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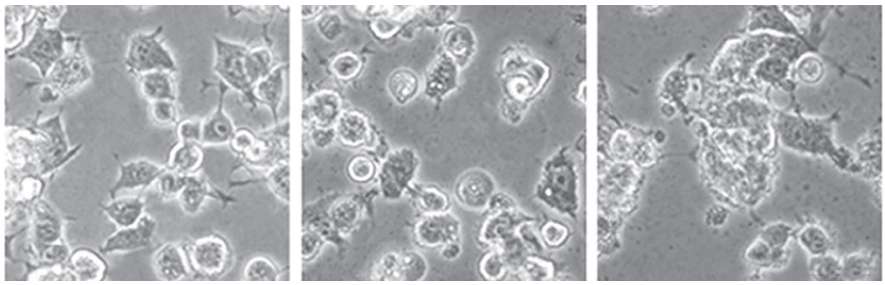

Contribution of c-Ret to the pathogenesis of ALS

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by loss of motor neurons in the spinal cord, brain stem, and motor cortex, resulting in progressive paralysis of limb, bulbar, and respiratory muscles. Mutations of superoxide dismutase-1 are associated with familial ALS, suggesting a role for free radical damage in the pathogenesis of the disease. Motor neurons are thought to be particularly vulnerable to oxidative stress. Microglia—macrophages of the central nervous system—play an important role in ALS by releasing reactive oxygen species, which damage motor neurons. c-Ret is the kinase component of the glial cell line–derived neurotrophic factor receptor complex, which is central to motor neuron health and function. Previous work has shown that c-Ret is differentially expressed in motor neurons as well as in non-neuronal cells in the spinal cord in an ALS transgenic mouse model. As reported in this issue, Ryu *et al* investigated the relationship between oxidative damage and both c-Ret levels and C-Ret phosphorylation patterns in ALS.

The authors discovered that c-Ret colocalized with neurofilament aggregates in motor neurons in a mouse model of ALS. When they examined c-Ret in a motor neuron–like cell line, they found that expression of a mutant form of superoxide dismutase-1 associated with ALS caused c-Ret to become dephosphorylated at critical tyrosine residues, followed by ubiquitin-mediated degradation. Exposure to reactive oxygen species also resulted in loss of c-Ret. Examination of mouse tissues revealed that the microglia of ALS mice contained increased amounts of c-Ret. This suggested to the authors that increased c-Ret in microglia might be a biomarker for ALS.

Mechanism of clearance of apoptotic intestinal epithelial cells

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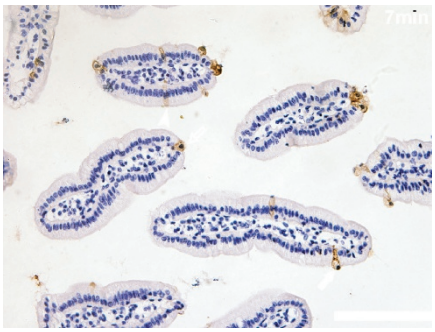

Intestinal epithelial cells die and are replaced in both normal and pathological processes within the intestine. It is critical for mucosal immune function to maintain epithelial barrier function during the process of elimination and replacement of apoptotic intestinal epithelial cells. Previous studies have shown that once apoptotic intestinal cell are extruded, a gap is left that eventually closes. It has been suggested that apoptotic epithelial cells are sensed by neighboring cells that contract to extrude apoptotic cells. However, it is difficult to reconcile how neighboring cells can extrude apoptotic epithelial cells and still leave a gap. To attempt to rectify this apparent discrepancy, Wang *et al* developed an *in vitro* system to study clearance of apoptotic intestinal epithelial cells.

