007).