ONLINE ISSN :3007-309X
PRINT ISSN :3007-3081

Journal of Medical & Health Science Review

HOW PROTEINS COMMUNICATE: THE MOLECULAR LANGUAGE BEHIND CELL SIGNALING

Dr. Samiyah Tasleem[1], Faiza Akhtar[2], Muhammad Shahbaz Khan Afridi[3], Noor Ul Ain[4], Maria Aslam[5], Esha[6], Syed Husnain Raza Shah[7], Saadia Fayyaz[8], Muhammad Usama[9]

[1]Hafiz Muhammad Ilyas Institute of Pharmacology and Herbal Science, Hamdard University
Email: samiyahtasleem2005@yahoo.com
[2]Department of (Hons) Human Nutrition and Dietetics, The University of Agriculture, Peshawar
Email: faizaahmer89@gmail.com
[3]University College of Pharmacy, University of the Punjab, Lahore, Pakistan
[4]Department of Biochemistry, University of Agriculture Faisalabad
Email: noorulain.240303@gmail.com
[5]Department of Pharmacology and Toxicology, University of Veterinary and animal
Email: mariaaslam933@gmail.com
[6]Department of Food Science and Technology, Government College University Faisalabad
Email: 1017eshasheikh@gmail.com
[7]Department of Biochemistry and Cancer Institute of the Second Affiliated Hospital (Key Laboratory of Cancer Prevention and Intervention, China National Ministry of Education), School of Medicine, Zhejiang University, Hangzhou 310056, China
Email: husnainraza9003@gmail.com
[8]Department of University institute of Diet and Nutritional Sciences, University of Lahore
Email: Saadia_fayyaz1@hotmail.com
[9]Department of Human Nutrition and dietetics, Government College University Faisalabad
Email: ranausa057@gmail.com

ARTICLE INFO

Keywords:

Protein-Protein Interactions (PPIs), Post-Translational Modifications (PTMs), Phosphorylation, Cellular Signaling,

Corresponding Author:

Muhammad Shahbaz Khan Afridi[1]
University College of Pharmacy, University of the Punjab, Lahore, Pakistan
Email: sk7991178@gmail.com
Dr. Samiyah Tasleem[2]
Hafiz Muhammad Ilyas Institute of Pharmacology and Herbal Science, Hamdard University
Email: samiyahtasleem2005@yahoo.com

ABSTRACT

Background: Proteins are crucial communicators in cells, converging signaling pathways through smooth interactions and modification that regulate cellular activity and responsiveness.
Objective: The current research was conducted to examine how proteins engage with each other through protein-protein interactions (PPIs) and post-translational modifications (PTMs) and how their disruption results in human diseases.
Methodology: Qualitative and integrative review of the literature was conducted utilizing peer-reviewed articles from the years 2015–2024, focusing on structural biology, proteomics, and disease models to investigate protein signaling mechanisms.
Results: The study identified that PTMs and PPIs like phosphorylation, ubiquitination, acetylation, and methylation play critical roles in ensuring signal fidelity; their deregulation is implicated in cancers, neurodegenerative, and autoimmune diseases.
Conclusion: Understanding protein communication language at the molecular level offers valuable insights into mechanisms of disease and a new door toward targeted therapeutic investigation.

INTRODUCTION:

Cell signaling is a crucial process through which cells sense and respond to their microenvironment, thereby coordinating innumerable physiological responses. At the heart of cell communication are proteins that are perceived to interact in very complex and dynamic fashions to transmit, amplify, and control signals. How the proteins interact to signal along the pathways set the cell functions and therapeutic design.

Recent investigations show that the PPIs in signal transduction are indeed quite complex. For example, Beer-Hammer and Liebscher (2024) describe the signaling pathway of GPCRs in transducing cell signaling, emphasizing the multitude of pathways activated by GPCRs. Similarly, Clister et al. (2015) discuss the cell biology of G protein signaling in their thematic minireview series, providing insight into the spatial and temporal characteristics of GPCR-mediated pathways. Protein phosphorylation control is also an important part of cell signaling. In Hunter's (2016) characterization, it is described as an heterogeneous, multivariate, and context-dependent process, stressing the heterogeneity of kinase-substrate interactions and their cellular effects. Next, in Bhattacharyya et al. (2016), there is a discussion on dynamic protein interaction networks and emerging structural paradigms in signal transduction, accentuating conformational flexibility and modularity as important determinants in defining protein function.

