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## INTERACTION BETWEEN THE ATAXIA TELANGIECTASIA MUTATED (ATM) AND TUBEROUS SCLEROSIS COMPLEX (TSC) PATHWAYS

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Ataxia Telangiectasia is a progressive neurodegenerative disorder caused by mutations in the ataxia telangiectasia mutated (atm) gene. Nuclear ATM has a well established role in response to DNA damage, however ATM has also been localized outside the nucleus where it has been demonstrated to participate in the insulin signalling pathway by phosphorylating eIF-4E binding protein(4EBP1). 4EBP1 is a target of Mammalian target of Rapamycin (mTOR) and its phosphorylation releases it from eIF-4E enabling translation of mRNA and protein synthesis. The Tuberous Sclerosis Complex (TSC) proteins, hamartin (TSC1) and tuberin (TSC2) act as a heterodimer to regulate mTOR activity. mTOR exists as two complexes, mTORC1 (rapamycin sensitive) and mTORC2 (insensitive to short term rapamycin). These complexes control many cellular functions including protein synthesis, autophagy, lipid metabolism, mitochondrial biogenesis and cytoskeletal organisation. Mutations in either of the TSC1 or TSC2 genes lead to Tuberous Sclerosis, an autosomal dominant, multisystem disorder of benign tumour growth and neurological abnormalities. Studies in our laboratory have demonstrated for the first time that ATM interacts with both tuberin and hamartin. The effects of ATM deficiency on the mTOR pathway under different growth conditions and stresses will be described.