Could CD44 signal death in diabetes?

CD44 is implicated in a number of autoimmune diseases, including insulin-dependent diabetes. Despite CD44’s proinflammatory capacity, however, inflammation might not be its only pathological mechanism. According to a presentation by David Naor (Hebrew University, Jerusalem, Israel), in diabetes CD44 might also transmit apoptotic signals that kill off insulin-producing pancreatic cells.

CD44 is a widely expressed cell surface protein that, among other functions, promotes cell migration by binding to extracellular matrix components. Its abundance on lymphocytes and neutrophils enables these cells to exit blood vessels and migrate to inflammation sites.

CD44 was implicated in diabetes when it was shown that blockade of CD44 activity delayed or relieved symptoms in a mouse model of type I diabetes called NOD. Naor and colleagues considered that the relief might be due to the inability of inflammatory cells lacking CD44 to migrate to, and create havoc in, the pancreas.

When the team transferred splenocytes from CD44-deficient NOD mice to normal wild-type recipients, however, the recipient mice still developed diabetes, suggesting the CD44-lacking cells were able to migrate to the pancreas. Yet when they tried the reverse, transferring NOD splenocytes expressing CD44 into recipients that lacked CD44, most of the recipients never developed diabetes.

In addition to its migratory functions, CD44 can also transmit apoptotic signals. Apoptotic destruction of insulin-producing pancreatic islet cells is a hallmark of type I diabetes. Naor therefore predicts that, although another molecule may compensate for CD44’s migratory function, expression of CD44 on pancreatic islet cells might be required to deliver a direct death sentence. Reference: Weiss, L., et al. 2000. Proc. Natl. Acad. Sci. USA. 97:285–290.

Human B regs?

If T cells can be regulatory, why not B cells? This proposition has piqued the interest of Sudhir Gupta (University of California, Irvine, CA) since regulatory T cells were first identified. A growing body of evidence now supports the existence of regulatory B cells (B regs), and Gupta’s presentation provided the first data suggesting their existence in humans.

Previous studies of mouse models of autoimmune disorders have indicated that certain subsets of B cells are capable of immune suppression and thus relief of disease symptoms. But, “nobody looked from the point of view of purifying the B cells themselves,” explained Gupta. Furthermore, nobody had looked for human regulatory B cells.

Gupta and colleagues have a long-standing interest in memory T cells, so as a starting point they looked at the effect of isolated human B cells on memory T cell development. Activation of naive T cells in culture promotes proliferation and then differentiation into central memory and effector memory T cells. But coculturing these cells in a particular way with activated B cells, Gupta showed, specifically inhibited the production of effector memory T cells.

It is unclear as yet whether the B cells inhibit the differentiation or proliferation of effector memory T cells. It is clear, however, that the lack of effector memory T cells was not a result of apoptosis. What’s also clear is that the B cells inhibit the T cells by using both a soluble factor (or factors) and cell–cell contact.

The team is currently determining which subset of human B cells are responsible for effector memory T cell inhibition and investigating whether B regs can suppress other subsets of T cells or other immune cell types. Reference: Mizoguchi, A., and A. K. Bhan. 2006. J. Immunol. 176:705–710.
Lupus and the CD5 switch

New data presented by Yves Renaudineau (Brest University Medical School, Brest, France) unraveled a chain of events leading from cell cycle arrest to autoimmunity via the switching on of a defective B cell dampener.

Loss of this dampener, called CD5, makes mice prone to autoimmune problems such as those experienced by lupus patients. CD5 is normally expressed on the cell surface, but Renaudineau and colleagues had previously identified an alternative transcript that produces a cytoplasmically retained form of the protein.

The cytoplasmic version arises from the inclusion of an upstream human endogenous retrovirus (HERV) element. Such retroviral elements are generally silenced by DNA methylation, but lupus has been linked to defective DNA methylation.

Renaudineau showed that the HERV-CD5 promoter region was indeed under-methylated in activated B cells from lupus patients. This was coupled with failed induction of the DNA methylator DNMT1. As a result, transcription of the cytoplasmic form of CD5 was strongly up-regulated. Too much cytoplasmic CD5 led to a decrease in cell surface CD5 expression.

The team blames the lack of DNMT1 on a failure of the patient cells to efficiently proliferate upon activation, as DNMT1 is normally up-regulated in cycling cells. Renaudineau suggests that the resulting lack of surface CD5 expression makes the B cells prone to promiscuous activation and thus to autoantibody production. JEM

Reference: Renaudineau, Y., et al. 2005. Blood. 106:2781–9.

Eating trash prevents lupus

Just as letting garbage accumulate can be a health risk, failure to clear-up dead and dying cells is a risk factor for lupus. Work presented by Martin Herrmann indicates why some lupus patients’ cells are not so good at taking out the trash.

The disposal of apoptotic cells is defective in approximately half of all lupus cases. As these cellular corpses decay, antigens that are normally hidden inside the cell become exposed to the immune system. This is thought to cause the production of autoantibodies against nuclear components, which is the main immunological characteristic of the disease.

Dying cells are normally eaten by phagocytes before their nuclear antigens are exposed. But the team found that phagocytes derived from blood stem cells of some lupus patients failed to gobble up artificial targets efficiently. This phagocytosis defect correlated with an adhesion defect, as the patients’ phagocytes were unable to bind regular plastic culture dishes. “The better the cells stick,” says Herrmann, “the better they eat.”

The cause of the adherence and phagocytosis defects is not yet known. Herrmann suspects that the patients’ blood stem cells might not be maturing correctly, as they initially appeared normal.

Failure to clear apoptotic cells is likely to be caused by different defects in different individuals. Although the adherence and phagocytosis defects were observed in approximately half of lupus patients, only phagocytosis was impaired in a smaller percentage. Herrmann also presented preliminary data suggesting that a failure of phagocytes to migrate toward apoptotic corpses could be to blame in some patients. JEM

Reference: Kuhn, A., et al. 2006. Immunol. Lett. 106:8–13.

Sleeping LINEs

For the safety of the genome, endogenous retroviral sequences, such as LINEs, are kept caged by DNA methylation. But these cages are thrown open in rheumatoid arthritis (RA), according to a presentation by Steffen Gay (University Hospital, Zurich, Switzerland).

The up-regulation of retroviral elements might thus be a common defect in autoimmunity (see also “Lupus and the CD5 switch”).

The destruction of bone and cartilage in RA is not solely the responsibility of immune cells. Synovial fibroblasts, which line the joints, also get activated and begin to aggressively attack the joints by producing matrix degrading enzymes as well as promoting the maturation of bone-destroying osteoclasts.

The discovery that synovial fibroblasts express Toll-like receptors led the team to consider that transformation into this invasively growing, activated state might be triggered by an environmental agent. However, the combination of a decade’s unsuccessful hunting for such an agent, with new findings that synovial fibroblast activation is coupled with strong up-regulation of retroviral LINEs, leads the team to now speculate that in fact these endogenous agents are to blame. DNA methylation was reduced in patient synovial fibroblasts, explaining how the LINEs are awakened.

Endogenous retroviral activation in these fibroblasts could explain why antiinflammatory treatment generally only slows joint destruction but rarely stops it altogether. Combining antiinflammatories with treatments that prevent the demethylation could prove to be a more effective remedy for RA. JEM

Reference: Karouzakis, E., et al. 2006. Immunol. Lett. 106:8–13.