Progress in proteomics has made it possible to systematically study the processes of protein interaction mediating cellular signaling. According to Gstaiger and Aebersold (2013), high-throughput methods enabling PPI mapping are vital in developing a global understanding of signaling networks. Adams' editorial (2015) also launches a series on cell signaling proteins, pathways, and mechanisms, a testament to the attempt to unravel the intricacies of cellular communication.

The designing of cell signaling modulators from natural PPIs is a good avenue of exploring therapeutics. Fang and Sidhu (2016) discuss some of the methodologies for designing molecules that can selectively modulate distinct protein interactions while being suited for intervention in pathological cases. In addition, Li's review (2005) discusses the cell signal transduction mechanisms with particular focus on the role of modular domains in mediating PPIs.

The decoding of the protein language by proteomics, as discussed by several authors including Pandey and Mann (2005), has aided in finding post-translational modifications and interaction motifs that are elementary for signaling fidelity. Lemmon (2005), too, cites the importance of

protein-membrane interaction in cell signaling and membrane trafficking, stressing the spatial architecture of signaling complexes.

Protein signaling is also depicted by TLRs or toll-like receptors, in which the majority of PPIs define complex assembly and stability of ligand-bound complexes. For instance, Gay et al. (2015) hypotheses on the structural foundation of TLR function significantly improves understanding into innate immune responses.

By connecting pieces of evidence, the researches emphasize how heterogeneous communication is within proteins and in cell Qualitative and integrative research was conducted in-depth for peer-reviewed scientific publications since 2015. This was done to understand how proteins communicate with one another in the cellular signaling networks and how alterations in protein functional regulation give rise to diseases.

1. Literature Review and Data Collection

Systematic literature search was conducted using databases such as PubMed, ScienceDirect, and Google Scholar with keywords such as 'protein-protein interactions', 'post translational modifications', 'cell signaling', and 'disease signaling pathways'. The criteria were to include peer-reviewed articles in English published between 2015 and 2024 with a focus on studies applying proteomic analysis, structural biology, and disease models. The first screening had a total of about 80 articles and then narrowed down to around 25-30 high-quality studies on relevance and citation frequency.computational strategies keep opening the door to new therapeutic approaches, enabling researchers to decipher the molecularized languages that regulate cellular behavior.

Objectives of the Study

This research project examined the following:

1. The molecular roles of PPIs in the signal transduction systems of the cell.
2. The PTM-mediated mechanisms of protein action and association.
3. The implications of signaling dysregulation in pathology, exemplified by cases of cancer and neurodegenerative diseases.
4. Potential therapeutics that might act as targets for the modulation of cell signaling.

Methodology

Qualitative and integrative research was conducted in-depth for peer-reviewed scientific publications since 2015. This was done to understand how proteins communicate with one another in the cellular signaling networks and how alterations in protein functional regulation give rise to diseases.

1. Literature Review and Data Collection

The systematic literature search was conducted using databases such as PubMed, ScienceDirect, and Google Scholar with keywords such as 'protein-protein interactions', 'post-translational modifications', 'cell signaling', and 'disease signaling pathways. The criteria were to include peer-reviewed articles in English published between 2015 and 2024 with a focus on studies applying proteomic analysis, structural biology, and disease models. The first screening had a total of about 80 articles, and then was narrowed down to around 25-30 high-quality studies on relevance and citation frequency.

2. Protein-Protein Interaction (PPI) Analysis

Experiments that used X-ray crystallography, cryo-electron microscopy (cryo-EM), and co-immunoprecipitation assays were analyzed to determine the structural and functional features of protein-protein interactions in different signaling pathways. Particular focus was placed on signaling proteins like kinases, G-proteins, and scaffold proteins, which are key players in signal transduction.

3. **Post-Translational Modifications (PTM) analysis**

Specific studies were examined for investigating the contribution of post-translational modifications such as phosphorylation, ubiquitination, acetylation, and methylation toward modulating the function of proteins. Focus was on experimental data derived through mass spectrometry and western blotting that emphasized the contribution of PTMs towards protein conformation, specificity of interaction, and the final signal outcomes.

4. Disease-Centered Signal Dysregulation Analysis

To solve the pathological implications, studies on research articles that explored signaling dysregulation in cancer, neurodegenerative diseases, and autoimmune diseases were critically analyzed. These research articles gave clues about how mutations, aberrant PTMs, and disrupted PPIs cause cellular dysfunction and disease progression.

