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Review

Emerging roles of the processing of nucleic acids and Toll‐like receptors in innate immune responses to nucleic acids

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Abstract

Nucleic acid (NA) is continuously degraded in lysosomes, cytoplasm, and nucleus. NA degradation has a key role in preventing hazardous activation of NA sensors. DNA degradation by lysosomal and cytoplasmic DNases prevents homeostatic activation of cytoplasmic DNA sensing pathways. Crude NA, however, is not sufficient for stimulating NA sensors. mRNAs and rRNAs need to be processed by inositol‐requiring enzyme 1 (IRE‐1) or RNase L before stimulating cytoplasmic RNA sensors. Activation of cytoplasmic RNA sensors by processed RNAs is tightly controlled by their degradation through the machineries, such as RNA editing, by adenosine (A) deaminases that act on RNA 1 (ADAR1) and the RNA exosome. Impaired degradation of processed RNAs in humans causes activation of cytoplasmic RNA sensors, leading to Aicardi‐Goutières syndrome or trichohepatoenteric syndrome. Lysosomal TLRs are also dependent on NA processing in lysosomes. Digestion of dsDNA by DNase II is required for TLR9 response to ssDNA. TLR7 and TLR8 respond to ribonucleosides and oligoribonucleotides, instead of ssRNA itself, indicating requirement for RNA processing. NA‐sensing TLRs themselves need to be processed by lysosomal proteases. Without processing, TLR8 and TLR9 fail to form dimers. In addition to NA degradation, the processing of NAs and TLRs by a variety of enzymes is an emerging concept on the control of innate immune responses to NAs.