



Translational Biophysics – 20th IUPAB Congress Session Commentary

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Biophysics, by its very nature, is a science that is perfectly placed to impact into societal well-being, health, and wealth. Being a bridge between physics and biology, with chemical and mathematical incursions, biophysics is ideal for exploitation and translating into applied research for applications, particularly in the field of medicine and healthcare. Numerous examples exist, and in this session, sponsored by the European Biophysical Societies' Association, (EBSA; www.ebsa.org), four such areas of translational biophysics were presented at the Congress.

Dietary control is a major focus in the health and well-being of populations, and the lipid components of diets, in particular cholesterol in its various forms and the way it integrates into biological structures and processes, are only now being understood at the molecular level (Kumar and Chattopadhyay 2021)(Kumar et al. 2019)). In a first example of translational biophysics, Kumar and Chattopadhyay focused on the largest family of proteins in higher life forms, G-protein-coupled receptors (GPCRs). This family of receptors numbers some hundreds, with yet more with no known function. Despite this, and the availability of a very limited number of high-resolution structures as 7-trans membrane α -helical proteins, they are known to be one of the primary targets of many drugs in clinical use that exert fine control over functional outcomes from these receptors in pathological conditions. Endocytosis and intracellular trafficking of GPCRs stringently regulate signaling outcomes from GPCRs within physiologically relevant spatiotemporal regimes (Weinberg and Puthenveedu 2019)). The membrane microenvironment around GPCRs has recently emerged as a

key player in receptor function, and Kumar and Chattopadhyay explored the contribution of membrane lipids, such as cholesterol (Kumar and Chattopadhyay 2020)), in spatiotemporal regulation of GPCR signaling, thereby enabling the development of therapeutic interventions fine-tuned to receptors residing in specific membrane microenvironments (Fig. 1).

Resistance to tropical disease such as malaria continues to undermine the efficacy of front-line drugs. Biophysical research is leading to new therapies based on cell based and targeted inhibitor screens, with enzymes in charge of post-translational modification systems presenting appealing targets. Wilkinson, in a presentation entitled “Drug discovery in parasitic and viral diseases using protein lipidation as a target,” discussed collaborative studies underpinning the investigation of *N*-myristoyltransferases (NMTs), where NMT catalyzes the co-translational transfer of a C14 fatty acid from myristoyl-CoA onto the N-terminal glycine residue of a significant subset of proteins in eukaryotic cells (Harupa et al. 2020)(Brannigan et al. 2014)(Wright et al. 2014)).

Biophysical approaches to analysis of the complex interactions of the substrate proteins with lipids and partner proteins were described, leading to structure-guided development of new lead compounds emerging from high-throughput screening campaigns. The targets for these studies are *Plasmodium* and kinetoplastid NMTs, revealing potent inhibitors which have been tested against human NMT and subsequently found to block the replication of the multiple strains of the common cold virus protecting cells from virus-induced killing (Mousnier et al. 2018)). The implication of these methods in discovering new drugs for a range of diseases is an important advance and was discussed in the presentation.

Water has been a focus of biophysical studies for many years, both at the molecular and macroscopic levels. In view of the importance of water to all biology, and since water scarcity affects the majority of the global populations, it is still a major focus of biophysics. In particular, since macroscopic laws of hydrodynamics do not apply at the molecular

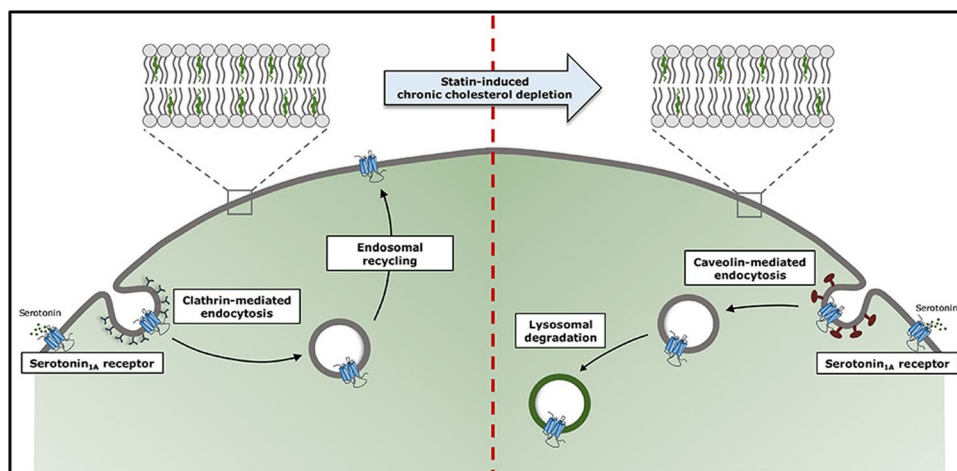
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Fig. 1 Some membrane factors determining GPCR internalization (Reproduced with permission from Kumar and Chattopadhyay ((Kumar and Chattopadhyay 2020)) ACS Chem. Neurosci. 11: 453–465)



scale (Horner and Pohl 2018)), biophysics can contribute to understanding and then exploitation of how water is selectively transported by specific water channels, rejecting all other solutes—illustrating the superbly selective character of biology, something that is elusive to man-made devices.