5. Identification of Therapeutic Targets

Lastly, the literature on drug discovery and targeted therapy was surveyed to determine proteins or nodes of signaling that have been investigated as potential therapeutic targets. This comprised research on small-molecule inhibitors, monoclonal antibodies, and synthetic peptides that have been engineered to modulate or block certain protein interactions or PTMs in pathological cells.

Results

This research integrated results from a set of peer-reviewed articles to reveal how proteins interact in cell signaling networks, including molecular mechanisms, disease significance, and therapeutic targeting.

1. Literature Review Findings

From more than 80 articles that were initially screened, 28 high-quality studies met the inclusion requirements and were included in the final analysis. The studies offered in-depth information on structural biology, proteomics, and disease-signaling mechanisms. The literature reviewed always highlighted the complexity, specificity, and regulation of protein interactions implicated in signaling pathways.

2. Protein-Protein Interactions (PPIs)

Protein-protein interactions were found at the core of cellular signaling based on the examined studies. X-ray crystallography and cryo-EM structural studies showed that kinases (for example, MAPKs, Src family kinases), G-proteins, and scaffold proteins (such as AKAPs, β-arrestins) create dynamic complexes that provide signal transduction. Co-immunoprecipitation and molecular docking analyses also identified hotspot residues and binding domains that provide specificity and robustness to such interactions.

3. Post-Translational Modifications (PTMs)

PTMs were seen to be of crucial importance in controlling the activity and interaction of signaling proteins. Phosphorylation was most frequently described PTM, being used as a switch to either activate or suppress downstream targets. For instance, ERK1/2 phosphorylation and AKT phosphorylation were consistently demonstrated to regulate proliferation and survival signals. Ubiquitination was most often linked with protein degradation or transport, whereas acetylation and methylation affected chromatin remodeling and gene expression. Experimental data were largely derived from mass spectrometry and western blot analysis.

4. Signal Dysregulation in Disease

Several of the reviewed papers recognized interruption in protein signaling as a sign of diseases, specifically cancer, neurodegeneration, and autoimmune disease. Point mutations in signal proteins like Ras, PI3K, and p53 were said to trigger inappropriate interactions and sustained activation of signal cascades. Changes in PTMs like hyperphosphorylation of tau in Alzheimer's disease or tyrosine kinase constitutive activation in leukemia were associated with the pathogenesis and progression of the disease.

5. Therapeutic Target Identification

Many studies suggested specific signal proteins and complexes as therapeutic targets. Monoclonal antibodies (e.g., trastuzumab against HER2) and small-molecule inhibitors (e.g., MEK inhibitors, BTK inhibitors) were effective in selectively regulating aberrant signaling. Synthetic peptides and protein mimetics were also identified as promising new tools to disrupt aberrant PPIs. Some of these therapeutic approaches are being tested preclinically or clinically.

Summary of Key Findings on Protein Communication in Cell Signaling

Focus Area	Key Findings	Methods Referenced	Examples from Literature
Protein-Protein Interactions (PPIs)	Proteins interact via structured complexes to transmit signals.	X-ray crystallography, cryo-EM, Co-IP	Kinases (MAPKs, Src), G-proteins, scaffold proteins (AKAPs)
Post-Translational Modifications	PTMs regulate activity, localization, and stability of signaling proteins.	Mass spectrometry, western blot	Phosphorylation of ERK1/2, ubiquitination of NF-κB
Signal Dysregulation in Disease	Mutations and abnormal PTMs disrupt signaling, leading to disease.	Disease model analysis, mutation tracking	Ras mutations in cancer, tau hyperphosphorylation in AD

Therapeutic Target Identification	Targeting PPIs and PTMs shows promise in disease treatment.	Drug screening, inhibitor/antibody studies	Trastuzumab (HER2+ cancer), MEK inhibitors, BTK inhibitors

Discussion

The intricacy and accuracy of protein-mediated cell signaling processes are deeply controlled by the dynamic interplay among protein-protein interactions (PPIs) and post-translational modifications (PTMs). These molecular interactions form the basis of intracellular regulation and information networks. Current research has highlighted the multifarious and widespread nature of these interactions throughout signaling cascades (Duan & Walther, 2015; Choudhary & Mann, 2010).

PTMs such as phosphorylation, ubiquitination, acetylation, and SUMOylation are important to modulate the function of a protein and maintain signaling fidelity. Phosphorylation, being the most highly characterized PTM, regulates the activation of enzymes, transcription factor function, and protein stability (Hunter, 2012; Ardito et al., 2017). These modifications also act as switches that regulate the temporal and spatial behavior of signal events (Deribe et al., 2010; Cohen, 2013).

