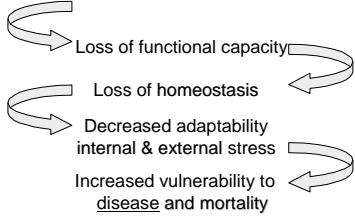


### Definition of Normal Biological Aging

- Aging is defined as the decline and deterioration of functional properties at the cellular, tissue and organ level




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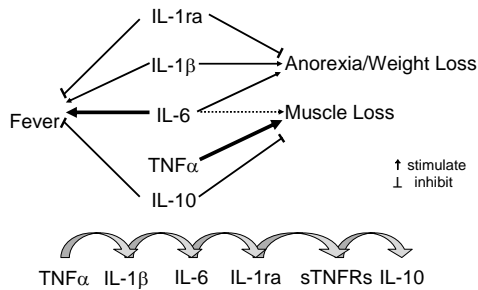
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### Dysregulated Cytokines: Sickness Behavior



Kozak et al. Sickness behavior in mice deficient in interleukin-6 during turpentine abscess and influenza pneumonitis. *Am J Physiol*, 1997, **272**:R21-30.  
 Inui A. Cytokines and sickness behavior: implications from knockout animal models. *Trends Immunol*, 2001, **22**(5):469-73.  
 Harden et al. Interleukin-6 and leptin mediate lipopolysaccharide-induced fever and sickness behavior. *Physiol Behav*, 2006, **89**(2):146-55.  
 Meador et al. Effects of IL-10 and age on IL-6, IL-1 $\beta$ , and TNF- $\alpha$  responses in mouse skeletal and cardiac muscle to an acute inflammatory insult. *J Appl Physiol*, 2008, **104**(4):991-7.  
 Adams et al. Induction of MuRF1 is essential for TNF- $\alpha$ -induced loss of muscle function in mice. *J Mol Biol*, 2008, **384**(1):48-59.

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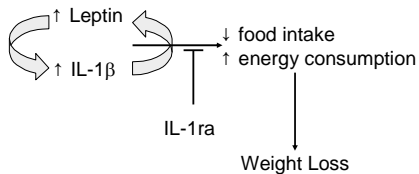
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### Dysregulated Cytokines: Nutrition



Kozak et al. Sickness behavior in mice deficient in interleukin-6 during turpentine abscess and influenza pneumonitis. *Am J Physiol*, 1997, **272**:R21-30.  
 Inui A. Cytokines and sickness behavior: implications from knockout animal models. *Trends Immunol*, 2001, **22**(5):469-73.  
 Harden et al. Interleukin-6 and leptin mediate lipopolysaccharide-induced fever and sickness behavior. *Physiol Behav*, 2006, **89**(2):146-55.

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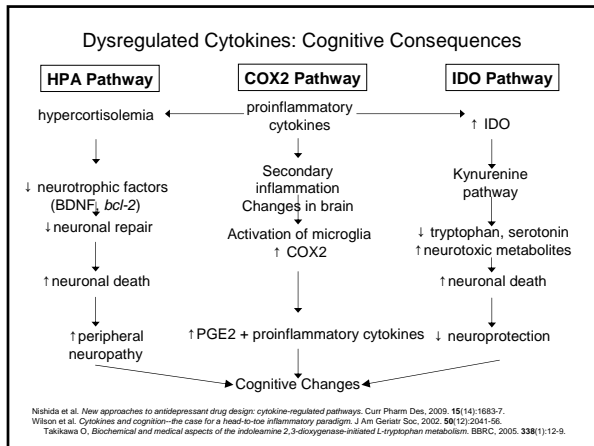
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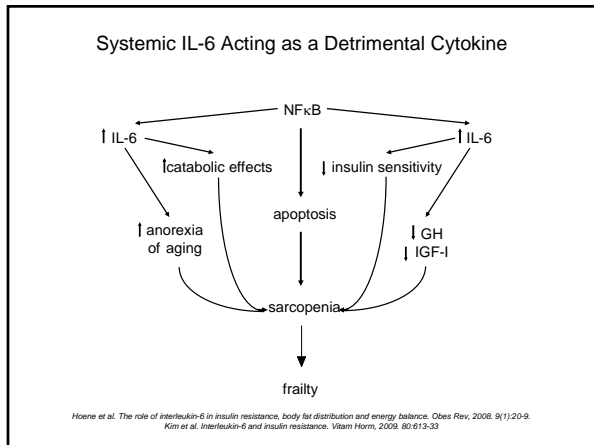
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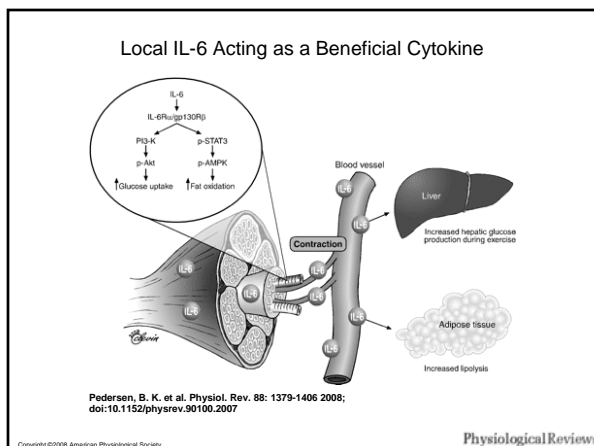
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### Mouse Studies

Cytokine dysregulation can have multiple causes  
disrupted tumor suppressors  
structural proteins  
feedback signaling

P53<sup>-/-</sup>, BubR1<sup>-/-</sup>, p63<sup>-/-</sup>, B6C3FeCol1a2<sup>-/-</sup>, IL-10<sup>tm/tm</sup>

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### Mouse Studies

Models exhibit facets of aging/frailty:

- Weight loss
- Sarcopenia
- Osteopenia
- Reduced stress tolerance
- Elevated pro-inflammatory cytokines

Overlap: apoptosis, senescence, inflammation

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