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Research Interests:

Functions and regulation of ubiquitination in mammalian systems

The ubiquitin-dependent proteolytic system is a major intracellular proteolytic pathway found in all eukaryotic cells. In this proteolytic pathway, chains of ubiquitin become covalently linked to proteins and targets them for recognition and degradation by the 26S proteasome. Although much progress has been made in our understanding of the biochemical mechanisms and cellular functions of this pathway, the roles and regulation of this pathway at an organismal level remain less well defined. In particular, my laboratory is interested in determining the functions and regulation of this system in atrophying skeletal muscle and during spermatogenesis. Our approach has been to identify enzymes in the pathway whose activities are regulated during these processes and to determine their physiological functions by determining the effects of manipulation of levels of these regulated enzymes by genetic methods. As an intermediate step in the process, we perform biochemical characterization of the enzymes that we identify and often investigate structure-function relationships. Monoubiquitination is now recognized to occur and serve other functions such as signaling endocytosis and trafficking to lysosomes and to modulate protein function and this is also being explored.

Ubiquitin-dependent proteolysis in skeletal muscle protein degradation

Skeletal muscle protein degradation plays a key role in metabolism by providing amino acid substrates for gluconeogenesis during starvation and in the pathological condition of diabetes. It is also activated in many diseases (e.g. cancer, infection) and therefore plays a role in the muscle protein loss and atrophy that complicates these conditions. A large body of evidence now indicates that the ubiquitin proteolytic pathway is activated in muscle atrophying in response to a wide variety of conditions and is probably responsible for the protein catabolism. We have recently identified a deubiquitinating enzyme that is induced in atrophying skeletal muscle and which when silenced activates myosin heavy chain expression. We are further characterizing the functions of this enzyme at both a cellular level and in vivo.

Ubiquitin-dependent proteolysis during spermatogenesis

The loss of germ cell proteins is an important part of the cellular remodeling that takes place as spermatids mature to their elongated form. The mechanisms of degradation of these proteins remain unclear, but our studies have implicated the ubiquitin system in these degradative events. To date we have identified UBC4-testis, a member of the UBC4 family of ubiquitin conjugating enzymes which is induced during spermatogenesis. To evaluate its physiological function, we have inactivated the gene encoding the ubiquitin conjugating enzyme in mice and found that this causes a slight delay in testis

maturation. To evaluate biochemical function, we have screened for ubiquitin protein ligases (enzymes which recognize substrates in the ubiquitin conjugating pathway) which interact with UBC4-testis. Interestingly, we have purified and identified a 500 kDa ligase (LASU1/Mule/ARFBP-1) which can polyubiquitinate histones which are degraded during spermatogenesis to permit chromatin condensation. We are further exploring the functions of this ligase.

Ubiquitination in regulating internalization and signaling of the insulin receptor

Monoubiquitination of receptor tyrosine kinases such as the EGF receptor is now well documented to promote trafficking of the receptor to the lysosomal system. However, whether ubiquitination also plays a similar role for the insulin receptor is unclear. The enzymes involved in controlling this ubiquitination are also incompletely defined. Using mass spectrometry, we are identifying proteins involved in ubiquitination that are present in endosomes purified from rat liver following stimulation with insulin or EGF. Using siRNA approaches, we will test the roles of these proteins in modulating EGF or insulin receptor trafficking and signaling in cultured cells.

Selected Publications

Activation of a UBC4-dependent pathway of ubiquitin conjugation during postnatal development of the rat testis. Rajapurohitam V, Morales CR, El-Alfy M, Lefrançois S, Bedard N, and Wing SS. Dev Biol 212: 217-228 (1999)

The tyrosine kinase negative regulator c-Cbl as a RING-type, E2-dependent ubiquitin-protein ligase. Joazeiro CAP, Wing SS, Huang H, Leverson JD, Hunter T, and Liu Y-C. Science; 286: 309-312 (1999)

Lin H, Yin L, Reid J, Wilkinson KD, and Wing SS. Divergent amino terminal sequences of a deubiquitinating enzyme modulate substrate specificity. J. Biol. Chem. 2001; 276: 20357-20363

Adegoke OAJ, Bedard N, Roest H, and Wing SS. Ubiquitin conjugating enzyme $E2_{14k}$/HR6B is dispensable for increased protein catabolism in muscle of fasted mice. Amer. J. Physiol. 2002; 283: E482-E489

Combaret L, Adegoke OAJ, Bedard N, Baracos V, Attaix D and Wing SS. USP19 is a ubiquitin specific protease regulated in rat skeletal muscle during catabolic states. Amer. J. Physiol. Endocrinol. Metab. 2005; 288: E693-E700

Liu Z, Oughtred R, and Wing SS. Characterization of $E3^{Histone}$, a novel testis ubiquitin protein ligase which ubiquitinates histones. Mol. Cell. Biol. 2005; 25: 2819-2831

Bedard N, Hingamp P, Pang Z, Karaplis A, Morales C, Trasler J, Cyr D, Gagnon C, and Wing SS. Mice lacking the UBC4-testis gene have a delay in postnatal testis development, but normal spermatogenesis and fertility. Mol. Cell. Biol. 2005, 25: 6346-6354.