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The kinase LRRK2 is a regulator of the transcription factor NFAT that modulates the severity of inflammatory bowel disease

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Leucine-rich repeat kinase 2 (LRRK2) has been identified by genome-wide association studies as being encoded by a major susceptibility gene for Crohn's disease. Here we found that LRRK2 deficiency conferred enhanced susceptibility to experimental colitis in mice. Mechanistic studies showed that LRRK2 was a potent negative regulator of the transcription factor NFAT and was a component of a complex that included the large noncoding RNA NRON (an NFAT repressor). Furthermore, the risk-associated allele encoding LRRK2 Met2397 identified by a genome-wide association study for Crohn's disease resulted in less LRRK2 protein post-translationally. Severe colitis in LRRK2-deficient mice was associated with enhanced nuclear localization of NFAT1. Thus, our study defines a new step in the control of NFAT activation that involves an immunoregulatory function of LRRK2 and has important implications for inflammatory bowel disease.

Inflammatory bowel disease (IBD), which is generally thought to develop from a dysregulated immune response to the gut luminal biota, includes two main forms: Crohn's disease (CD) and ulcerative colitis. Both genetic and environmental factors contribute to the development of CD[1]. Genome-wide association studies (GWAS) for CD have identified over 40 susceptibility loci[2–4]. The large number of susceptibility genes probably reflects the complexity of the inflammatory process that takes place along the gastrointestinal tract in IBD. The lymphoid tissue in the gastrointestinal tract constantly encounters commensal microbiota as well as potentially pathogenic bacteria; hence, it is critical that a delicate balance be maintained between immune responsiveness and tolerance at this location. Research on susceptibility genes identified by GWAS has exemplified this and has yielded important insights into the pathogenesis of IBD. For example, the immunoregulatory function of regulatory T cells, autophagy and signaling events via interleukin 23 (IL-23) and its receptor have been linked to IBD[5]. Despite such progress, the products of most susceptibility genes have no known mechanism to explain their involvement with CD.

Leucine-rich repeat kinase 2 (LRRK2; also known as dardarin) is encoded by a major susceptibility gene for CD and ulcerative colitis[2,3,6]. LRRK2 is a 2,527–amino acid (286-kilodalton), mainly cytoplasmic protein with several functional domains, including leucine-rich repeats (LRRs), a ROC domain ('Ras of complex proteins'), a COR domain ('C-terminal of ROC'), a kinase domain and a WD40-repeat domain. *LRRK2* has been identified as the gene mutated most frequently in autosomal dominant familial Parkinson's disease, but the pathological functions of LRRK2 in that context are not well understood[7,8]. Many single-nucleotide polymorphisms (SNPs) in the *LRRK2* locus have been associated with CD by GWAS. A rare SNP (rs11175593) in the noncoding region of *LRRK2* is associated with the disease with a P value of 3.08×10^{-10} (odds ratio, 1.54)[2]. Those findings have been verified by independent meta-analyses of the GWAS[3,6]. Searching for a pathogenic function for LRRK2 requires careful examination of subtle effects, because most of the common variants identified by GWAS have thus far been shown to have quantitatively small effects on protein expression or biochemical activities. Disease susceptibility is due to the combined effects of multiple independent loci. In the gastrointestinal tract of patients with CD, LRRK2 expression is restricted to lamina propria macrophages, dendritic cells (DCs) and B lymphocytes[9]. Furthermore, LRRK2 expression is induced by interferon-γ, consistent with the idea that it may have a role in IBD[9]. LRRK2 may also affect the production of reactive oxygen species, which would indicate in a role in antimicrobial activities[9]. The complex domain structure of LRRK2 suggests that it may be an important orchestration node in cellular regulation, but how it participates in the molecular mechanisms of CD pathogenesis is not clear.

NFAT comprises a family of transcription factors important for regulating immune responses. NFAT was originally identified as a transcription factor in T lymphocytes that regulates expression of the gene encoding IL-2 by translocating from the cytoplasm to the nucleus, where it actively binds cognate DNA motifs at enhancer sites in response to Ca^{2+} influx triggered by antigen recognition[10]. NFAT1 regulates innate immune responses in macrophages, DCs and neutrophils, in addition to having well-recognized roles in T cell cytokine production, neuronal differentiation, stem cell maintenance

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