Pohl discussed how an understanding of plasma membrane channels may reveal the design principles for synthetic water channels. While size exclusion and the lack of surrogates for the waters of ion hydration are important for water selectivity, water confinement may reduce the transport rate. A range of contemporary methods are used to

permit direct observation of water movement through selective water channels, and the rates differ by several orders of magnitude through various narrow pores. The new observation that water permeability increases exponentially with a decreasing number of hydrogen bond donating or accepting residues in the channel wall of a range of channels will be of significance in designing synthetic water channels (Horner et al. 2015)(Horner 2018)). More details can be found in an accompanying paper that is focused on the energetics of water transport through narrow membrane channels (Pfermann 2021)).

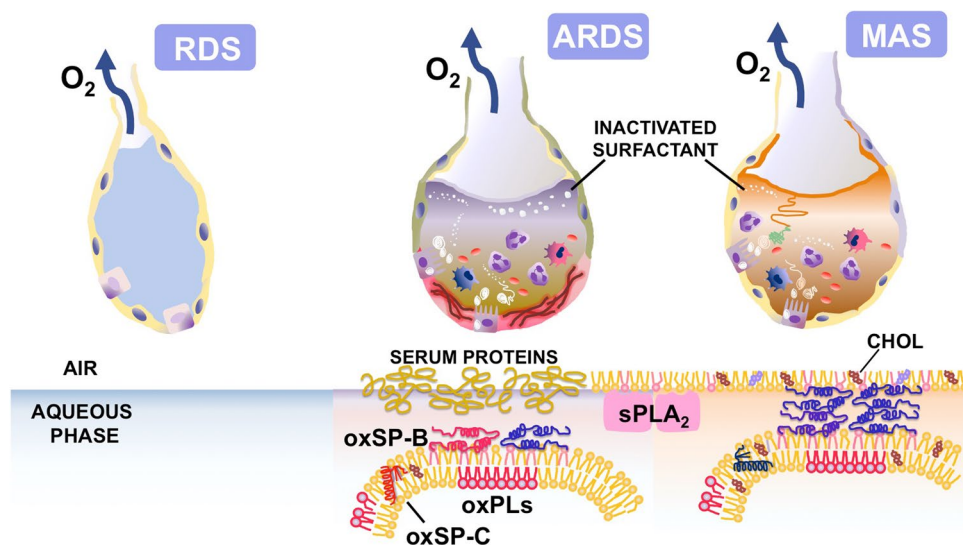


Fig. 2 Different biophysical models have been developed to characterize molecular and biophysical mechanisms of pulmonary surfactant, the lipid-protein complex that stabilizes the respiratory air-liquid interface in the alveoli of mammalian lungs, under healthy and pathological conditions. This research has been crucial to develop therapeutic materials to treat premature babies developing respiratory distress syndrome (RDS) (left) as a consequence of lung immaturity. Biophysical research is also revealing the mechanisms behind surfactant inactivation in pathologies associated with lung injury and

inflammation such as acute respiratory distress syndrome (ARDS) (middle) or meconium aspiration syndrome (MAS) (right). Inactivation of surfactant action occurs as a consequence of leakage of serum into the airways, oxidation of phospholipids (oxPPLs) and surfactant proteins (oxSP-B, oxSP-C), degradation of surface active lipids by secretory phospholipase A2 (sPLA₂), or exacerbated proportions of cholesterol (CHOL). Modified from Autilio and Perez-Gil, Arch. Dis. Child. Fetal Neonatal. ((Autilio and Perez-Gil 2019)) 104, F443-F451

The key role of mammalian lungs to promote the efficient and continuous gas exchange required to maintain metabolic functions depends critically on the presence of a system of pulmonary surfactant, responsible for reducing surface tension at the respiratory air–liquid interface (Autilio and Perez-Gil 2019)).

The lack or inactivation of pulmonary surfactant is incompatible with life and is a major contribution to devastating pathologies. In a last example of translational biophysics, Pérez-Gil presented in his talk a few biophysical approaches to assess lung surfactant function under physiologically meaningful conditions (Fig. 2) and how they can aid to understand how surfactant impairment is associated with several acute and chronic respiratory diseases (Echaide et al. 2017)(Zuo et al. 2008)). This is a particularly relevant issue with direct relevance to the current challenges faced by COVID-19 patients (Veldhuizen et al. 2021)). The talk presented some studies illustrating how the understanding of the biophysical and molecular mechanisms of pulmonary surfactant in health and disease is opening new therapeutic opportunities to treat still unresolved problems.

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Declarations

Ethical approval Not applicable

Conflict of interest The authors declare no competing interests.

