

Témavezető indoklása

OTDK-ra nevező, de már abszolutóriumot szerzett hallgató neve:

Erdélyi Viktor

Az OTDK-ra nevezni kívánt dolgozat címe:

A Hsf-1 transzkripció faktor és az ER-stressz kapcsolatának vizsgálata emlős sejtvonalakban

A hallgató diplomamunkájának címe:

ER-stressz útvonalak és a HSF1 transzkripció faktor között fennálló lehetséges kapcsolat vizsgálata emlős sejtvonalakban

Egyezik-e a két dolgozat témája: (Igen / Részben / Nem)

Amennyiben (legalább részben) egyezik:

Mekkora az átfedés a két dolgozat között?

70%

(0-100%)

Milyen mértékben készült az OTDK dolgozat egyetemi keretében?

50%

kötelező tanóra

(0-100%)

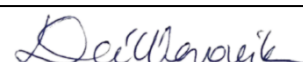
Adja meg azon publikáció(ka)t, konferenciárészvétel(eke)t, esetleg más dokumentum(ok) elérhetőségét, amellyel igazolható, hogy a hallgató már hosszú ideje, jóval a diplomamunka megkezdése előtt már adott témán dolgozott:

Poszter a Magyar Genetikusok Egyesülete által szervezett V. Sejt-, Fejlődés- és Óssejtbiológiai (SFB) Konferencián: „*HSF1 functions in alleviating ER-stress in Caenorhabditis elegans and human cell lines*”

Kelt:

Budapest, 2025.01.08.

Témavezető aláírása:



Témavezető neve:

Dr. Deák Veronika

HSF1 functions in alleviating ER-stress in *Caenorhabditis elegans* and human cell lines

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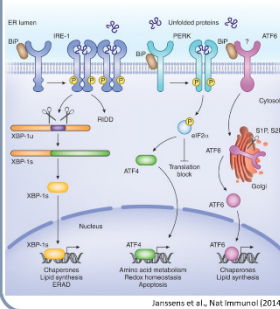
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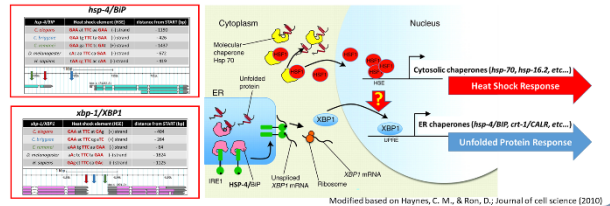
UPR^{ER} is a conserved response to ER-stress



The unfolded protein response of the endoplasmic reticulum stress (UPR^{ER}) is the major pathway that maintains proteostasis of the ER (1). UPR^{ER} dysfunction (deficiency or hyperactivity) has been implicated in ageing and age-related diseases such as neurodegenerative disorders, diabetes, heart disease and cancer. The UPR^{ER} can be activated by three parallel intracellular signalling pathways; the first is mediated by IRE1α/XBP1s (inositol-requiring protein 1α/spliced X-box-binding protein 1) proteins, the second involves PERK/ATF4 (protein kinase RNA-like endoplasmic reticulum kinase/activating transcription factor 4) proteins, while the third relies on ATF6/ATF6 (activating transcription factor 6)/cytosolic domain fragment of ATF6 proteins (2). The basic molecular machinery of the above-mentioned stress pathways has been elucidated, but how the UPR^{ER} interacts with other cellular stress responses to maintain cellular proteostasis is still a vibrant area of research.

HSF1 may regulate the UPR of the ER

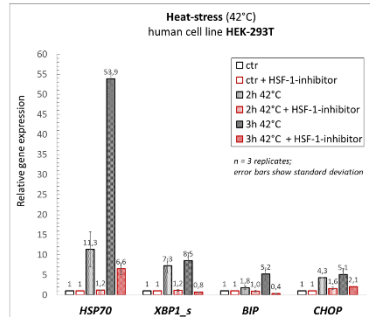
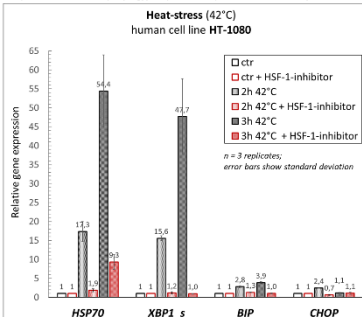
Heat shock transcription factor 1, HSF1, is an evolutionarily conserved transcription factor that, in addition to its function in the stress response, plays an important role in essential biological processes such as ageing and in certain diseases (neurodegenerative disorders, carcinogenesis and tumour progression) (3,4). Despite extensive research, the role of HSF1 in these processes is still not fully understood. HSF1 plays a central role in maintaining cytoplasmic proteostasis, but several studies have shown that it interacts with other stress response pathways (3, 5, 6, 7). Our bioinformatic analysis showed that the promoter of key UPR^{ER} genes contains a conserved HSF1 binding site, suggesting that there may be an interaction between the UPR^{ER} and HSF1.



