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Highlights

Perturbing purinergic signaling: A pathogen's guidebook to counteracting inflammatory responses

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ABSTRACT

In this issue of the *Biomedical Journal*, we learn how bacteria and parasites alike counteract inflammatory signaling by manipulating purinergic signaling. We also focus on an original article shedding light on the role of an Epstein–Barr virus encoded gene in metastasis in nasopharyngeal carcinoma. Finally, we learn about a possible link between *Trichomonas vaginalis* and recurrent urinary tract infection.

Spotlight on reviews

Perturbing purinergic signaling: a pathogen's guidebook to counteracting inflammatory responses

Best known as the universal currency of energy, the nucleotide triphosphate, ATP, powers every living organism on this planet known to human kind. Yet, outside the cell, ATP and its derivatives, take on an important role in inflammatory signaling, capable of controlling the fate of infected cells and the strength of inflammatory responses. It should thus come as no surprise that many human pathogens are able to manipulate this signaling pathway to their advantage. This issue of the *Biomedical Journal* includes three reviews describing the evasive tactics of three of such pathogens, *Trichomonas vaginalis* [1], *Leishmania* [2] and *Porphyromonas gingivalis* [3].

In the extracellular neighborhood, ATP is an important signaling molecule that is recognized by purinergic P2 receptors, divided into P2Y G-protein coupled receptors and P2X nucleotide-gated ion channels. Intracellular ATP is liberated as cells die, but its release can also occur in a controlled manner during cellular stress through pannexins and connexin channels [4,5]. Thus, extracellular ATP constitutes a danger signal that stimulates the immune system to mount an inflammatory response (mostly mediated through the P2X7 receptor [6]) and acts as a molecular flare to attract macrophages and neutrophils to apoptotic cells [7].

To terminate P2 signaling and return to status quo, ATP is broken down by widely expressed extracellular enzymes. The most important of these in immune cells are the ecto-NTPDase CD39, which breaks ATP down into ADP and subsequently to AMP, and the ecto-5′ nucleotidase CD73, which converts AMP into adenosine [8]. Extracellular adenosine binds to P1 receptors, which

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counteract the inflammatory responses elicited by ATP [9]. Thus, the strength of the inflammatory response depends on the balance between extracellular ATP and adenosine.

To tip the scales in favor of adenosine, several pathogens express enzymes capable of breaking down ATP. The protozoan parasites *T. vaginalis* and *Leishmania* are just two examples. *T. vaginalis* causes Trichomoniasis, a sexually-transmitted infection (STI) that facilitates the transmission of other STIs [10], has a negative impact on pregnancy outcome [11], and increases the risk of cervical cancer [12]. With 80% of cases going undetected, Trichomoniasis is a major public health problem [13]. Tasca and her team recently showed that *T. vaginalis* expresses five putative ecto-NTPDases [14]. It is thought that the expression of these enzymes favors the accumulation of extracellular adenosine. By binding to the A2A receptor, adenosine inhibits neutrophils from secreting nitric oxide products that are cytotoxic to *T. vaginalis* [15]. In *Leishmania*, the expression of ATP-hydrolyzing enzymes has been directly linked with virulence [16]. This parasite, which is transmitted by the bit of infected sandflies and causes 300,000 cases of Leishmaniasis each year, cannot synthesize purine rings and hence expresses ecto-nucleotidases as part of a purine salvaging pathway [17]. In the case of this intracellular parasite, it is an advantage to be able to prevent or delay apoptosis of host cells by degrading extracellular ATP.

Another intracellular pathogen, *Porphyromonas gingivalis* (*P. gingivalis*), also impairs ATP-mediated apoptosis by secreting an ATP-hydrolyzing enzyme [18]. This oral pathogen also inhibits the secretion of IL-1β by macrophages in a P2X7-dependent manner [19]. Besides influencing immune cells, modulation of ATP/adenosine levels may also promote infection by *P. gingivalis* effects on the dental epithelium. Indeed, recent work shows that gingival epithelial cells (GECs) express adenosine receptors, and that stimulation of the A2A receptor enhances the proliferation of *P. gingivalis* [20].

