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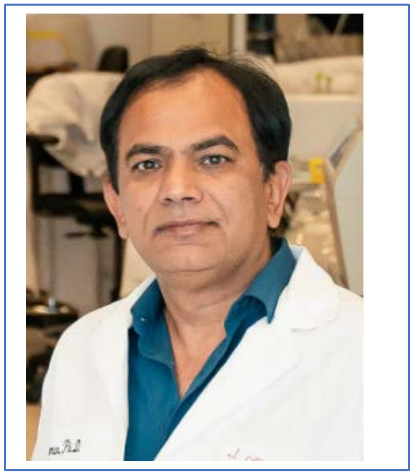
Department of Biomedical Engineering



Ashok Kumar, Ph.D.

Professor of Pharmacology, Department of Pharmacological and Pharmaceutical Sciences, University of Houston

Date Friday, November 7, 2025

Time 12:00 to 1:00 PM

Location SEC 203

Title: *Molecular pathways driving skeletal muscle wasting in cancer cachexia*

Abstract: Cancer cachexia is a debilitating syndrome characterized by the progressive loss of skeletal muscle mass with or without fat loss. Recent studies have implicated dysregulation of the endoplasmic reticulum (ER) stress-induced unfolded protein response (UPR) pathways in skeletal muscle under various conditions, including cancer. However, the role of individual arms of the UPR in regulation of cancer-induced cachexia remains poorly understood. In this study, we demonstrate that the inositol-requiring protein 1 (IRE1)/ X-box protein 1 (XBP1) branch of the UPR promotes the activation of proteolytic systems ubiquitin-proteasome system and autophagy, stimulates JAK-STAT3 signaling, and augment fatty acid oxidation in the skeletal muscle of the KPC mouse model of pancreatic cancer cachexia. Moreover, we show that the IRE1 /XBP1 pathway is a key contributor to muscle wasting. Skeletal muscle-specific deletion of the XBP1 transcription factor significantly attenuates tumor-induced muscle wasting. Mechanistically, transcriptionally active XBP1 binds to the promoter regions of various genes, which encode proteins known to drive muscle proteolysis. Pharmacological inhibition of IRE1 using a small molecule attenuates cachexia-associated molecular changes and improves muscle mass and strength in KPC tumor-bearing mice. Collectively, our findings suggest that targeting IRE1 / XBP1 pathway may offer a therapeutic strategy to counteract muscle wasting during pancreatic cancer-induced cachexia.

Bio:Dr. Ashok Kumar is the Founding Director of the Institute of Muscle Biology and Cachexia (MBC) at the University of Houston, Houston, Texas. He is also Else and Philip Hargrove Endowed Professor of Drug Discovery. He served as the Chair of the Department of Pharmacological and Pharmaceutical Sciences at the University of Houston from 2019-2023. Before joining University of Houston in 2019, he was working as Professor and Distinguished University Scholar at the University of Louisville, School of Medicine in Louisville, Kentucky. His research interests are focused on unraveling the molecular and signaling mechanisms involved in the regulation of skeletal muscle mass in various physiological and pathological conditions, including cancer. He is also investigating signaling mechanisms regulating tumorigenesis and growth of Rhabdomyosarcoma in children. His major contribution to medical science research includes the identification and characterization of TWEAK as a key muscle wasting cytokine. His research has also identified the mechanisms of action of many signaling proteins, such TRAF6, TAK1, and MyD88 in the regulation of skeletal muscle mass and muscle stem cell function. He has mentored over 40 graduate students and post-doctoral research fellows in his laboratory and published over 120 peer-reviewed research articles in well-known journals, such as “Nature Communications”, “Journal of Clinical Investigation”, “Journal of Cell Biology”, “EMBO Reports”, “EMBO Molecular Medicine”, “Molecular and Cellular Biology”, “Science Signaling”, etc. He is a frequent reviewer of over 80 scientific journals and grant reviewer for many national and international funding agencies. His laboratory is continuously funded through multiple R01 awards from NIH and other funding agencies.