Cell Cycle 12:20, 3237–3238; October 15, 2013; © 2013 Landes Bioscience

Aging, MnSOD, and hormesis mechanisms converge on liver mUPR

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Mild stress treatments applied early in adult life, such as heat, irradiation, or reactive oxygen species (ROS) stress, can sometimes increase lifespan, a phenomenon often referred to as "hormesis." In a recent study, we compared gene expression changes caused by heat, ionizing radiation, hyperoxia, and hydrogen peroxide to changes observed during normal aging.[1] The results revealed that each stress condition and aging shared a core set of 18 upregulated genes, including the heat shock protein genes *Hsp70*, *Hsp83* (*Hsp90*-family member), and *l(2)efl* (shsp-family member), and the mitochondrial unfolded protein response (mUPR) genes *CG5966* (an apparent mitochondrial triacylglycerol lipase) and *ref(2)P* (ortholog of mammalian *p62*). *ref(2)P* encodes a protein implicated in marking mitochondria with mUPR for autophagy.[2] This shared set of 18 upregulated genes indicates that one common feature of aging and hormesis-type stress is an unfolded protein response in the cytoplasmic and mitochondrial compartments. The fact that hormesis-type stress gene expression patterns are similar to the normal aging pattern is consistent with the general model for hormesis, in which mild stress causes upregulation of stress-response genes that protect the animal from subsequent stresses, such as those associated with aging. The results also confirmed and extended our previous observations that aging is associated with a failure in mitochondrial maintenance, as the data showed that aging is associated with downregulation of numerous mitochondrial genes, including electron-transport-chain (ETC) genes and mitochondrial metabolism genes, and a subset of these changes was also observed under the stress conditions.[1]

Overexpression of the mitochondrial gene *MnSOD* in *Drosophila* can extend lifespan, and this causes upregulation of many genes that are normally upregulated during aging.[3] These targets include the mitochondrial chaperone gene *Hsp22* (shsp-family) and 4 members of the core set described above: *Pepck*, *CG32103*, and the mUPR genes *CG5966* and *ref(2)P*.[1] These results suggest that *MnSOD* lifespan extension proceeds through a hormesis-type mechanism involving the mitochondria. In another recent study, we reported that the upregulation of *Hsp22* during aging is particularly dramatic in a subset of the oenocytes (liver-like cells) indicating an age-related mUPR in these cells.[4] *MnSOD* overexpression caused *Hsp22* upregulation specifically in the oenocytes, consistent with the idea that *MnSOD* overexpression increases lifespan through a hormesis-type mechanism involving a mUPR in the oenocytes. Moreover, overexpression of *Hsp22* itself is reported to increase lifespan, and this was also associated with *Hsp22* induction in the oenocytes.[4] Taken together our results indicate that *Drosophila* lifespan extension caused by *MnSOD* overexpression involves a mUPR response that is particularly dramatic in the liver-like oenocytes and a hormesis-type mechanism (**Fig. 1**).

The involvement of mUPR and hormesis-type mechanisms in lifespan extension is supported by recent results with additional model organisms. In both *Drosophila* and *C. elegans*, knockdown of expression of an ETC component can extend lifespan.[5] In *C. elegans,* this intervention was found to activate the mUPR preferentially in gut tissue, including induction of mitochondrial chaperone genes *hsp-6* (*Hsp70*-family member) and *hsp-60*, and these effects were dependent upon function of the mUPR pathway gene *ubl-5*.[6] Interestingly, in *C. elegans* the gut is thought to be the liver-like tissue. Another study of *C. elegans* revealed that extension of lifespan caused by MnSOD overexpression is associated with upregulation of the mUPR chaperone gene *hsp-6*, again consistent with a hormesis-type mechanism involving the mUPR.[7] Finally, a recent study of mice identified a strong correlation between longevity and a polymorphism near the mitochondrial ribosomal protein (MRP) gene *Mrps5*, and expression levels for *Mrps5* were negatively correlated with mouse strain lifespan.[8] Knockdown of the homologous *mrps-5* gene in *C. elegans* increased *C. elegans* lifespan, and this intervention was again associated with induction of the mUPR genes *hsp-6* and *hsp-60* and required function of the mUPR pathway gene, *ubl-5*. These investigators also provided evidence that the drugs doxycycline, rapamycin, and resveratrol increase *C. elegans* lifespan by activating the mUPR, and can also activate the mUPR in cultured mammalian hepatocytes, suggesting possible conserved mechanisms acting on liver-like cells.

In summary, the recent studies suggest that several interventions that can increase lifespan across species, including MnSOD overexpression, hormesis-type environmental stress, and knockdown of ETC and MRP genes, have in common the activation of the mUPR and may act

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Submitted: 07/01/2013; Accepted: 07/12/2013
http://dx.doi.org/10.4161/cc.26354
Comment on: Landis G, et al. Aging (Albany, NY Online) 2012; 4:768-89; PMID:23211361

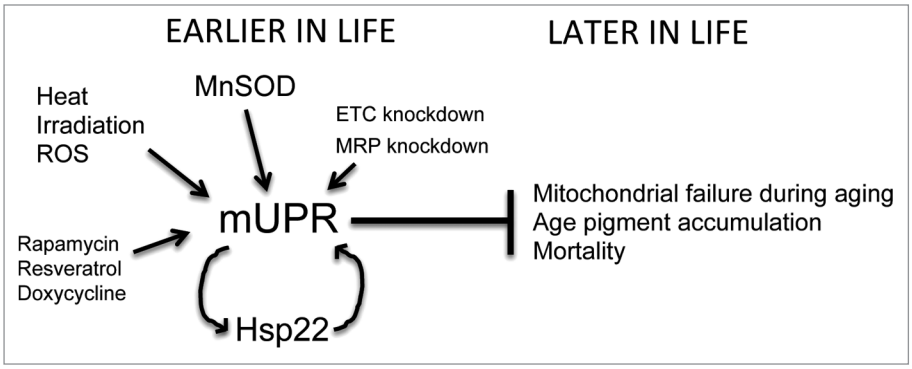

Figure 1. Model for mUPR in aging interventions. Several environmental and genetic interventions that can extend lifespan have in common the activation of the mUPR, preferentially in liver-like cells (the oenocytes of *Drosophila*, the intestinal tissue of *C. elegans*, and the hepatocytes of mouse). The mUPR is characterized by the induction of mitochondrial chaperone genes, including *Hsp22* in *Drosophila* (as indicated). The induction of the mUPR in young animals can extend lifespan, and in *Drosophila*, this has been shown to correlate with reduced accumulation of age pigment.

preferentially in liver-like cells (**Fig. 1**). Because our data indicate that normal *Drosophila* aging is associated with an age-dependent mUPR in liver-like cells,[4] these studies support a hormesis-type model, in which a mUPR early in life buffers against mitochondrial failure during aging, and implicate the liver as a critical target tissue. One possible mechanism is that the mUPR early in life favors mitochondrial turnover through autophagy ("mitophagy"), and this provides the animal with a pool of newly synthesized and better-functioning mitochondria that favor longevity; additional possibilities include reduced production of toxic metabolites such as age pigment. In the future, it will be important to further explore the role of mUPR in hormesis and lifespan, and to determine the precise mechanisms by which an early mUPR favors subsequent mitochondrial maintenance and animal survival.

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