Published in final edited form as:

J Mol Cell Cardiol. 2012 March ; 52(3): 519. doi:10.1016/j.yjmcc.2012.01.004.

The Expanding World of Post-Translational Modifications

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Phosphorylation has long been known to regulate protein activity and has played a central role in most signal transduction pathways. Indeed 20 years ago, in 1992 the Nobel Prize in Medicine was awarded to Drs. Edmond Fischer and Edwin Krebs for “their discoveries concerning reversible protein phosphorylation as a biological regulatory mechanism”¹. However, in the past 10 years it has become apparent that phosphorylation is only one of many post-translational modifications (PTMs). Acetylation, ubiquitination, O-GlcNAc, S-nitrosylation, and glutathiolation have also been reported. In recent years a number of novel PTMs have been reported and JMCC has published several studies showing how these novel PTMs modulate cell function^{2–6}. This mini-special issue will highlight some of the newly identified PTMs.

Modification can be classified based on the amino acid residues that they target. Lysine can be modified by acetylation, ubiquitination and sumoylation. Acetylation of histones has been known for many years, but acetylation of cytosolic and mitochondrial proteins has been recently shown to be a common PTM that regulates many cell functions, especially metabolism. The role of acetylation will be review by Sack⁷. Acetylation is just one of the modifications that occur on lysine residues. Ubiquitination and sumoylation also modify lysines and there is some suggestion for cross-talk between these PTMs. As reviewed by Portbury et al⁸, ubiquitination can target proteins for degradation, but it can also modify protein activity and localization. Serine and threonine amino acids are sites of phosphorylation. As reviewed by Darley-Usmar⁹, serines and threonine residues can also be modified by an O-linked attachment of the monosaccharide -N-acetyl-glucosamine (O-GlcNAc), and this modification has been shown to modulate a number of important cardiovascular functions. Cysteines are site of a number of redox modifications that will be reviewed by Shao et al¹⁰. A specific consideration of glutathiolation (Hill et al¹¹) and S-nitrosylation (Murphy et al¹²) are also included.

PTMs can alter protein conformation and thereby alter function, activity or localization. The identification of these new PTMs raises the question of how the cell integrates these different signals. This will be an important area for future studies. For example, with just phosphorylation as a PTM, it has been suggested that phosphorylation of different serines or threonines can serve as a “barcode”¹³. Nobles et al showed that the beta-adrenergic receptor can be phosphorylated on distinct sites leading to distinct conformations and functions of the protein. If this barcode is extended with additional PTMs, it provides an exquisite mechanism to fine tune cell signaling.

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The field of cardiovascular research has provided exquisite methods to assess the mechanisms of normal cardiovascular function and to understand the pathophysiological deficits that underlie diseases of the heart and blood vessels. We are now in a position to understand how the symphony of PTMs that alter proteins in cardiac tissues fine tune cardiovascular responses and, when aberrant, lead to the heart diseases that are the most common cause of death and disability in our society.

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