Oral Contributions

[MS7 - 05] Structures of the nuclear membrane protease ZMPSTE24 explain premature aging mutations Andrew Quigley[1,2], Yin Yao Dong[1,2], Ashley Pike[1,2], Liang Dong[1], Nicola Burgess-Brown[1], Liz Carpenter[1].

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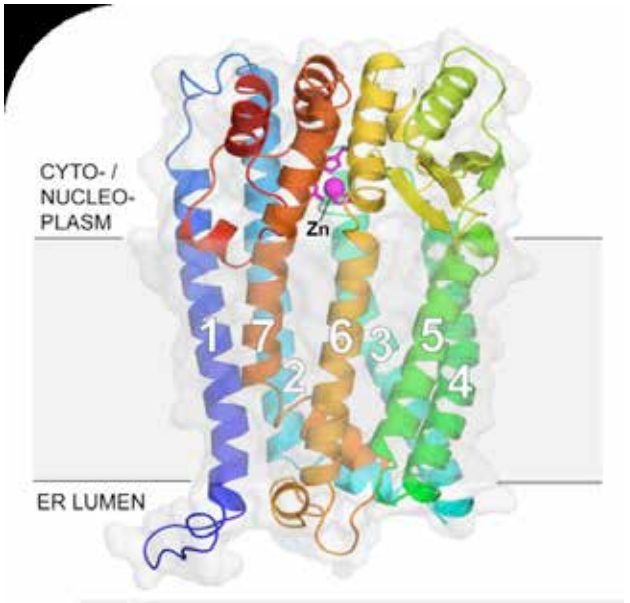
The nuclear lamina has a diverse function within vertebrates, regulating nuclear shape, chromatin positioning and gene expression [1]. The lamina consists of three proteins including Lamin A. ZMPSTE24 (also known as farnesylated-protein converting enzyme 1, FACE-1) is a nuclear membrane-embedded zinc metalloprotease which cleaves farnesylated prelamin A sequentially, at two sites, producing mature Lamin A [2]. Failure of this cascade results in accumulation of farnesylated, membrane associated prelamin A. This causes a series of premature aging (Progeria) diseases such as neonatal lethal restrictive dermopathy (RD) [3], Hutchinson-Gilford Progeria syndrome (HGPS) [4], mandibuloacral dysplasia type B (MAD-B) [5] and metabolic diseases (MS) [6]. During normal aging a reduction in ZMPSTE24 expression has been linked with the accumulation of unprocessed prelamin A in smooth muscle cells [7].
Here we present the crystal structure of the human ZMPSTE24 at 3.4Å (PDB: 4aw6) [8]. It has a novel seven transmembrane α-helix barrel structure surrounding a vast, water-filled chamber (12,000Å3) which spans a large part of the nuclear membrane. This cavity is sealed on the membrane side and capped by a zinc metalloprotease fold. Using synthetic peptide substrates, matching the C-terminus of prelamin A we probed the proteolytic activity of ZMPSTE24. We observed peptide cleavage at the expected sites, as well as additional cleavage sites depending on the length of the peptide substrate. A potential substrate binding site has been identified from a 3.8Å (PDB: 3ssb) [8] complex between ZMPSTE24 and a tetrapeptide corresponding to the four C-terminal amino acids of prelamin A. A series of point mutations in ZMPSTE24 were identified in patients with HGPS [9,10], MAD-B [5,11] and MS [6]. These mutations lead to reductions in ZMPSTE24 activity. The crystal structure explains how these mutations reduce ZMPSTE24 function, leading to prelamin A accumulation and disease.



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