

TREX1: A nuclease linked to granzyme A-mediated death, HIV infection and retrotransposition, inflammation and autoimmunity

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TREX1 is the most abundant exonuclease in cells. We first became interested in TREX1 when we identified it as a component of the endoplasmic reticulum-associated SET complex, a 270-420 kDa multiprotein complex that translocates to the nucleus in response to oxidative stress, which we have hypothesized is an oxidative repair complex. The SET complex, which contains 3 nucleases (the base excision repair endonuclease APE1, the endonuclease NM23-H1 and the exonuclease TREX1), is the key to DNA damage during programmed cell death executed by the killer lymphocyte serine protease, granzyme A. Granzyme A activates superoxide production by entering mitochondria and cleaving NDUF3 in electron transport complex I. The superoxide generated drives the SET complex into the nucleus, where granzyme A cleaves the SET protein, an inhibitor of NM23-H1, activating NM23-H1 to make single-stranded DNA nicks. These nicks are extended by TREX1.

TREX1 was recently implicated in genetic mutations associated with a noninfectious neonatal inflammatory disease that resembles congenital infection (Aicardi-Goutiere's syndrome), lupus syndromes and systemic lupus erythematosus (work of Crow, Lee-Kirsch). Mice genetically deficient in *Trex1* develop a fatal inflammatory cardiomyopathy (Barnes and Lindahl). All of these diseases are associated with elevated Type I IFN production. *Trex1*^{-/-} cells accumulate cytosolic retrotranscripts and produce Type I interferons in response to transfected oligonucleotide DNA (Barnes, Medzhitov). These studies suggest that recognition and digestion of cytosolic DNA by TREX1 inhibits triggering of the innate immune response to produce Type I interferons in response to endogenously produced or exogenous DNA.

We have also found that the SET complex plays an important role in promoting HIV infection. The SET complex binds in the cytoplasm to the HIV preintegration complex, which forms after reverse transcription of the viral genomic RNA, and protects it from nonproductive and suicidal autointegration. Although early in its lifecycle, HIV produces numerous cytoplasmic nucleic acid intermediates (viral RNA, RNA:DNA hybrids, double-stranded DNA), HIV infection does not activate a cell autonomous interferon response. In this talk we will present preliminary evidence that TREX1 digestion of HIV DNA intermediates is required for HIV to avoid triggering innate antiviral immunity and thereby facilitates viral infection.

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