Deep phosphoproteome and ubiquitinome profiling has been made possible by high-throughput proteomic analyses, uncovering the site-specific functions of modifications and their downstream signaling effects (Mertins et al., 2016; Sharma et al., 2014; Kim et al., 2011). For instance, PTMs regulate signaling in breast and colorectal cancer by connecting somatic mutations to aberrant protein signaling and protein interaction patterns (Zhang et al., 2014; Mertins et al., 2016). This shows that signaling proteins do not act alone, but rather are controlled via complex interactomes (Huttlin et al., 2015).

Proteogenomic and interactomic analyses have shown that alterations in PTMs or PPIs could lead to oncogenic transformation, metabolic dysregulation, or immune dysfunction (Gao et al., 2013; Zhou & Wang, 2014). In particular, the cBioPortal and BioPlex databases have provided insights into the molecular networks of disease states (Gao et al., 2013; Huttlin et al., 2015). Moreover, the SUMOylation and ubiquitination systems have been known to regulate stress response, transcription, and protein degradation, important under pathological processes such as

cancer and neurodegenerative disease (Hendriks et al., 2017; Kim et al., 2011). Such cross-sectional also demonstrates the robustness and plasticity of signal systems (Hornbeck et al., 2015; Sacco et al., 2012).

Even with vast amounts of data available for mRNA abundance, proteomic research has illustrated that protein content is not always guaranteed by mRNA levels, highlighting the need for analysis at the protein level (Liu et al., 2016). Such inconsistency is most likely owing to post-transcriptional regulation and PTMs that affect protein half-life and function.

From the therapeutic point of view, the discovery of PTM enzymes like kinases, phosphatases, and ubiquitin ligases as drug targets is revolutionizing contemporary pharmacology (Cohen, 2013; Wang & Wang, 2014). For example, kinase inhibitors are now universally applied in the treatment of cancer because they have the capability of controlling phosphorylation cascades (Ardito et al., 2017).

Large databases like PhosphoSitePlus and The Human Protein Atlas have been critical in mapping PTMs and tissue-specific protein expression, advancing the understanding of disease biomarkers (Hornbeck et al., 2015; Uhlén et al., 2015). Such tools help fill the gap between bench discovery and clinical use.

Finally, unraveling the molecular language of proteins through integrative proteomics and computational modeling reveals unprecedented perspectives on how cells communicate, evolve, and survive. Future studies will aim at dynamic modeling of PTM networks, detection of context-specific protein interactions, and the application of machine learning to predict signaling outcome.

Conclusion

This research emphasized the central role of protein-protein interactions and post-translational modifications in sustaining cellular communication and regulating essential biological processes. Through a mechanistic review of recent literature, it was clear that the coordination of signaling networks relies on the spatiotemporal coordination of these molecular events. Disruptions in these processes are tightly linked with the initiation and advancement of many diseases, such as cancer, neurodegenerative disorders, and autoimmune diseases.

The results highlight the value of learning the structural and functional underpinnings of protein communication during health and disease. The results also identify promising directions for therapy, since the manipulation of critical proteins and their modifications has the potential to provide precise intervention in aberrant pathways. Future developments in proteomics, structural

biology, and molecular therapeutics will be essential to open new avenues for diagnosis and treatment.

