THE ROLE GSK-3β; IN C. ELEGANS LIFESPAN DETERMINATION

G. McColl (P) and G. J. Lithgow

Buck Institute for Age Research, Novato, CA 94945

Insulin/IGF-like signaling (INS) is a major determinate of lifespan and stress resistance in C. elegans. GSK-3β; is a putative substrate for regulation by components of the INS pathway and a signaling molecule involved in many cellular processes. Here we discuss a series of studies that define the role of GSK-3β; in the modulation of stress and lifespan phenotypes. We find that wild type GSK-3β; activity is required for the increased stress resistance resulting from lowered DAF-2 signaling. Furthermore, GSK-3B; regulates a daf-16 independent component of stress resistance. Lifespan studies show GSK-3B; is also required for wild type lifespan, with GSK-3B; (RNAi) resulting in a minor but significant reduction in lifespan. Interestingly, GSK-3B; (RNAi) profoundly reduces the extended lifespan of INS mutants (eg. daf-2 and age-1). We propose that the INS pathway is branched, with one branch regulating DAF-16 and the other GSK-3B;. Both branches regulate stress resistance and lifespan, but via different underlying mechanisms.