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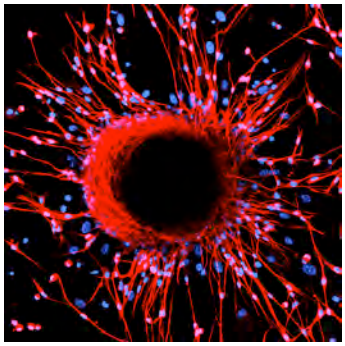
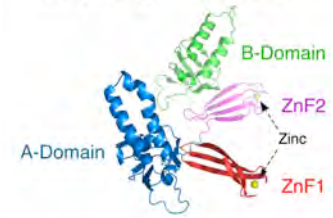
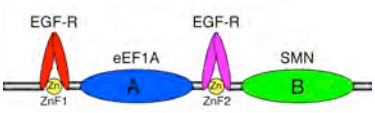


Current Research Interests: The role of ZPR1 protein complexes in human diseases, including neuromuscular disorders and cancer. Protein complexes play a critical role in the fundamental biological processes, including transcription, translation, DNA replication, splicing, signal transduction and regulation of the cell cycle that are essential for the normal cell growth and development of mammals. Disruption of protein-protein complexes due to mutations is a major cause of diverse human genetic diseases ranging from cancer to neurodegenerative disorders.

Atomic structure of
Zinc Finger Protein ZPR1

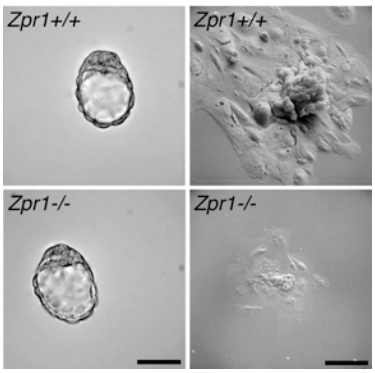


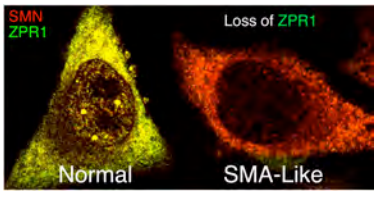


Research Programs:

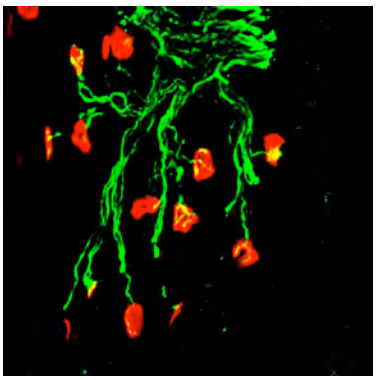
A). *The role of ZPR1-SMN complexes in neuromuscular disorders:* The focus of our research program is to understand the molecular mechanisms of neurodegeneration associated with the pathogenesis of neuromuscular disorders such as spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS). SMA is caused by mutations of the *survival motor neurons* (*SMN1*) gene and characterized by degeneration of spinal motor neurons. The molecular mechanisms of motor neuron degeneration are unknown and no treatment is available for SMA. The zinc finger protein ZPR1 interacts with SMN protein. The interaction of ZPR1 with SMN is disrupted in SMA patients and both proteins have defects in sub-cellular localization. The defect in nuclear accumulation of SMN is one of the hallmarks of SMA pathogenesis. ZPR1 is required for accumulation of SMN in the nucleus. However, the mechanism of nuclear accumulation and function of ZPR1-SMN complexes in the survival and maintenance of spinal motor neurons is unknown. The current focus is to delineate the molecular mechanisms of nuclear accumulation and to examine the role of ZPR1-SMN complexes in the pathogenesis of SMA.

Cultured mouse embryos
0 hr 96 hr



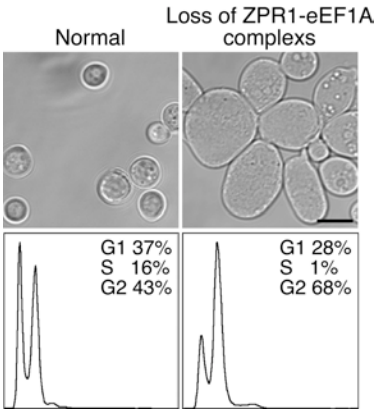


B). *The role of ZPR1-eEF1A complexes in neuromuscular and neurological diseases:* The focus of this research program is to understand the molecular basis of mammalian development associated with developmental and progressive neuromuscular and neurological disorders. ZPR1 interacts with both isoforms of translation elongation factor (eEF1A and eEF1A2) protein. Selective tissues such as skeletal muscle and neurons switch to predominately expressing eEF1A2 isoform during development. Deletion of eEF1A2 results in the loss of spinal motor neurons and severe muscle wastage. Mutations in the eEF1A2 associated with developmental disorder and neurological diseases similar to neuromuscular and motor defects, epilepsy, autism and intellectual disability.