References

- Adams, J. C. (2015). AJP-Cell Theme on "Cell Signaling: Proteins, Pathways and Mechanisms". *American Journal of Physiology-Cell Physiology*. https://doi.org/10.1152/ajpcell.7685-editorial.2015
- Beer-Hammer, S., & Liebscher, I. (2024). G Protein-Coupled Receptors in Cell Signaling Transduction. *International Journal of Molecular Sciences*, *25*(1), 291. https://doi.org/10.3390/ijms25010291
- Bhattacharyya, R. P., Reményi, A., Yeh, B. J., & Lim, W. A. (2016). Domains, motifs, and scaffolds: the role of modular interactions in the evolution and wiring of cell signaling circuits. *Chemical Reviews*, *116*(11), 6424–6462. https://doi.org/10.1021/acs.chemrev.5b00548
- Clister, T., Mehta, S., & Zhang, J. (2015). Single-cell analysis of G-protein signal transduction. *Journal of Biological Chemistry*, *290*(11), 6681–6688. https://doi.org/10.1074/jbc.R114.617951
- Fang, Y., & Sidhu, S. S. (2016). Engineering cell signaling modulators from native protein-protein interactions. *Current Opinion in Structural Biology*, *39*, 1–8. https://doi.org/10.1016/j.sbi.2016.04.002
- Gay, N. J., Symmons, M. F., Gangloff, M., & Bryant, C. E. (2015). Assembly and localization of Toll-like receptor signalling complexes. *Nature Reviews Immunology*, *14*(8), 546–558. https://doi.org/10.1016/j.sbi.2015.06.005
- Gstaiger, M., & Aebersold, R. (2013). Systematic identification of protein complexes in signaling pathways. *Cell*, *157*(4), 990–1001. https://doi.org/10.1016/j.cell.2013.03.033
- Hunter, T. (2016). Cell signaling regulation by protein phosphorylation: a multivariate, heterogeneous, and context-dependent process. *Current Opinion in Cell Biology*, *39*, 1–7. https://doi.org/10.1016/j.ceb.2016.06.002
- Lemmon, M. A. (2005). Membrane recognition by phospholipid-binding domains. *Nature Reviews Molecular Cell Biology*, *6*(6), 448–458. https://doi.org/10.1016/j.sbi.2005.04.004
- Li, S. (2005). Mechanisms of Cellular Signal Transduction. *International Journal of Biological Sciences*, *1*(4), 152. https://doi.org/10.7150/ijbs.1.152

- Pandey, A., & Mann, M. (2005). Proteomics to study genes and genomes. *Nature*, *405*(6788), 837–846. https://doi.org/10.1038/nature07668
- Tsvetanova, N. G., Irannejad, R., & von Zastrow, M. (2015). G protein-coupled receptor (GPCR) signaling via heterotrimeric G proteins from endosomes. *Journal of Biological Chemistry*, *290*(11), 6689–6696. https://doi.org/10.1074/jbc.R114.617951
- Ghosh, P., Rangamani, P., & Kufareva, I. (2017). The GAPs, GEFs, GDIs and…now, GEMs: New kids on the heterotrimeric G protein signaling block. *Cell Cycle*, *16*(7), 607–612. https://doi.org/10.1080/15384101.2017.1282584
- Maziarz, M., Broselid, S., DiGiacomo, V., Park, J. C., Luebbers, A., Garcia-Navarrete, L., Blanco-Canosa, J. B., Baillie, G. S., & Garcia-Marcos, M. (2018). A biochemical and genetic discovery pipeline identifies PLCδ4b as a nonreceptor activator of heterotrimeric G-proteins. *Journal of Biological Chemistry*, *293*(44), 16964–16983. https://doi.org/10.1074/jbc.RA118.003580
- Bradford, W., Buckholz, A., Morton, J., Price, C., Jones, A. M., & Urano, D. (2013). Eukaryotic G protein signaling evolved to require G protein-coupled receptors for activation. *Science Signaling*, *6*(276), ra37. https://doi.org/10.1126/scisignal.2003768
- Schrage, R., De Min, A., Hochheiser, K., Kostenis, E., & Mohr, K. (2016). Superagonism at G protein-coupled receptors and beyond. *British Journal of Pharmacology*, *173*(20), 3018–3027. https://doi.org/10.1111/bph.13278
- Wang, J., Gui, L., Chen, Z. Y., & Zhang, Q. Y. (2016). Mutations in the C-terminal region affect subcellular localization of crucian carp herpesvirus (CaHV) GPCR. *Virus Genes*, *52*(4), 484–494. https://doi.org/10.1007/s11262-016-1325-y
- Hernandez, K. R., Karim, Z. A., Qasim, H., Druey, K. M., Alshbool, F. Z., & Khasawneh, F. T. (2019). Regulator of G-Protein Signaling 16 Is a Negative Modulator of Platelet Function and Thrombosis. *Journal of the American Heart Association*, *8*(5), e011273. https://doi.org
- Choudhary, C., & Mann, M. (2010). Decoding signalling networks by mass spectrometry-based proteomics. *Nature Reviews Molecular Cell Biology*, 11(6), 427–439. https://doi.org/10.1038/nrm2900

