New Advances in Immune System Health

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Cellular Health

Key Cytoprotective Pathways

- Nrf2/ARE
- Sirt1 or Sirtuin-1
- Heat shock proteins (HSPs)
Heat Shock Proteins (HSPs)

- Found in the cells of all living things:
  - Bacteria
  - Fungi
  - Plants
  - Animals

- Fundamental to cell survival

HSP Discovery 1962

Drosophila – Fruit fly
Heat Shock Factor (HSF)

- HSF1 is master switch \(\rightarrow\) Heat shock protein (HSP)
- HSF1 is a primary integrator of transcriptional responses during stress
- Cellular homeostasis
- HSF1 also involved in development, metabolism and aging

Normal Cellular Conditions

- HSPs are involved in cellular housekeeping
- Act as molecular chaperones to assist in the folding of newly synthesized proteins
- Prevent protein aggregation
- Degrade unstable and misfolded proteins
- Transport proteins between cellular compartments
- Insert proteins into membranes

Stressful Cellular Conditions

- Stress induced activation of HSF1 induces up-regulation of HSPs
- HSPs maintain cellular homeostasis
- HSPs develop and regulate cellular survival functions
- Over expression of HSP is protective

Stressful Cellular Conditions

- Heat
- Low oxygen
- pH extremes
- Nutrient deprivation
- Oxidative stress

- Natural chemicals
- Exposure to inflammatory cytokines
- Naturally occurring heavy metals

Different HSP Families

- HSP 100: Cytosol, mitochondria
- HSP 90: Cytosol, endoplasmic reticulum (ER)
- HSP 70: Cytosol, mitochondria, ER
- HSP 60: Cytosol, mitochondria
- HSP 40: Cytosol
- Small HSP: Cytosol

HSP70

- Most conserved of all HSP families
- Constitutive and inducible
- Key stress HSP
- Regulates apoptosis
- Profound effects on immune and inflammatory pathways and immune signaling within and outside the cell

Intracellular Effects of HSP70 on Immune System Pathways

- Decreases NFkappaB leading to decreased levels of TNF, IL-1 and Matrix Metalloproteinase (MMP) MMP9 and MMP2
- Decreases iNOS and levels of free radicals
- Decrease MMP progressing from inactive to active forms
- Overall the effects generally serve to suppress or dampen immune system responses


Extracellular Effects of HSP70 on Immune System Pathways

- HSPs act like cytokines and can modulate immune system responses\(^1\),\(^2\)

Extracellular Effects of HSP70 on Immune System Pathways

- HSP released by stressed, challenged or necrotic cells
- Act as Danger signals activating innate immune system responses
- Secretion of pro-inflammatory cytokines and chemokines
- Dendritic cell maturation
- Possibly activating Tregs which have anti-inflammatory properties by suppressing the immune responses to other antigens


Summary

- Proper expression of HSPs under normal and stressed conditions is essential for optimal cellular health and health of the whole organism
- HSP expression is linked to maintaining good health
- HSPs play important roles in both innate and acquired immune system function
- HSPs are important to healthy aging and longevity

Thank You