C). *The role of ZPR1-eEF1A complexes in cancer:* The focus of this research program is to understand alterations in the cellular and molecular mechanisms of cell growth and development of cancer. The zinc finger protein ZPR1 is evolutionary conserved in eukaryotes and is essential for cell viability. ZPR1 interacts with both isoforms of translation elongation factor (eEF1A and eEF1A2) protein. Interaction of ZPR1 with eEF1A is required for the normal cell growth and proliferation. Disruption of interaction between ZPR1 and eEF1A causes defects in yeast cell growth and result in accumulation of cells in G2/M phase of the cell cycle. The defects in G2/M phase of the cell cycle are known to contribute to genomic instability and cancer development. The overexpression of eEF1A2 is associated with ovarian and breast cancer.

The function of ZPR1-eEF1A complexes in mammalian cell growth and development is unclear. The loss-of-function and gain-of-function of these protein complexes might be associated with diverse diseases such as neurological disorders to cancer. The current focus is to understand the function of ZPR1-eEF1A complexes in mammalian cell growth and development and human diseases using diverse approaches, including cellular, molecular and genetic approaches.



APPROACHES: We use state-of-the-art biochemical, molecular and genetic approaches, including yeast and mouse knockout models, and primary cell cultures to examine the molecular mechanisms of disease development and progression. The development of novel mouse models to examine *in vivo* function ZPR1 protein complexes is underway. Testing of therapeutic potential of newly identified molecular targets using molecular, pharmacological and genetic approaches.

FUNDING: National Institutes of Health (NIH), Muscular Dystrophy Association (MDA), Families of SMA (FSMA)

PUBLICATIONS: http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed&cmd=search&term=Gangwani+L

Selected Publications:

Ahmad, S. Wang, Y., Shaik, G.M., Burghes, A.H.M., and Gangwani, L. (2012). The Zinc Finger Protein ZPR1 is a potential modifier of spinal muscular atrophy. ***Human Molecular Genetics***, 21 (12), 2745-2758. (*Highlighted in News by the MDA and FSMA*).

Singh, N., Shishimorova, M., Cao, L.C., Gangwani, L. and Singh, R. (2009). A short antisense oligonucleotide masking a unique intronic motif prevents skipping of a critical exon in spinal muscular atrophy. ***RNA Biol.***, 6 (3), 341-350 (*Special Focus Research Paper with Cover Illustration*).

Mishra, A., Gangwani, L., Davis, R.J. and Lambright, D.G. (2007). Structural insights into the interaction of the evolutionarily conserved ZPR1 domain tandem with eEF1A, receptors and SMN complexes. ***Proc. Natl. Acad. Sci. (USA)***, 104 (35), 13930-13935.

Gangwani, L. (2006). Deficiency of the zinc finger protein ZPR1 causes defects in transcription and cell cycle progression. ***J. Biol. Chem.***, 281:40341-40353. (*with Cover Illustration*)

Doran, B., Gherbesi, N., Hendricks, G., Flavell, R.A., Davis, R.J. and Gangwani, L. (2006). Deficiency of the Zinc Finger Protein ZPR1 Causes Neurodegeneration. ***Proc. Natl. Acad. Sci. (USA)***, 103 (19): 7471-7475.

Gangwani, L., Flavell, R.A. and Davis, R.J. (2005). ZPR1 is essential for survival and is required for localization of the Survival Motor Neurons (SMN) Protein to Cajal bodies. ***Mol. Cell. Biol.,*** 25:2744-56. (*with Cover Illustration*)

Gangwani, L., Mikrut, M., Theroux, S.J., Sharma M. and Davis, R.J. (2001). Spinal Muscular Atrophy Disrupts the Interaction of ZPR1 with the SMN Protein. ***Nature Cell Biol.*** 3: 376-383. (*with News & Views --* *http://www.nature.com/ncb/journal/v3/n4/full/ncb0401_e93.html*).

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