Thus, these pathogens promote their survival by having antagonistic effects on P1 and P2 receptors [Fig. 1]. Hence, this work identifies clear pharmacological targets for therapeutic studies, which should be relevant not only for a whole range of infections but also for the treatment of inflammatory disorders.

Spotlight on original articles

Viral gene bypasses immune system to induce metastasis in head and neck cancer

Nasopharyngeal carcinoma (NPC) is a type of head and neck cancer, which although rare, is notoriously metastatic. Although the exact causes of the disease are unknown, it has been strongly linked to infection with Epstein–Barr virus

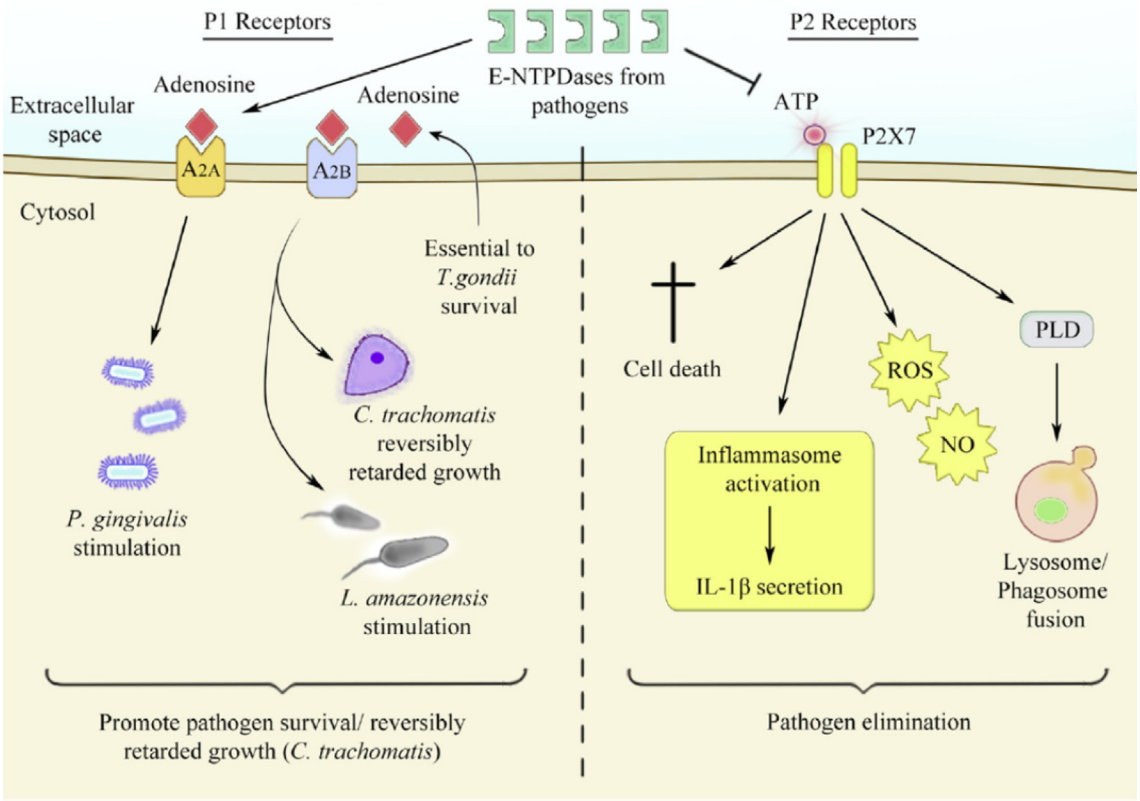

Fig. 1 – Several pathogens express ecto-nucleotidases (E-NTPDases) which reduce extracellular levels of ATP while promoting the accumulation of extracellular adenosine. This in turn inhibits signaling through P2 receptors and promotes signaling through P1 receptors, leading to the evasion of immune responses and pathogen survival. Figure kindly provided by Coutinho Almeida da Silva et al., see reference [3] for more details.