By isolating and culturing whole intestinal crypts either with or without basal lamina, and using beautiful, state-of-the-art imaging techniques, the authors observed that apoptosis preceded the extrusion of epithelial cells and that in the presence of basal lamina the apoptotic epithelial cell nuclei were extruded apically, leaving the cytoplasm to plug the gap. Contrary to the prevailing idea that the neighboring cells contract to extrude the apoptotic cell nuclei, they found that the apoptotic cells themselves were responsible for extruding their nuclei. Once the nucleus was extruded, neighboring cells were in a position to cover the gap with their cell membranes, thus maintaining barrier function. These results offer novel insights into how altered apoptotic epithelial shedding may contribute to various pathological conditions.

A critical role of TNFR2 in mediating response to TNF-α in podocytes

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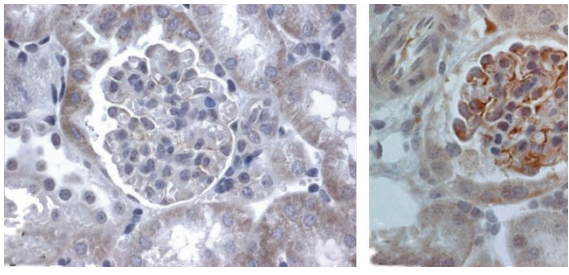
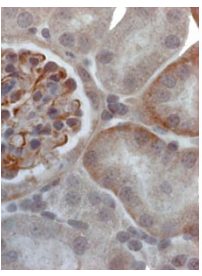
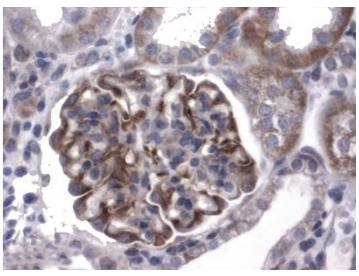
Crescentic glomerulonephritis and collapsing glomerulopathy are proliferative podocytopathies that are thought to have a common pathogenesis. Although there is considerable evidence linking the tumor necrosis factor-α (TNF-α)-TNF receptor 2 (TNFR2) signaling axis to both diseases, many issues remain unresolved. One important question is whether



podocytes themselves express TNFR2 and thus serve as the direct target of TNF-α in both crescentic glomerulonephritis and collapsing glomerulopathy or whether the presence of TNFR2 on other glomerular cells mediates the pathogenesis of both diseases. To address this issue, Bruggeman and colleagues asked whether TNF-α binding of TNFR2 on podocytes could precipitate changes characteristic of crescentic glomerulonephritis and collapsing glomerulopathy.

The investigators found that TNFR2 was present on podocytes in a mouse model of collapsing glomerulopathy and in human renal biopsies from patients with crescentic glomerulonephritis and collapsing glomerulopathy. Furthermore, they showed that levels of serum TNF-α and soluble TNFR2 correlated with the degree of renal injury. Analysis of podocytes *in vitro* demonstrated that TNF-α stimulated proliferation and activation of pro-inflammatory nuclear factor-κB (NF-κB) signaling, which was ablated by a blocking antibody to TNFR2 or RNA interference–mediated depletion of TNFR2. Finally, they demonstrated that TNF-α-stimulated podocytes induced the transcription of many pro-inflammatory genes. In summary, these results show that TNF-α binding to TNFR2 on podocytes stimulates podocyte proliferation and also results in podocyte-mediated inflammation via NF-κB signaling. Further studies are required to determine the stimuli that lead to TNFR2 production by podocytes or whether there is an inherent defect in the podocytes of patients who are susceptible to proliferative podocytopathies that makes them more sensitive to TNF-α stimulation.





