Cell Biology Symposium: Regulation of growth through amino acid sensing

385 Role of amino acid transporters in amino acid sensing. Peter M. Taylor*, *College of Life Sciences, University of Dundee, Dundee, UK.*

Amino acid (AA) transporters have functional importance in nutrient sensing as well as in delivering tissue nutrient supplies. These transmembrane proteins mediate AA transfer and exchange between extracellular and various intracellular fluid compartments. AA transporters at the cell surface, particularly those for large neutral AA such as leucine, interact functionally with intracellular AA sensors and nutrient-signaling pathways which regulate metabolism; for example, the mTORC1 pathway which promotes cell growth and the GCN pathway activated by AA starvation. Upregulated expression of these AA transporter; for example, the leucine transporter SLC7A5 (System L1; LAT1), is required under some circumstances to initiate AA-dependent activation of the mTORC1 pathway. Transporter activity for leucine and other essential AA may be an important determinant of baseline insulin-sensitivity. Gastrointestinal-endocrine interactions contribute to dietary regulation of AA transporter expression and activity in the intestine. Certain AA transporters (e.g., SLC38A2, SLC38A9) may have dual receptor-transporter functions, operating as "transceptors" to sense extracellular (or intracellular) AA availability upstream of intracellular signaling pathways. SLC38A2 (System A; SNAT2) at the cell surface provides a repressive signal for gene transcription during AA sufficiency, thus echoing AA sensing by transceptor orthologs in yeast (e.g., Gap1). Expression and activity of SLC38A2 is upregulated by AA starvation by a mechanism dependent on both SLC38A2 gene transcription and enhanced stabilization of SLC38A2 protein. This forms part of an integrated cellular stress response to availability of nutrients, including unsaturated fatty acids which promote SLC38A2 protein degradation via the ubiquitin-proteasome system. SLC38A9 at the lysosomal membrane may act as the endosomal AA sensor for mTORC1 activation by glutamine and arginine. New opportunities for nutritional therapy may include targeting of AA transporters (or mechanisms which regulate their expression) to promote protein-anabolic signals for growth or retention of lean-tissue mass. Research funded by the Wellcome Trust, BBSRC UK and RERAD (Scottish Government).

Key Words: amino acid, membrane transport, cell signaling

386 Integration of amino acid signaling and metabolism in the mTORC1 pathway. John Blenis*, Gwen Buel, Anders Mutvei, Alfredo Csibi, Jing Li, Gina Lee, Sang Gyun Kim, and Andy Choo, *Sandra and Edward Meyer Cancer Center, Department of Pharmacology, Weill Cornell Medical College, New York, NY.*

The mTOR complex 1 (mTORC1) signaling pathway has evolved to sense and respond to amino acid availability, cellular energy status, surrounding oxygen concentrations and stress conditions. In addition, mTORC1 can be further activated by mitogen- and hormone-stimulated kinases including Akt, ERK, and RSK, and suppressed by mTORC1-regulated S6K1 via a variety of negative feedback loops. The integration of these multiple inputs control the strength and duration of downstream signaling, which is important in differentially regulating mTORC1-dependent processes such as protein synthesis and cellular metabolism. Importantly, amino acid-mediated regulation of mTORC1 is reportedly dominant over mitogen-dependent activation of mTORC1 signaling and therefore has attracted much interest as a therapeutic target in mTORC1-driven diseases such as obesity, diabetes, aging, and cancer. The molecular basis for amino acid signaling is complex but many gaps in our knowledge of this regulatory system remain. We will discuss our recent observations regarding amino acid-dependent regulation of mTORC1 and the ability of mTORC1 to regulate cellular metabolism.

Key Words: mTOR complex, amino acid signaling, cellular metabolism

387 Integration of signals generated from nutrients, hormones, growth factors, and exercise. Scot R. Kimball*, *Penn State College of Medicine, Hershey, PA.*

The stimulation of protein synthesis that occurs in skeletal muscle in response to either nutrient intake or a bout of resistance exercise requires activation of the protein kinase known as the mechanistic (a.k.a. mammalian) target of rapamycin in complex 1 (mTORC1). The activation state of mTORC1 is controlled by several upstream signaling pathways that function in a combinatorial manner to integrate positive (e.g., re-feeding and/or resistance exercise) or negative (e.g., inactivity or glucocorticoid treatment) inputs to the kinase. For example, amino acids and insulin act through independent pathways to activate mTORC1 in an additive manner. In contrast, hindlimb immobilization attenuates the stimulatory effect of leucine on mTORC1 activity in muscle. A growing body of evidence implicates a protein known as REDD1 (regulated in development and DNA damage response 1) as a critical regulator of mTORC1 signaling, and in a variety of studies REDD1 expression has been shown to be inversely proportional to the activation state of mTORC1. For example, REDD1 abundance is reduced and mTORC1 signaling is elevated after a bout of resistance exercise, but the opposite effects are observed after endurance exercise. Moreover, compared with freely fed rats, REDD1 abundance is elevated and mTORC1 signaling is reduced after an overnight fast, and re-feeding rapidly reverses both effects. The important role played by REDD1 in controlling mTORC1 activity is emphasized in studies demonstrating that both re-feeding and muscle contraction activate mTORC1 signaling to a significantly greater extent in muscle of REDD1 deficient mice compared with wildtype mice. This presentation will focus on the signaling pathways through which amino acids, insulin, and resistance exercise act to activate mTORC1 as well as the role of REDD1 in governing the stimulatory effect of these inputs on the kinase. Work in the author's laboratory is supported by NIH grants DK13499, DK15658, and DK094141.

Key Words: mTOR, amino acid, insulin

388 Distributed nutrient sensing in the integrated control of energy balance. Gary J. Schwartz*, *Albert Einstein College of Medicine, Bronx, NY.*

The presence of nutrients in the gut following ingestion of a meal gives rise to multiple neural and humoral signals that depend on the mechanical and chemical properties of the ingested food. Specialized sensors within the gut are able to transduce these properties to activate a central brainstem-forebrain network that includes the brainstem dorsal vagal complex as well as forebrain hypothalamic and striatal sites. Both extrinsic nerves supplying the gut as well as nutrient stimulated, gut secretory factors mediate the transmission of gut of meal-related stimuli to this central network. Once activated, this network engages multiple effector systems that drive behavioral and physiological responses to

peripheral gut nutrient availability to determine energy balance. These effectors include the negative feedback control of food intake, hepatic glucose production, thermogenesis, and food seeking behavior for palatable diets. Activity in effector pathways can limit body weight gain and adiposity, as well as improve glucose tolerance and insulin sensitivity. The responsiveness of this sensory-motor network to meal-related signals is modulated by the neuroendocrine metabolic context in which signals are received and processed, depending on the adiposity of the organism. We have identified important roles for vagal and non-vagal gut afferents linking gut nutrient availability to activation of the brainstem-forebrain network. Furthermore, growing evidence suggests that local nutrient sensing at both hindbrain and forebrain sites is acutely engaged to drive behavioral and physiological effectors. Results from neuroanatomical and neurochemical studies of each effector response suggest distinct yet overlapping neurohumoral circuits linking the gut to the brain network can be identified to modulate each distinct effector systems. As gut nutrient stimuli drive each of these pathways simultaneously during gut–meal related meal stimulation, major challenges for the field are (1) to understand the temporal and spatial patterns of neural activity during simultaneous activation of these pathways, and (2) how or whether they interact during a meal to coordinate effector responses.

Key Words: feeding, nutrient sensing, neurobiology