References

- Autilio C, Perez-Gil J (2019) Understanding the principle biophysics concepts of pulmonary surfactant in health and disease. *Arch Dis Child Fetal Neonatal Ed* 104(4):F443–F51. <https://doi.org/10.1136/archdischild-2018-315413>
- Brannigan JA, Roberts SM, Bell AS, Hutton JA, Hodgkinson MR, Tate EW, Leatherbarrow RJ, Smith DF, Wilkinson AJ (2014) Diverse modes of binding in structures of *Leishmania major* N-myristoyltransferase with selective inhibitors. *IUCrJ* 1:250–260. <https://doi.org/10.1021/acs.jmedchem.9b01343>
- Echaide M, Autilio C, Arroyo R, Perez-Gil J (2017) Restoring pulmonary surfactant membranes and films at the respiratory surface. *Biochim Biophys Acta Biomembr* 1859(9 Pt B):1725–39. <https://doi.org/10.1016/j.bbamem.2017.03.015>
- Harupa A, De Las Heras L, Colmenarejo G, Lyons-Abbott S, Reers A, Caballero Hernandez I, Chung CW, Charter D, Myler PJ, Fernandez-Menendez RM, Calderon F, Palomo S, Rodriguez B, Berlanga M, Herreros-Aviles E, Staker BL, Fernandez Alvaro E, Kaushansky A (2020) Identification of selective inhibitors of plasmodium N-myristoyltransferase by high-throughput screening. *J Med Chem* 63:591–600. <https://doi.org/10.1021/acs.jmedchem.9b01343>
- Horner A, Zocher F, Preiner J, Ollinger N, Siligan C, Akimov SA, Pohl P (2015) The mobility of single-file water molecules is governed by the number of H-bonds they may form with channel-lining residues. *Sci Adv* 1(2):e1400083. <https://doi.org/10.1126/sciadv.1400083>
- Horner A and Pohl P (2018) Comment on “Enhanced water permeability and tuneable ion selectivity in sub-nanometer carbon nanotube porins” *Science*, 359(6383). <https://doi.org/10.1126/science.aap9173>
- Horner A, Pohl P (2018) Single-file transport of water through membrane channels. *Faraday Discuss* 209:9–33. <https://doi.org/10.1039/C8FD00122G>
- Kumar GA, Chattopadhyay A (2020) Statin-induced chronic cholesterol depletion switches GPCR endocytosis and trafficking: insights from the serotonin_{1A} receptor. *ACS Chem Neurosci* 11:453–465. <https://doi.org/10.1021/acscchemneuro.9b00659>
- Kumar GA, Chattopadhyay A (2021) Membrane cholesterol regulates endocytosis and trafficking of the serotonin_{1A} receptor: insights from acute cholesterol depletion. *Biochim Biophys Acta Mol Cell Biol Lipids* 2021:158882. <https://doi.org/10.1016/j.bbalip.2021.158882>
- Kumar GA, Sarkar P, Jafurulla M, Singh SP, Srinivas G, Pande G, Chattopadhyay A (2019) Exploring endocytosis and intracellular trafficking of the human serotonin_{1A} receptor. *Biochemistry* 58:2628–2641. <https://doi.org/10.1021/acs.biochem.9b00033>
- Mousnier A, Bell AS, Swieboda DP, Morales-Sanfrutos J, Perez-Dorado I, Brannigan JA, Newman J, Ritzefeld M, Hutton JA, Guedan A, Asfor AS, Robinson SW, Hopkins-Navratilova I, Wilkinson AJ, Johnston SL, Leatherbarrow RJ, Tuthill TJ, Solari R, Tate EW (2018) Fragment-derived inhibitors of human N-myristoyltransferase block capsid assembly and replication of the common cold virus. *Nat Chem* 10:599–606. <https://doi.org/10.1038/s41557-018-0039-2>
- Pfeffermann J, Goessweiner-Mohr N, Pohl P. The energetic barrier to water flow through narrow channels. *Biophys Rev*. 2021 (in press)
- Weinberg ZY, Puthenveedu MA (2019) Regulation of G protein-coupled receptor signaling by plasma membrane organization and endocytosis. *Traffic* 20:121. <https://doi.org/10.1111/tra.12628>
- Wright MH, Clough B, Rackham MD, Rangachari K, Brannigan JA, Grainger M, Moss DK, Bottrill AR, Heal WP, Broncel M, Serwa RA, Brady D, Mann DJ, Leatherbarrow RJ, Tewari R, Wilkinson AJ, Holder AA, Tate EW (2014) Validation of N-myristoyltransferase as an antimalarial drug target using an integrated chemical biology approach. *Nat Chem* 6:112–121. <https://doi.org/10.1038/nchem.1830>
- Veldhuizen RAW, Zuo YY, Petersen NO, Lewis JF, Possmayer F (2021) The COVID-19 pandemic: a target for surfactant therapy? *Expert Rev Respir Med* 15(5):597–608. <https://doi.org/10.1080/17476348.2021.1865809>
- Zuo YY, Veldhuizen RA, Neumann AW, Petersen NO, Possmayer F (2008) Current perspectives in pulmonary surfactant–inhibition, enhancement and evaluation. *Biochim Biophys Acta* 1778(10):1947–1977. <https://doi.org/10.1016/j.bbamem.2008.03.021>

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