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Editorial

Lysine Methylation of Non-Histone Proteins

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Proteomics, or the large-scale study of protein structure and function, has contributed greatly to our understanding of cellular biology and disease. Over time, it has become apparent that the proteome is spatially, temporally, and chemically dynamic allowing for the same protein to perform very different functions and fufill completely unrelated roles in a cell through small chemical changes. This can be described as epiproteomics (just as epigenetic are changes to DNA not encoded in the DNA sequence) and mainly covers Post-Translational Modifications (PTMs) such as phosphorylation, ubiquitination, acetylation or methylation, among over 200 or more [1]. These vary depending on cell type, signalling, stress condition, micro-environment and so on, leading to some sort of change in protein properties, which consequently, either directly or indirectly, alters the function.

One of the PTMs that is gaining new interest for various reasons is methylation on lysine in non-histone proteins. Lysine can undergo mono (Kme1), di (Kme2) or tri (Kme3) methylation on its epsilon amine and these reactions are catalysed by protein lysine methyltransferases (PKMTs). Initially, lysine methylation was extensively studied on various histone residues, playing important roles in the regulation (both activation and repression) of chromatin packing and gene transcription [2].

Subsequently, it has been found to play many important roles in non-histone proteins (mainly transcription factors and chaperones) by impacting function via domain activity, interaction strength to target proteins or DNA, localisation and protein stability or half-life. Moreover, as lysine can undergo various alterations, methylation can compete with other PTMs, adding another level of regulation [3]. A good example to illustrate this point is the tumour suppressor p53, in which methylation of different lysine residues or different degrees of methylation (mono or di) leads to alteration of very different properties from suppresion of gene transcription to increased affinity for 53BP1 [3].

More recently, two very interesting phenomena have been identified. The first is the report of Heat Shock Protein 70 (HSP70) acting as a transcription factor following lysine methylation, translocation to the nucleus and enhanced the kinase activity of Aurora kinase B (AURKB) [4] and the second is the isolation of a group of PKMTs that do not act on histones but appear to act mainly on specific categories of non-histone proteins such as transcription factors and chaperones [5].

As expected, dysregulation of PKMTs leads to disease, for example, SUV39H1 [6] and EZH2 [7] have been shown to be over-expressed in a variety of human tumors and a gain-of-function mutation in EZH2 has been shown to increase catalytic activity and lead to tumorigenesis [8]. Interestingly, truncation mutations in METTL23 have been linked to Intellectual Disability (ID) [9,10]. This implies that such enzymes make potential therapeutic targets, and there is an ongoing search for PRMT-inhibiting small molecules [11].

HSPs have also been linked to various insulin signalling pathways and Type 2 diabetes mellitus (T2DM), such that HSP70 [12], HSP90 and 78-kDa glucose-regulated protein (GRP78) [13] were significantly up-regulated in the skeletal muscles of T2DM patients. We have therefore developed a custon sandwich ELISA for investigating the presence and quantification of lysine methylation on HSP27, HSP60 (mitochondrial), HSP70, GRP78 and HSP90 in the serum of diabetics and matched non-diabetic controls and are currenly going through our first round of 100 patients.

However, despite recognising the importance of lysine methylation in both cellular biology and human disease, much is still unknown regarding target proteins, modified

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residue position, degree, enzyme and function. The main reasons for this are a lack of reliable tools and methods for studying these modification. Top-down proteomic methods allow the sequencing of proteins and the identification of PTMs but the resolution of the mass spectrometry system used needs to be very high. So far the best studied PTMs by such methods is phosphorylation and the reason for this is that while the addition of a phosphate group to a protein increases the mass by 80Da (and gives an overall negative charge) or an acetyl group adds 42Da (and neutralizes the positive charge on the lysine residue), the addition of a methyl group adds only 14Da (and does not change the charge). This makes the mass on charge (m/z) change following methylation, extremely small. Another hurdle is the limited availability and low quality of commercial antibodies to detect lysine methylation.

The good news is that these are only short-term inconveniences. The technological advances in mass spectrometry are extremely fast both in terms of improved resolution, especially using electron transfer dissociation (ETD), and in the development of enrichment techniques which improve the stoichiometric presence of modified species. Similarly, antibodies are constantly being developed and tested. As interest in the subject picks up, more and more robust and reliable anti-methyl lysine antibodies will become available as has happened with anti-phospho and anti-acetyl antibodies. In time, lysine methylation will become part of standard biomarker assays and diagnostic kits as has already happened with phosphorylation.

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