B-lineage lymphoma B) and CTLA4 (cytotoxic T-lymphocyte antigen 4), also have T cells that are hypersensitive to suboptimal TCR stimulation and are either equally susceptible or more susceptible to autoimmune disease than control animals. However, there were no signs of spontaneous autoimmunity in DRAK2-deficient mice. Furthermore, DRAK2-deficient animals were resistant to induced experimental autoimmune encephalomyelitis (EAE), and this correlated with a decrease in the number of cells infiltrating the central nervous system.

This study identifies a new pathway of negative regulation of T-cell activation, which is mediated by DRAK2. Understanding the surprising observation that DRAK2-deficient mice are resistant to EAE but respond normally to infection with lymphocytic choriomeningitis virus will require further study, but the authors suggest that DRAK2 could be a specific target for the treatment of autoimmune disease.

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References and links

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INFLAMMATION

RIP2 leaves calling card for Crohn's disease

The inflammatory bowel disease Crohn's disease is commonly thought to result from an inappropriate immune response to commensal bacteria in the gut. Although several genetic loci have been associated with disease susceptibility in humans, the link between these disease-associated mutations and intestinal inflammation is not entirely clear. This study further elucidates the involvement of one of the most common associated loci, *CARD15*, which encodes the cytoplasmic protein nucleotide-binding oligomerization domain 2 (NOD2).

After binding its ligand, muramyl dipeptide (MDP), which is derived from intracellular or phagocytosed bacteria, NOD2 is known to bind the protein kinase RIP2 (receptor-interacting protein 2), leading to activation of nuclear factor-κB (NF-κB) signalling through the inhibitor of NF-κB (IκB)-kinase complex (the IKK complex; which consists of IKK-α, IKK-β and NF-κB essential modulator, NEMO).

Previous studies have led to the proposal that RIP2 has a scaffolding role, bringing NOD2 and IKK into close proximity, but Cantley and colleagues now show that RIP2 has a more active role. Co-expression of RIP2 with NEMO led to increased ubiquitylation of NEMO, which is associated with NF-κB activation. Use of a 'kinase-dead' RIP2 mutant showed that the protein-kinase activity of RIP2 is not required for this function. NOD2 was also shown to induce NEMO ubiquitylation, but only in the presence of the NOD2 agonist MDP. A loss-of-function polymorphism in NOD2 that is associated with Crohn's disease reduced the level of NEMO ubiquitylation, and another NOD2 mutation associated with more severe disease inhibited NEMO ubiquitylation entirely.

Next, they tested whether the NEMO ubiquitylation that is associated with MDP-activated NOD2 is due to the known binding of RIP2. Compared with wild-type NOD2, the disease-associated mutants bound significantly less RIP2. Furthermore, when the expression of RIP2 was inhibited by RNA interference, MDP-activated NOD2 failed to ubiquitylate NEMO. This indicates that RIP2 is required for the effects of NOD2 on the NF-κB-signalling pathway and that the NOD2 mutants are associated with Crohn's disease as a result of their failure to bind RIP2 and activate the NF-κB pathway.

Although ubiquitylation of proteins is commonly associated with proteasomal degradation, addition of a proteasome inhibitor to cells producing RIP2 and NEMO did not alter the level of expression of NEMO, showing that NEMO ubiquitylation does not lead to degradation. Instead, NEMO ubiquitylation through the NOD2–RIP2 pathway increases NF-κB activity, as shown by a decrease in activity in the presence of a deubiquitinase. Failure to activate NF-κB signalling through this pathway provides a novel mechanism for the dysregulated inflammatory responses in Crohn's disease.

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