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Dnases in health and disease

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ABSTRACT

DNA degradation is critical to healthy organism development and survival. Two nuclease families that play key roles in development and in disease are the Dnase1 and Dnase2 families. While these two families were initially characterized by biochemical function, it is now clear that multiple enzymes in each family perform similar, non-redundant roles in many different tissues. Most Dnase1 and Dnase2 family members are poorly characterized, yet their elimination can lead to a wide range of diseases, including lethal anemia, parakeratosis, cataracts and systemic lupus erythematosus. Therefore, understanding these enzyme families represents a critical field of emerging research. This review explores what is currently known about Dnase1 and Dnase2 family members, highlighting important questions about the structure and function of family members, and how their absence translates to disease.

1. Introduction

Regular development and healthy function of humans, mice and other organisms requires two understudied families of endonucleases that specifically target DNA called Dnases. These two Dnase families were initially assumed to be only two enzymes, based on the biochemical properties of their respective DNase activities. Dnase1 activity typically requires divalent cations (Ca^{2+} or Mg^{2+}), shows peak activity at neutral pH, and leaves 5' phosphates following DNA cleavage (Table 1) (Shiokawa and Tanuma, 2001). In contrast, Dnase2 activity typically does not require divalent cations, shows peak activity at an acidic pH, and leaves 3' phosphates following DNA cleavage (Table 1) (Counis and Torriglia, 2006; Evans and Aguilera, 2003). However, through molecular cloning it became clear that these DNase activities are shared by multiple, related enzymes. While most of these enzymes are full-time nucleases, one Dnase2 enzyme arises from the transformation of the serine protease inhibitor SerpinB1 (also called Monocyte/Neutrophil Elastase Inhibitor/MNEI or Leukocyte Elastase Inhibitor/LEI) into L-DnaseII (Padron-Barthe et al., 2007; Torriglia et al., 1998). These Dnases have varied historical names, but are now methodically named Dnase1, Dnase1L1, Dnase1L2, Dnase1L3, Dnase2a, Dnase2b, L-DnaseII (Table 1). The diversity of these enzymes allow the body to regulate Dnase activity in different organs according to the needs of that organ. Overall, the absence of members from these two families of Dnases leads to a wide variety of diseases (Table 2), highlighting the necessity of regulated degradation of endogenous DNA throughout development. This review will examine the tissue expression of Dnase1 and Dnase2 families, their structural and functional characteristics, their roles in disease and their mechanisms of action. Based on this current knowledge, this review will also consider important needs and questions in this maturing field.

2. Tissue expression

In order to understand how Dnase1 and Dnase2 family members regulate health and development, it is important to understand their tissue distribution. In contrast to the well-known and ubiquitously expressed nucleases Caspase-activated Dnase (CAD) and Endonuclease G (EndoG) (Enari et al., 1998; Liu et al., 1997; Li et al., 2001; Widlak and Garrard, 2005; Apostolov et al., 2007; Larsen and Sorensen, 2017; Nagata, 2005), Dnase1 and Dnase2 family members are typically highly expressed in a limited number of tissues or cell-types, and poorly expressed in a few others (Table 2). Due to the enzymatic nature of these proteins, the lower expression level could be biologically relevant. The most widely expressed Dnase1 family member is Dnase1. Dnase1 is expressed primarily in exocrine cells in the digestive tract (Napirei et al., 2000). However, Dnase1 is also present in blood, where it helps clear free DNA from circulation (Napirei et al., 2000). Dnase1L3 is also present in blood, though it is primarily secreted by myeloid cells (Sisirak et al., 2016; Napirei et al., 2009). Myeloid cells from the liver and spleen represent one major source of Dnase1L3, accounting for its early name "liver-spleen Dnase" or LS-Dnase (Liu et al., 1998; Shiokawa et al., 1998). Within the liver and spleen, Dnase1L3 is primarily expressed by dendritic cells and macrophages (Liu et al.,

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Table 1
Biochemical properties of Dnase family members.