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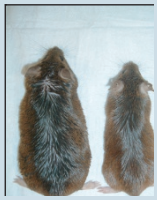
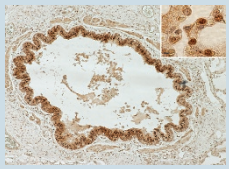
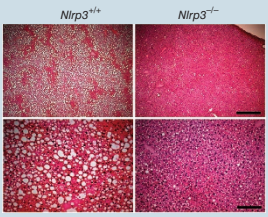
MYD88 mutations activate NF-κB in large B-cell lymphoma Diffuse large B-cell lymphomas (DLBCLs) are subclassified as activated B-cell-like (ABC), germinal center B-cell-like (GCB), or primary mediastinal B-cell (PMBL) subtypes. In a recent letter in *Nature*, Staudt and colleagues describe their RNA interference screen to identify genes required for proliferation and survival in DLBCLs. They found that small hairpin RNAs targeting *MYD88* were toxic to ABC DLCBCL cell lines but not to GCB DLBCL cell lines. Subsequent analysis revealed a leucine-to-proline mutation at position 265 of the *MYD88* coding region in 29% of ABC DLBCL biopsies whereas it was rare or absent in GCB or PMBL subtypes of DLBCL or in Burkitt's lymphoma. However, it was found in 9% of gastric mucosa–associated lymphoid tissue lymphomas. Mechanistically, the authors demonstrated that *MYD88* mutations promoted nuclear factor-κB and JAK-STAT3 signaling, promoting cell survival.
Nature, published online 22 December 2010; doi:10.1038/nature09671



CRTC3 plays a critical role in energy balance CREB (cyclic AMP (cAMP) response element binding)-regulated transcriptional coactivator 3 (CRTC3), as its name implies, binds CREB to activate transcription. CRTC3 signaling is regulated by cAMP signaling, which leads to nuclear entry of CRTC3, thus allowing it to bind CREB. Because cAMP signaling links catecholamine signaling to CRTC3 activation, and because CRTC3 is particularly abundant in white and brown adipose tissue, Song *et al*, as recently reported in *Nature*, constructed a *Crtc3* knockout mouse to study the effect of Crtc3 on adipose tissue metabolism. They showed that *Crtc3*$^{-/-}$ homozygous knockout mice use more energy than heterozygous or homozygous wild-type mice under high-fat-diet conditions. Unexpectedly, they also discovered that one normal role of Crtc3 is to attenuate intracellular cAMP signaling so that loss of Crtc3 results in sustained cAMP signaling and greater energy usage. Finally, they found that a *CRTC3* missense variant (S72N) was associated with increased obesity in Mexican Americans.
Nature 2010;468:933–939; doi:10.1038/nature09564



Unusual distribution of severe 2009 H1N1 influenza disease explained In 2009, a new H1N1 influenza A virus caused severe disease and several deaths, predominantly in middle-aged individuals. Previous pandemic influenza viruses also caused disproportionately severe disease in middle-aged individuals. The mechanism underlying the greater severity in this age group is unknown. In a study described in a letter in *Nature Medicine*, Monsalvo *et al* sought to explain this observation. They observed that elderly individuals were protected from the 2009 H1N1 by neutralizing cross-reactive antibodies to an H1N1 virus encountered before 1957, and young patients lacked previous exposures to seasonal influenza. Middle-aged individuals, however, produced low-avidity antibodies for H1-2009 that were nonprotective and instead resulted in severe immune complex–mediated pulmonary injury that was often fatal. The authors surmised that these nonprotective antibodies were produced as a result of repeated exposure to seasonal influenza.
Nature Medicine, published online 10 December 2010; doi:10.1038/nm.2262



Mechanism of inflammation associated with obesity Obesity-induced inflammation has been linked to the development of type 2 diabetes. Nod-like receptors (NLRs) are a family of proteins that are implicated in identifying signals leading to caspase-1 activation and subsequent inflammation. Inflammasomes are multiprotein scaffolds where caspase-1 is activated. In a recent article in *Nature Medicine*, Vandanmagsar *et al* report that Nlrp3 (nucleotide-binding domain, leucine-rich-containing family, pyrin domain–containing-3), an NLR family member, senses obesity-associated inducers of caspase-1 activation and therefore regulates the development of inflammation and the downstream effects on insulin signaling. These findings highlight the potential for targeting molecules that regulate caspase-1 activation in the management of type 2 diabetes.
Nature Medicine, published online 9 January 2011; doi:10.1038/nm.2279