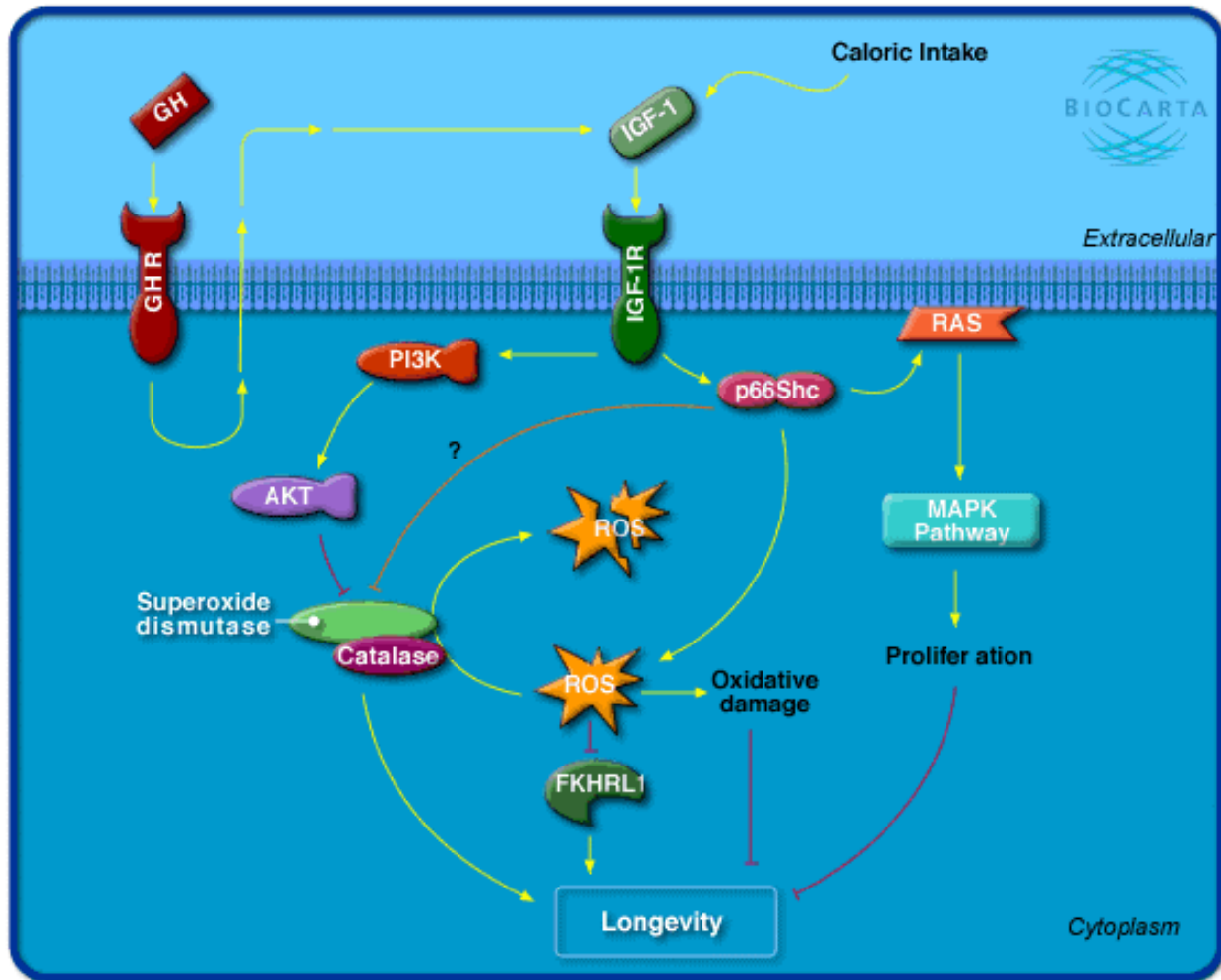


## Caloric Restriction & Longevity



A demonstrated means to increase lifespan in a wide range of organisms is through the restriction of caloric intake. Reducing the consumption of calories increases the lifespan of many different organisms, including mice. Although caloric restriction has not been demonstrated experimentally to increase human lifespan, short-term changes in physiological measures like insulin responsiveness have been observed. Caloric restriction not only increases lifespan, but decreases age-related deterioration of systems and physiological responses, reducing age related diseases like cancer and neurodegenerative disease. Caloric restriction in animals reduces the levels of plasma glucose and insulin and reduces inflammatory responses and may reduce oxidative stress through reduced oxidative metabolism, further contributing to the health benefits of reduced calorie intake. The reduction in inflammation may be related to reduces plasma glucose and in humans could reduce an inflammation connection to cancer, heart disease, and Alzheimer's disease.

Genetic analysis has indicated several genes that influence lifespan, particularly those that alter pituitary development, reduce growth hormone secretion, reduce food intake, and reduce apoptosis (p66 Shc). All of these appear to converge on an IGF-1 receptor pathway and to reproduce many of the effects of caloric restriction. Although dwarf mice with defective growth hormone or IGF-1 signaling also have significantly increased lifespan, humans with defects in growth hormone signaling tend to develop diseases that shorten their lifespan. One of the downstream targets of IGF-1 signaling is to repress stress resistance proteins including antioxidant enzymes like superoxide dismutase, and heat shock proteins, so a reduction in IGF signaling may extend lifespan by increasing the expression of stress resistance genes. The link between caloric restriction and IGF signaling may be that a reduction in food intake reduces the expression of IGF-1, increasing the expression of stress resistance proteins. In addition to the IGF-1R mutation, p66 Shc mutation also increases lifespan without significant aberration of other systems. Shc is a target of IGF-1R phosphorylation, and a major inducer of cellular responses to oxidative stress. Shc increases levels of intracellular reactive oxygen species, repressing the forkhead factor FKHRL1. Although FKHRL1 is also involved in apoptosis, in the absence of Shc, FKHRL1 mediates increased resistance to oxidative stress. Exploration of the genes that induce longevity in animals models may enlighten the role of these genes in human disease and lifespan.