

S002 TREX1 exonuclease of mammalian cells, association with DNA replication and inherited inflammatory disease
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The major DNA- specific 3' to 5' exonuclease of mammalian cells is TREX1 (previously called DNase III). The human enzyme is encoded by a single exon on chromosome 3p21, and like many 3' exonucleases occurs as a homodimer. TREX1 degrades ssDNA faster than dsDNA, and its catalytic properties are similar to those of *E.coli* exonuclease X. However, TREX1 contains a unique C-terminal leucine-rich domain specific to the mammalian enzyme. This hydrophobic region is employed for attachment of the protein to the perinuclear endoplasmic reticulum, but in normal S-phase and also in response to genotoxic stress TREX1 redistributes to the cell nucleus. In collaboration with Yanick Crow (Leeds), we have demonstrated TREX1 enzyme deficiency in Aicardi-Goutières Syndrome. AGS1 cells exhibit chronic ATM-dependent check point activation, and these TREX1-deficient cells accumulate ssDNA fragments of distinct size generated during DNA replication. Other groups have shown that the syndromes of familial chilblain lupus as well as systemic lupus erythematosus, and the distinct Retinal Vasculopathy and Cerebral Leukodystrophy, may be caused by separate mutations at different sites within the TREX1 gene.