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DNase 1 and systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown aetiology with a complex genetic basis that includes many susceptibility genes on multiple chromosomes. As many complex human diseases, SLE involves multiple, interacting genetic and environmental determinants, and identifying genes and enzymes for complex traits is challenging and has had limited success so far. DNase1 has been implicated in the pathophysiology of SLE since the 1950s. The importance of DNase1 has grown up since the description that apoptotic cells can be the source of self-antigens in SLE. Many articles have focused in disturbed apoptosis and in the defects of the apoptotic cell debris as the origin of nucleosomes against which the immune response can be induced. The enzyme DNase1 plays a role in the clearance of apoptotic debris, and is therefore of capital interest in this process. In this review we highlight the current findings in the pathophysiology, genetics, and therapeutical role of DNase1 in SLE.
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Keywords: DNase1; SLE; Apoptosis; Nucleosomes

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1. Introduction

Like most autoimmune diseases, the development of systemic lupus erythematosus (SLE) is believed to be influenced by a combination of genetic, environmental,

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and hormonal factors [1]. The hallmark of this disease is the presence of antibodies against molecules that have roles in important cellular processes. Indeed, the autoimmune response is dominated by the reaction against two structures: the chromatin and the spliceosome.

The observation that autoantibodies may develop against components normally sequestered into the cell nucleus was intriguing. Today, there is a mounting body of evidence that apoptotic cells are the source of autoantigens in lupus. A defect in apoptosis regulation or apoptotic cell clearance has been suggested to be involved in lupus development. Chromatin is indeed degraded by nucleases during apoptosis to generate nucleosomes [2].

In addition to processes that protect or prime chromatin for disposal, impaired degradation of chromatin is another process that may be involved in the development of SLE and DNase1 is an important enzyme which participates in its degradation by cleavage of dsDNA.

2. Biochemical properties of DNase1

Since its discovery in the bovine pancreas in 1905 by Sachs et al. [3], DNase1 has primarily been regarded as a digestive enzyme of the gastrointestinal tract that is required for the digestion of DNA and DNA-nucleoproteins in food. The second DNase known at that time was DNase2, which is a lysosomal enzyme that acts at an optimum pH around 5.

DNase1 is a specific endonuclease that hydrolyses double-stranded (ds) DNA generating tri- and/or tetra-oligonucleotides having 5′-phosphate and 3′-hydroxyl termini [4]. For full enzymatic activity a pH of around 7.5, and micromolar concentrations of Ca^{2+}, Mg^{2+}, or Mn^{2+} are required. Its molecular mass is around 31–34 KDa depending on the amino acid composition and the extent of glycosylation, both varying in a tissue- and species-specific manner [5].

The crystal structure of bovine DNase1 defined at a 2 A resolution shows two Ca^{2+} ions that stabilize surface loops as well as an additional metal ion binding site at the active site [6]. The crystal models of DNase1 have implicated over 20 amino acids in catalysis or DNA recognition.

A heat labile inhibitor of DNase1 was described by different authors [7–9]. It was suggested that this inhibitor was released from white blood cells [8] and platelets [7]. This heat labile inhibitor was identified as actin, by Lazarides et al. [10], the most abundant protein in mammalian cells. G-actin is a 42 KD molecule with an important role in the biology of cells, not only as an intracellular cytoskeletal element, but also as a protein that is a specific inhibitor of DNase1 [11]. Monomeric G-actin binds to and almost completely inhibits the nucleolytic activity of DNase1. The inhibition of DNase1 by actin (about 95% inhibition at equimolar ratio) requires ATP and leads both to the inhibition of DNase1 and the depolymerization of the actin [12,13]. Also Zn^{2+}, as well as chelators of bivalent cations, are known inhibitors of the DNase1 [4,14].

Methods for the quantification of DNase1 include colorimetry [15,16], precipitation, fluorometry, and viscometry. Immunoreactive DNase1 (immunochemical concentration) has been measured by radioimmunoassay [17]. Enzymatic activity has been assayed using ^{32}P-labelled *E. coli* DNA as the substrate [18]. Chitrabamrung et al. [19] and Nadano et al. [12] have reported the measurement of DNase1 activity in human tissues and body fluids by single radial enzyme-diffusion methods. This method is based on the hydrolysis of DNA in a DNA-agar plate.

3. Genetics of DNase1

In 1989, Kishi et al. [20] reported that the isozyme patterns of human urine DNase1 from different individuals could be separated into 10 phenotypes thus demonstrating the presence of genetic polymorphism.

DNase1 gene is located at chromosome 20. Four codominant alleles have been found: *DNASE*1*, *DNASE*2*, *DNASE *3*, *DNASE *4* Yasuda et al. [21] described in 1995 the complete sequence of the human DNase1 gene, and showed that it was approximately 3.2 kilobases long, and it comprised 9 (I–IX) exons separated by eight introns.

Three additional members of a protein family displaying high similarity in their nucleotide and amino acid sequences with DNase1 have been described. These genes were termed DNase1-like 1, 2, and 3 [22,23], and are expressed in heart and skeletal muscle (DNAS1L1), in brain (DNAS1L2), and in macrophages (DNAS1L3).

4. DNase1 and SLE

Endogenus DNase1 has been regarded as a candidate endonuclease facilitating chromatin breakdown during apoptosis [14]. Napirei et al. [24] showed that extracellular (serum) DNase1 was implicated in the chromatin breakdown of necrotic cells *in vitro*, and it was achieved by its diffusion from the extracellular fluid through the ruptured plasma membrane into the cytoplasm and nucleus of necrotic cells. By DNAse1 action, chromatin was degraded into fragments of low molecular weight.

Several studies have found a connection between DNase1 activity and the development of human or animal

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