kinases and phosphatases

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Editorial

Kinases and Phosphatases: The Challenge of a New Journal Entirely Focused on Post-Translational Modifications

Mauro Salvi

Department of Biomedical Sciences, University of Padova, 35131 Padua, Italy; mauro.salvi@unipd.it

On behalf of all the Editorial Board members and the MDPI staff, I'm pleased to announce the publishing of the inaugural issue of the *Kinases and Phosphatases* journal [1] (ISSN: 2813-3757), a peer-reviewed and open-access online journal for high-profile articles that aims to become the publishing platform of choice for all the researchers working on protein phosphorylation and in general on post-translational modifications (PTMs). What exactly do we mean by PTMs? We mainly refer to the addition of a functional group on a target amino acid in a protein (e.g., small chemical groups, such as in phosphorylation, acetylation, or methylation; proteins, such as in ubiquitination and sumoylation; or complex molecules, such as in glycosylation, acylation, and prenylation) that regulates the protein's biological activity. However, our journal will consider papers that study any enzymatic and non-enzymatic covalent modifications of a protein during or after the synthesis affecting its structure, functional regulation, or signaling properties.

Protein phosphorylation is the most common and widely studied PTM, as the name of the journal emphasizes. Hundreds of papers are published each year on protein phosphorylation, and there is probably no cellular signaling pathway that is not controlled in some way by this modification. The link between aberrant phosphorylation and the pathogenesis and progression of various human diseases is well-established, and a large number of kinase inhibitors are in clinical trials or are in clinical use for their treatment [2]. However, it should be considered that research on drugs targeting protein kinases has focused on only a small part of the human kinome [3], as one third of protein kinases are largely unknown [4]. Not to mention that protein phosphorylation is a reversible event and the enzymes removing the phosphate group from a protein, the protein phosphatases, have gained increasing attention from drug developers, and are certainly no longer regarded as the passive housekeepers counteracting protein kinases, but have emerged into important signaling modulators in their own right [5]. Another aspect that should not be underestimated is that most knowledge about protein phosphorylation is based on human cell models. Moreover, if we consider all the phosphosites identified so far by large-scale approaches (see the PhosphositePlus database [6]) we realize that the vast majority of these phosphorylation events are not linked to a specific function, and much less is known about the identity of the kinase(s) responsible for their generation. This leads us to wonder whether what we know about protein phosphorylation is just the tip of the iceberg, even assuming the existence of some background noise due to a fraction of nonfunctional phosphosites at low stoichiometry [7].

What about the other PTMs? Dozens of different post-translational modifications occur in a cell. Many of these are reversible, resulting in dynamic events with a central role in regulating a variety of biological processes, and in some cases, their aberration has been associated with human diseases [8]. Some of them have been known for decades but only a handful of PTMs have attracted the wide attention of the scientific community, such as ubiquitination, glycosylation, sumoylation, acetylation, acylation, and methylation (the major PTMs in human based on the number of modified sites collected in the PhosphositePlus database are shown in Table 1). Most of them are relegated to a niche of specialized fields, and for other PTMs their actual importance is still unclear, often due to the lack of

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specific tools to detect and investigate them (such as specific antibodies, ad hoc enrichment strategies, etc.).

Table 1. The five most representative PTMs in human based on the number of modified sites. Non-redundant modified sites in the human proteome (PhosphositePlus database—September 2022; https://www.phosphosite.org).

PTM	Non-Redundant Modified Sites
Phosphorylation	230,529
Ubiquitination	92,763
Acetylation	21,512
Methylation	14,521
Sumoylation	7209

Another important issue, still poorly characterized, is crosstalk between PTMs: a single protein is generally subject to different PTMs at multiple sites. Thus, it is not uncommon for the modification of a specific site to positively or negatively affect the modification of neighboring residues. Therefore, different combinations of PTMs (the so-called "PTM code") can generate specific biological results [9]. Again, the same amino acid may be subject to different competitive PTMs. For example, some lysine can be alternately modified by ubiquitination, acetylation, methylation or sumoylation, to name only the most relevant ones [10]. Figure 1 shows the number of lysine subjected to one or more PTMs, suggesting that direct competition between PTMs on specific sites is more common than might be expected.

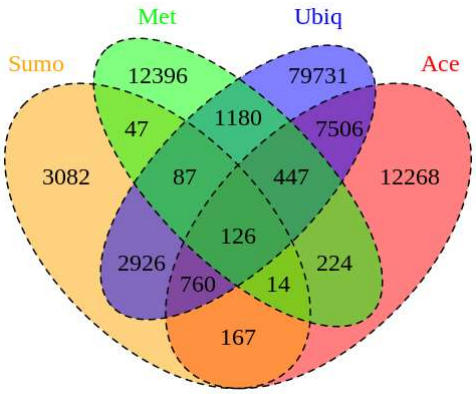

Figure 1. Venn diagram showing the number of lysine subjected to one or more PTMs. Data extracted from PhosphositePlus database-September 2022.

To summarize, I would like to emphasize that the main interest of the *Kinases and Phosphatases* Journal is the identification of PTMs with a central role in physiological and pathological processes, the dissection of the molecular mechanisms upstream and downstream of these events, the development of useful tools to manipulate these signals, and the design of new chemical entities and therapeutic strategies for the treatment of human diseases.

The *Kinases and Phosphatases* journal welcomes articles on every aspect of PTMs and in any biological system from bacteria to humans, covering a wide range of disciplines, including biochemistry, molecular biology, structural biology, cell biology, medicinal chemistry, pharmacology, cell pathology, and clinical disciplines. Different types of articles will be considered, such as original research articles, comprehensive reviews, mini-reviews (focused on a specific topic), commentaries on selected articles published in other journals, and viewpoints.

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Short Biography of Author

Dr. Mauro Salvi, is an associate Professor of Biochemistry at the Department of Biomedical Sciences, University of Padova. He has authored over 80 publications in international peer-reviewed journals. His research interests focus on post-translational modifications, with an emphasis on protein phosphorylation, combining a variety of in silico, in vitro and cell-based experimental approaches.