Dnase1 Family in Autoimmunity

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The deoxyribonuclease 1 (Dnase1) family is a key family of endonucleases that degrades DNA. Loss of Dnase1 family function causes several diseases where the host's immune system targets the host, such as systemic lupus erythematosus, hypocomplementemic urticarial vasculitis syndrome.

nuclease lupus ehrlichiosis psoriasis HUVS NETs cell-free DNA

Discovery of Dnase1 Family Members

Deoxyribonuclease (Dnase) activity was described in bovine organs in the 1800s, and the proteins responsible for this activity have been characterized over the last century. In the early 1900s, digestion of nucleic acids by liver, spleen, pancreas, and other organs was investigated. As reviewed [1], the enzymatic activity was given a succession of names, including desoxyribonuclease, and determined to function optimally at neutral pH [2]. The founding member of the Dnase1 family, Dnase1, was isolated and crystallized in 1950 [1]. Dnase1 activity was generally recognized to require divalent cations (Ca^{2+} or Mg^{2+}), to act optimally at neutral pH, and to leave 5′ phosphates following DNA cleavage [1][2][3][4]. As reviewed [5], in 1947 a second, "acid DNase" activity was described in mammals [6]. Acid DNase activity had an ubiquitous tissue distribution and showed peak activity at acidic pH [5]. To distinguish the acid DNase from the pancreatic DNase, which was called Dnase I, and later Dnase1, the term Dnase II (later Dnase2) was suggested as an alternative to acid DNase [3]. Dnase2 has no requirement for divalent cations and hydrolyzes double stranded DNA into short oligonucleotides bearing 3′ -phosphate groups [5]. Multiple proteins possess acid and neutral DNase activity. The Dnase II/Dnase2 family now consists of Dnase2a, Dnase2b, and L-Dnase II/SerpinB1 [7]. In the 1990s, three new members of the Dnase I family were discovered, and termed "DNase1-like" proteins: Dnase1L1, Dnase1L2, and Dnase1L3 [8][9][10][11][12][13]. Dnase1-like 1 (Dnase1L1) was discovered in 1995 and first named human Dnase I lysosomal-like (DNL1L) [8]. Dnase1L2 was first described in 1997, during the gene mapping of the Dnase1 [9]. Finally, Dnase1L3 was identified in 1994 from nuclei of rat thymocytes as the third of three nucleases and consequently termed 'Dnase γ' [12]. Dnase1L3 was also called novel human Dnase (nhDnase) [13], and liver/spleen DNase (LS-Dnase) [14].

Dnase1 family members often show restricted tissue expression. In humans, Dnase1 is primarily secreted in saliva, intestine, pancreas, kidneys, and urine, but is also present in serum [1][15]. Dnase1L1 is restricted to skeletal muscle and cardiomyocytes [16]. Dnase1L2 is primarily restricted to keratinocytes, and tissues containing them, like the skin [17]. Dnase1L3 is secreted into blood, primarily by myeloid cells [18]. Distinct Dnase1 family members enable tissue-specific DNA degradation, dependent on the function of that tissue. Overall, Dnases are essential for DNA degradation in most animals.

Evolution of Dnases

Consistent with an essential role for DNA degradation, all Dnase1 family members are widely expressed throughout Metazoa. The phylogenetic distribution of *Dnase1* and *Dnase1L3* in Animalia predicts that *Dnase1L3* is closest to the common ancestral Dnase [19]. *Dnase1L3* is present in animals from humans down to corals and sponges, whereas the phylogenetically lowest organism containing both *Dnase1* and *Dnase1L3* is the placozoan *Trichoplax adhaerens* [19]. Interestingly, Dnase1 and Dnase1L3 are absent in Protostomia, including arthropods and nematodes [19], though nematodes express Dnase2 [20]. A role for Dnase1 family members in digestion has been proposed for sponges [19]. Both Dnase1 and Dnase1L3 may act in this role in phylogenetically lower organisms, with specialization between these enzymes potentially occurring in higher organisms. For example, the sponge *Amphimedon queenslandica* secretes Dnase1L3 to digest DNA from its prey [19]. However, some specialization between neutral and acid Dnases is present in sponges. The orange sea sponge *Tethya aurantium* has both neutral and acid Dnases, which show functional specialization [21]. The Dnase1 activity is present in the cortex, which interacts with the environment, while acid Dnase is expressed in endosomes to facilitate digestion [21]. Overall, the Dnase1 family represents a highly conserved enzyme family for removing DNA.

Extranuclear DNA Is Inflammatory

Removal of DNA is needed not just for digestion, but also to prevent aberrant inflammation. One key danger signal indicating infection or damage in animals is DNA found outside of its expected locations in the nucleus or mitochondria. Consequently, DNA is a potent inducer of inflammation and autoimmunity. Inflammation and cell death can be triggered after cytoplasmic DNA is sensed by several intracellular DNA sensors, including STimulator of INterferon Genes (STING) and Absent In Melanoma 2 (AIM2) [22]. Toll-like Receptor 9 (TLR9) can sense extracellular DNA [22]. Inflammatory DNA is produced during immunity by the release of Neutrophil Extracellular Traps (NETs). NETs are networks of polynucleosomes released from activated neutrophils that primarily consist of chromatin and histones [23]. These 15–17 nm diameter fibers are lined with antimicrobial enzymes and peptides. NETs are used by neutrophils to kill pathogens. NETs are primarily released by NETosis. NETosis is a form of programmed cell death wherein chromatin, nuclear, and granular contents are decondensed and released in the extracellular area [23]. While effective for clearing pathogens, the failure to degrade NETs causes harmful inflammatory responses [24]. DNA in NETs can be internalized and activate STING, leading to the release of pro-inflammatory interferons [25]. DNA is also antigenic. Anti-DNA antibodies characterize several autoimmune diseases, including Systemic Lupus Erythematosus [26]. Anti-DNA-DNA immune complexes promote Complement deposition, inflammation, and tissue damage [26]. Consequently, DNA degradation after necrosis or programmed cell death is critical to preventing autoimmunity. While the intracellular Dnase2a promotes DNA degradation after phagocytosis, Dnase1 family members degrade DNA prior to phagocytosis [7]. Thus, the Dnase1 family plays a key role in preventing autoimmunity from a host's own DNA, due to its catalytic ability to degrade DNA.

References

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