Receptors in Health and Diseases: Purinergic Signaling in Parasites

Cells' ability to sense the microenvironment to modulate a myriad of processes focuses on the work of several labs elsewhere. Pharmaceutical companies are interested in receptors, and the topic represents about 40% of drugs in the market.

However, several labs point out that the strategy of sensing extracellular medium for regulating cellular processes can also be applied to lower eukaryotic cells, particularly to pathogens. We have tried to address in this Thematic issue of CTMC, namely: Receptors in health and diseases: Purinergic Signaling in Parasites the ability of cells to sense external nucleotides.

Our lab had made the seminal discovery that the addition of recombinant Schistosoma apyrase enzyme in the malaria parasite's in vitro culture's etiological agent, Plasmodium falciparum, leads to the depletion of ATP. Moreover, the addition of purinoreceptor antagonists (KN62 and Ip51) inhibits parasites' ability to invade new red blood cells. ATP also leads to cytosolic calcium increase in isolated parasites at either trophozoite and schizont stages. The authors concluded that ATP has a role in the Plasmodium falciparum invasion processes of host cells (Levano-Garcia et al. 2010).

Ecto-Nucleoside Triphosphate Diphosphohydrolase (E-NTPDase) is an enzyme that hydrolyzes extracellular tri- and di-phosphate nucleotides and exerts diverse functions such as cell signaling molecules through purine and pyrimidine receptors. Borges et al., 2017 reported that the P. falciparum genome encodes for a single E-NTPDase gene. Incubation of P. falciparum with known E-NTPDases inhibitors affects parasite development within RBC. Quantification of apyrase mRNA by qRT-PCR shows that this enzyme is differentially expressed through the parasite cycle.

Pedro Scarpelli and Celia R.S. Garcia described the recent advances in the malaria field at the review “Evidence of G Coupled-Protein Receptor (GPCR) signaling in the human malaria parasite Plasmodium falciparum for sensing its microenvironment and the role of purinergic signaling in malaria parasites” [1].

Moreover, the parasite Trichomonas vaginalis causes trichomoniasis, the most common non-viral sexually transmitted infection worldwide. This mucosal pathogen establishes infection through multifactorial mechanisms. Extracellular purine nucleotides are released by cells in physiological and pathological conditions, and they are hydrolyzed by enzymes called ectonucleotidases.

The cellular effects of nucleotides and nucleosides occur via binding to purinoceptors or through nucleoside transporters' uptake via purine salvage essential for parasite survival. This Review by Dr. Tiana Tasca and colleagues updates the data on “Purinergic signaling involved in T. vaginalis biology and relation with host cells and reveals this pathway as a potential new mechanism for drug targets” [2].

Human schistosomiasis is a neglected tropical disease and current sub-optimal pharmacological treatment awakens global public health concerns. The morbidity of chronic illness takes into account the level of granulomatous fibrosis and inflammation. Present data in the murine model unveil a CD39L-ADP-P2Y1/P2Y12 receptors axis linked to liver and mesenteric exacerbations of schistosomal inflammation. Therefore, it could be a putative pharmacological target to reduce schistosomal morbidity. The highlight in the field was the Review “Unveiling the potential of purinergic signaling in schistosomiasis treatment” by Dr. Claudia Martins Silva's lab [3].

Toxoplasmosis is caused by the protozoan parasite Toxoplasma gondii, which infects virtually all nucleated cells. After active entry into the cell, Toxoplasma gondii proliferates indiscriminately, inducing cell death, culminating in escaping the parasite and releasing nucleotides. Marques-da-Silva's Review explores the mechanisms of how the host detects the presence of Toxoplasma gondii and assembles the immune response using purinergic receptors as sensors. The authors also reassess the findings related to the role of purinergic signaling in the disease infection models and the human in the Review: The complexity of purinergic signaling during Toxoplasma infection [4].

The Review entitled “ENTPDases from Pathogenic Trypanosomatids and Purinergic Signaling: Shedding light towards Biotechnological Applications” shown an extensive revision of the literature of ENTPDases from pathogenic trypanosomatids (TpENTPDases) who causes Leishmaniasis and Chagas disease. These enzymes are essential to the parasites' purine salvage pathway and can affect the nucleotide signaling, adhesion, and infection favoring the infection. These roles make the TpENTPDases good targets for biotechnological applications to fight against the parasites. This Review highlights the already known applications in the field, such as diagnosis and vaccines, and shows possible and exciting future developments [5].
Finally, to illustrate the potential application of studies in receptors, we have included a contribution from one of the leaders in GPCR (G-protein coupled receptor) in pain and inflammation, Prof. Frederic Simonin. His contribution is “GPRASP/ARMCX protein family: Potential involvement in health and diseases revealed by their novel interacting partners”. This review focuses on a family of intracellular proteins that interact not only with GPCRs but also with numerous other partners within the cell, highlighting the vast diversity of functions in which GPRASP/ARMCX proteins are involved [6].

Elucidating the mechanisms by which cells detect external molecules is fundamental not only for health in mammalian cells but also to dissect diseases caused by pathogens. I hope you enjoy the reading of all the contributions.

REFERENCES


**Celia R.S. Garcia**¹ and **Robson Coutinho-Silva**²

*Current Topics in Medicinal Chemistry*  
¹Department of Clinical and Toxicological Analyses  
School of Pharmaceutical Sciences, University of São Paulo  
Av. Prof. Lineu Prestes, 580  
São Paulo, SP 05508-900,  
Brazil  
Tel: 5511-2648-0954  
E-mail: celiaregarcia@gmail.com  
²Laboratory of Immunophysiology  
Biophysics Institute Carlos Chagas Filho  
Federal University of Rio de Janeiro  
Rio de Janeiro  
Brazil  
Tel: + 55 21 3938 6565  
Fax: +55 21 2280 8193  
E-mail: rcsilva@biof.ufrj.br