FOXO Transcription Factors & Gene Expression

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Evolutionarily conserved, partially redundant Forkhead box subfamily O transcription factors (FOXO -1, -3 and -4) perform diverse functions in a context-dependent manner, impacting fundamental biological processes such as stem cell homeostasis, cell fate determination, cell cycle, metabolism, and apoptosis. Highly homologous and partially redundant FOXO -1, -3 and -4 factors are differentially localized in U87MG glioblastoma cells and myoblasts, with FOXO4 strongly targeted to the nucleus, while FOXO -1 or -3 are mostly cytoplasmic in U87MG cells and not translocated to the nucleus by TNFα in myoblasts. We hypothesize that sequences within the FOXO4 protein direct its distinct subcellular localization in U87MG cells and myoblasts. Using a battery of chimeric fusion constructs, we will map regions within each FOXO factor that determine specific cellular localization patterns. Then, based on chimeric fusion studies, mutants will be made to examine specific regulatory mechanisms that underpin FOXO localization. Chimeric fusions will ultimately be investigated in functional assays to identify specificity determinants. This project will produce innovative tools to better understand the roles and regulation of FOXO transcription factors to elucidate mechanisms that drive distinctive subcellular localization patterns (and ultimately functions) in the contexts of U87MG and myoblasts.