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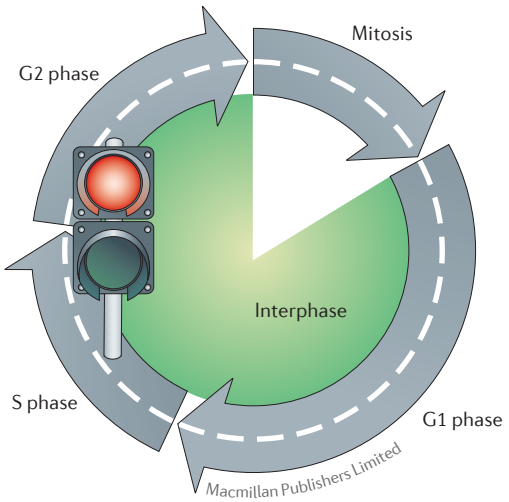
RHEUMATOID ARTHRITIS

Cell cycle stalling linked to arthritis

> In the K/B×N serum transfer model of murine arthritis, mice deficient for LBH had more severe disease…

A single nucleotide polymorphism (SNP) in the enhancer region of *LBH* (which encodes the transcriptional cofactor protein LBH) causes low levels of LBH expression and is associated with rheumatoid arthritis (RA), although the mechanisms involved in this association are unknown. Now, a new study has revealed a role for LBH in progression through the cell cycle and in preventing the accrual of DNA damage.

"Our decision to focus on LBH comes from our unbiased informatics approach," explains corresponding author Gary S. Firestein. "LBH not only appeared in multiple datasets, but also has SNPs associated with other immune-mediated diseases," he continues. "We felt that the computational methods were telling us something important about autoimmunity and how *LBH* might be a seminal gene at the centre of immune dysregulation."



The research team explored the role of LBH in the cell cycle of fibroblast-like synoviocytes (FLS) from patients with RA. FLS with small interfering RNA (siRNA)-induced LBH deficiency failed to progress through the cell cycle, remaining in S phase for ≥72h. Delayed cell cycle progression in LBH-deficient FLS was associated with increased levels of DNA damage compared with scrambled siRNA-transfected control FLS. In addition, checkpoint kinase CHK1 was hyperphosphorylated and the expression of DNA polymerase α was decreased in LBH-deficient FLS compared with controls, suggesting that the accumulation of DNA damage in these cells could lead to activation of the S phase checkpoint and cell cycle arrest.

"A defect in cell division as a mechanism of autoimmunity seems counter-intuitive because immune diseases are usually thought to result from increased proliferation," states Firestein. "However, defects in DNA polymerase due to LBH deficiency led to the accumulation of DNA fragments, which in other systems is known to cause arthritis."

In the K/B×N serum transfer model of murine arthritis, mice deficient for LBH had more severe disease and increased levels of IL-1β compared with wild type mice. These results suggested to the authors that defective proliferation rather than just increased proliferation is important in the pathogenesis of RA.

"This is one of the few genes in RA where a disease-associated SNP is functional, and the results could provide clues about why LBH polymorphisms are associated with so many autoimmune diseases," remarks Firestein.

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