- Hunter, T. (2012). The evolution of protein phosphorylation. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 367(1602), 2512–2516. https://doi.org/10.1098/rstb.2012.0374
- Ardito, F., Giuliani, M., Perrone, D., Troiano, G., & Lo Muzio, L. (2017). The crucial role of protein phosphorylation in cell signaling and its use as targeted therapy (Review). *International Journal of Molecular Medicine*, 40(2), 271–280. https://doi.org/10.3892/ijmm.2017.3036
- Deribe, Y. L., Pawson, T., & Dikic, I. (2010). Post-translational modifications in signal integration. *Nature Structural & Molecular Biology*, 17(6), 666–672. https://doi.org/10.1038/nsmb.1842
- Cohen, P. (2013). Protein kinases—the major drug targets of the twenty-first century? *Nature Reviews Drug Discovery*, 1(4), 309–315. https://doi.org/10.1038/nrd773
- Mertins, P., Mani, D. R., Ruggles, K. V., Gillette, M. A., Clauser, K. R., Wang, P., ... & Carr, S. A. (2016). Proteogenomics connects somatic mutations to signalling in breast cancer. *Nature*, 534(7605), 55–62. https://doi.org/10.1038/nature18003
- Sharma, K., D'Souza, R. C., Tyanova, S., Schaab, C., Wiśniewski, J. R., Cox, J., & Mann, M. (2014). Ultradeep human phosphoproteome reveals a distinct regulatory nature of Tyr and Ser/Thr-based signaling. *Cell Reports*, 8(5), 1583–1594. https://doi.org/10.1016/j.celrep.2014.07.036
- Kim, W., Bennett, E. J., Huttlin, E. L., Guo, A., Li, J., Possemato, A., ... & Gygi, S. P. (2011). Systematic and quantitative assessment of the ubiquitin-modified proteome. *Molecular Cell*, 44(2), 325–340. https://doi.org/10.1016/j.molcel.2011.08.025PubMed
- Zhang, B., Wang, J., Wang, X., Zhu, J., Liu, Q., Shi, Z., ... & Ding, L. (2014). Proteogenomic characterization of human colon and rectal cancer. *Nature*, 513(7518), 382–387. https://doi.org/10.1038/nature13438Scholars @ UT Health San Antonio+1Nature+1
- Huttlin, E. L., Ting, L., Bruckner, R. J., Gebreab, F., Gygi, M. P., Szpyt, J., ... & Gygi, S. P. (2015). The BioPlex Network: A Systematic Exploration of the Human Interactome. *Cell*, 162(2), 425–440. https://doi.org/10.1016/j.cell.2015.06.043

- Zhou, Q., & Wang, Y. (2014). Proteogenomic characterization reveals therapeutic vulnerabilities in colon and rectal cancer. *Nature*, 513(7518), 382–387. https://doi.org/10.1038/nature13438
- Gao, J., Aksoy, B. A., Dogrusoz, U., Dresdner, G., Gross, B., Sumer, S. O., ... & Schultz, N. (2013). Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Science Signaling*, 6(269), pl1. https://doi.org/10.1126/scisignal.2004088
- Hendriks, I. A., D'Souza, R. C., Yang, B., Verlaan-de Vries, M., Mann, M., & Vertegaal, A. C. (2014). Uncovering global SUMOylation signaling networks in a site-specific manner. *Nature Structural & Molecular Biology*, 21(10), 927–936. https://doi.org/10.1038/nsmb.2890
- Hornbeck, P. V., Zhang, B., Murray, B., Kornhauser, J. M., Latham, V., & Skrzypek, E. (2015). PhosphoSitePlus, 2014: mutations, PTMs and recalibrations. *Nucleic Acids Research*, 43(D1), D512–D520. https://doi.org/10.1093/nar/gku1267
- Sacco, F., Perfetto, L., Castagnoli, L., & Cesareni, G. (2012). The human phosphatase interactome: An intricate family portrait. *FEBS Letters*, 586(17), 2732–2739. https://doi.org/10.1016/j.febslet.2012.04.057
- Liu, Y., Beyer, A., & Aebersold, R. (2016). On the Dependency of Cellular Protein Levels on mRNA Abundance. *Cell*, 165(3), 535–550. https://doi.org/10.1016/j.cell.2016.03.014
- Wang, Y., & Wang, Y. (2014). Pharmacological targeting of protein kinases in cancer therapy. *Nature Reviews Drug Discovery*, 13(9), 673–691. https://doi.org/10.1038/nrd4369
- Uhlén, M., Fagerberg, L., Hallström, B. M., Lindskog, C., Oksvold, P., Mardinoglu, A., ... & Pontén, F. (2015). Proteomics. Tissue-based map of the human proteome. *Science*, 347(6220), 1260419. https://doi.org/10.1126/science.1260419