Poster

NF-Y acts as a molecular platform to guide the binding of the ER stress response factor to the ER-stress elements ERSE and ERSE II. A case of molecular "asymmetric symmetry"

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Physiological and environmental stress conditions can cause protein unfolding/misfolding in the endoplasmic reticulum (ER stress), where newly synthesized proteins fold and assemble. In eukaryotic cells a strategy to cope with accumulation of unfolded proteins is the induction of molecular chaperones and folding enzymes. This homeostatic response, known as the unfolded protein response (UPR), is achieved by transcriptional induction of groups of genes by selected Transcription Factors (TFs). Among these, the ER stress response factor (ERSF) is a complex that binds to cis-acting ER stress response elements (ERSEs) in promoters of inducible genes [1, 2].

ERSE is a composite sequence CCAAT-9N-CACCG found in many ER-stress inducible genes [3-5] and a second reverse and shorter configuration -CCACG-1N-ATTGG- is known as ERSE II [6, 7]. ERSF is a heterologous complex consisting of the constitutive component NF-Y, binding to CCAAT, and an inducible component, ATF6, binding to a CCACG motif. NF-Y is a trimeric TF acting as a pioneer in opening chromatin domains [8, 9]. ATF6 is a dimeric basic leucine zipper-type (bZIP) TF, synthesized as a ER transmembrane protein and proteolyzed in response to ER stress, allowing translocation into the nucleus of its bZIP moiety [10, 11].

Here we report the cryo-EM structure of the ERSF complex, with NF-Y and ATF6 bound to the ERSE and ERSE II motifs (both complexes < 85 kDa). Surprisingly, NF-Y and ATF6 bind similarly to both ERSE and ERSE II, despite the completely different configurations of the two ERSEs. An interesting asymmetric symmetry is at the basis of the architecture of the NF-Y/ATF6 assembly on ERSE and ERSE II.

Our data shed first light on three important aspects: (i) the specific NF-Y/ATF6 contacts mediating binding cooperativity on ERSEs; (ii) the ATF6-CCACG binding details within ERSEs, unusual for bZIP TFs; (iii) the specific ATF6 homodimerization interactions and the prospective heterodimerization with selected members of the bZIP family.

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