7. Ubiquitination: regulating activity and destruction

Ubiquitin is a 76 amino acid protein that is ubiquitously expressed and highly conserved in all eukaryotes. It is attached to specific lysines on target proteins via an enzymatic pathway creating a reversible isopeptide bond.

Ubiquitin-proteasome system
The resulting chain of ubiquitins targets substrate proteins to the proteasome. Ubiquitin chains may have affinity for the 19S proteasome cap, but they also “activate” it. We will discuss potential mechanisms.

While attachment of ubiquitin chains were first thought to be primarily important in the removal of damaged or misfolded proteins (“garbage disposal”), it is now apparent that the system plays a major regulatory role in cells.

There are hundreds of human E3 ligases that fall into three families:
- HECT domain: homologous to E6-AP carboxyl terminus
- RING finger: really interesting novel gene
- U box: first identified as an E4, but it is also an E3.

Regulating protein destruction as a signaling mechanism
1. WNT pathway: stabilization of β-catenin allows its accumulation in the nucleus to regulate gene expression as a coactivator for TCF.
2. p53 pathway: stabilization of p53 by inhibiting Mdm2 activity or access to p53 is a first required step in p53 activation.
3. IκB/NF-κB pathway: destabilization of IκBα allows NF-κB to bind DNA and accumulate in the nucleus.
4. p105 processing: partial proteolysis by the proteasome generates a pool of NF-κB dimer that can then be activated via IκB destruction.
5. TF degradation and co-factor exchange: promoter clearance allows for regulation and may be required for multiple rounds of transcription.

Gao and Karin 2005 Molec Cell 19, pp581
Alternate ubiquitin linkages
K63 linked chains and mono-ubiquitination

Signaling to regulate inflammatory responses
TLR/TNFR superfamilies signal to NF-κB, IRFs, AP-1 etc via the TRAF proteins. TRAF2-5 contain RING fingers have several have been shown to have E3 activity for K63 linkages. These linkages do not target the protein for degradation but are required for signal transduction.
Examples:
TRAF6 and TRAF2 ubiquitination
NEMO ubiquitination
A20: feedback control with multiple activities

Other small polypeptide covalent linkages – potential functions in signaling
1. SUMO
2. ISG15