Nuclease	Other Names	pH Maxima	Cleavage Products	Ca^{2+}/Mg^{2+} Dependence	Common Inhibitor (s)	Refs
Dnase1	dornase alfa	Neutral	3'OH 5'P	Yes	G-Actin, Zn^{2+}	(Shiokawa and Tanuma, 2001; Linberg, 1964)
Dnase1L1	Dnase1L1	Neutral	3'OH 5'P	Yes	G-Actin, Zn^{2+}	(Shiokawa and Tanuma, 2001; Los et al., 2000)
Dnase1L2		Acidic	3'OH 5'P	Yes	Zn^{2+}	(Shiokawa and Tanuma, 2001)
Dnase1L3	Dnase1L3	Neutral	3'OH 5'P	Yes	Zn^{2+}, FCA, PV, DR396	(Shiokawa and Tanuma, 2001; Yamada et al., 2011; Shi et al., 2017)
Dnase2a	Dnase2	Acidic	3'P 5'OH	No	Mg^{2+}, Nitroprusside, RNA	(Counis and Torriglia, 2006; Shiokawa and Tanuma, 1999; Bernardi and Griffe, 1964; Kocic et al., 2004)
Dnase2b	Dnase2b	Acidic	3'P 5'OH	No	Mg^{2+}, Zn^{2+}	(Counis and Torriglia, 2006; Shiokawa and Tanuma, 1999)
L-DnaseII	(SerpinB1/MNEI/LEI)[a]	Acidic	3'P 5'OH	No		(Counis and Torriglia, 2006)
CAD	DFF40, DFFB	Neutral	3'OH 5'P	Mg^{2+}	ICAD	(Counis and Torriglia, 2006; Enari et al., 1998; Liu et al., 1997)
EndoG	Endonuclease G	Neutral; Basic	3'OH 5'P	Mg^{2+}	EndoGI; Zn^{2+}	(Counis and Torriglia, 2006; Li et al., 2001; Ruiz-Carrillo and Renaud, 1987; Widlak et al., 2001; Loll et al., 2009)

[a] SerpinB1/MNEI/LEI is proteolytically processed to generate L-DnaseII.

Table 2
Disease relevance of Dnase family members.

Nuclease	Knockout Disease Phenotype	Main Tissue Expression[a]	Main Cell Type[a]	Localization	Refs
Dnase1	SLE	salivary glands, kidney, gut	exocrine cells; Paneth cells	secreted	(Shiokawa and Tanuma, 2001; Napirei et al., 2000, 2004; Yasutomo et al., 2001; Lacks, 1981)
Dnase1L1	(Pompe disease)[b] muscle weakness	skeletal and cardiac muscle	myocytes	surface, lysosomes	(Malferrari et al., 1999; Shiokawa et al., 2005, 2007; Los et al., 2000; Lichtenbelt et al., 2006)
Dnase1L2	Parakeratosis; Psioriasis	epidermis	keratinocytes	ER	(Fischer et al., 2011, 2007)
Dnase1L3	Pediatric-onset SLE	spleen, liver	macrophages, dendritic cells	secreted, nucleus	(Sisirak et al., 2016; Wilber et al., 2002; Napirei et al., 2005; Al-Mayouf et al., 2011; Errami et al., 2013)
Dnase2a	Embryonic lethal; Rheumatoid Arthritis; Lupus Nephritis	most tissue, bone marrow	macrophages	lysosome	(Kawane et al., 2001, 2006; Shin et al., 2005; Rossol et al., 2009; Krieser et al., 2002)
Dnase2b	Cataracts	lens, salivary gland, lungs	fibre cells	lysosome	(Nishimoto et al., 2003)
L-DnaseII	Pseudomonas sensitivity	bone marrow	neutrophils	nucleus	(Benarafa et al., 2007; Torriglia et al., 2008)
CAD	Cancer	ubiquitous	ubiquitous	nucleus	(Enari et al., 1998; Liu et al., 1997; Zhang et al., 1998; Widlak and Garrard, 2005; Zhang et al., 1998; Yan et al., 2006)
EndoG	Cardiac Hypertrophy	ubiquitous	ubiquitous	mitochondria/nucleus	(Li et al., 2001; Widlak and Garrard, 2005; McDermott-Roe et al., 2011; Irvine et al., 2005)

[a] Other tissues and cell types can also express these nucleases.
[b] Controversial.