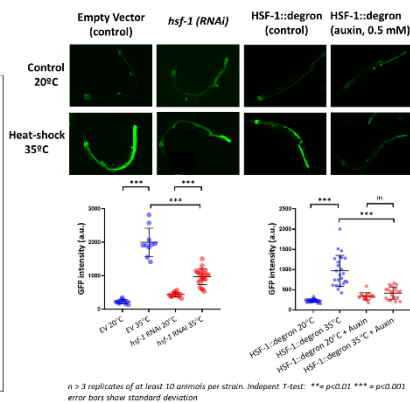
HSF1 activates UPR upon heat-stress in the nematode *C. elegans* and human cell lines

We used qPCR to measure the mRNA levels of spliced *XBP1* (*XBP1_s*), *BIP* and *CHOP* in two human cell lines (below). To inhibit HSF1 activity, we treated the cells with KRIBB11 (8). We observed an HSF1 activity dependent increase in the mRNA levels of these genes, suggesting that HSF1 activates the UPR^{ER} in both cell lines upon heat shock.

We used fluorescence microscopy to monitor the expression of *hsp-4::GFP*, a well-characterised reporter of UPR^{ER} activity in *C. elegans* (right). To silence *hsf-1*, we used RNAi and we also used an auxin-inducible degron (AID) system to deplete HSF1 (9). We observed that heat shock-induced expression of the *hsp-4p::gfp* reporter requires HSF1 activity.

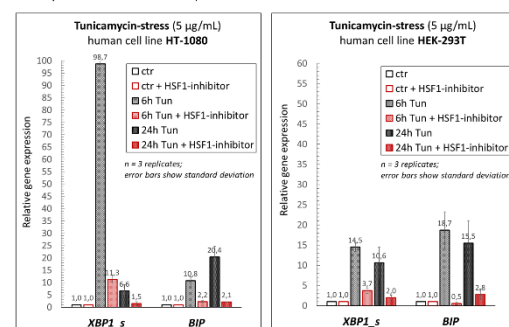


HSF-1 activates *hsp-4/BIP* upon heat-shock



HSF1 activates UPR upon tunicamycin induced ER-stress

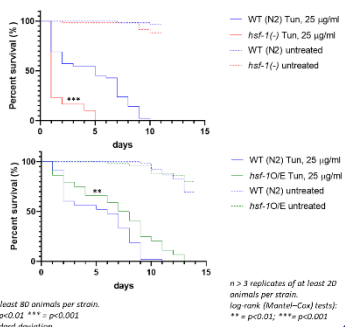
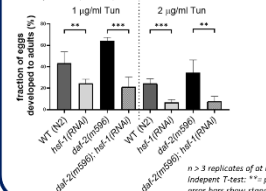
Using qPCR, we observed that mRNA levels of spliced *XBP1* (*XBP1_s*) and *BIP* are increased after tunicamycin treatment in an HSF1-dependent manner in human cell lines.



HSF-1 has a protective role during tunicamycin induced ER-stress in *C. elegans*

We tested the tunicamycin tolerance of adult wild-type and *hsf-1* mutant animals and observed that the survival rate of *hsf-1(-/-)* worms was significantly lower than that of wild-type animals. When *hsf-1* was overexpressed (10), the ER stress tolerance of adult worms was significantly increased (right).

We also observed that HSF-1 activity is required for tunicamycin tolerance during *C. elegans* development (below).



CONCLUSIONS

- HSF1 regulates the expression of several genes involved in the UPR^{ER} during heat stress in *Caenorhabditis elegans* and human cell lines.
- HSF-1 plays an important role in the activation of UPR-related genes upon ER stress in human cell lines.
- HSF-1 functions to alleviate ER stress in *Caenorhabditis elegans* and possibly in human cell lines, suggesting a closer relationship between these two cellular stress response pathways than previously thought.

REFERENCES



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