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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

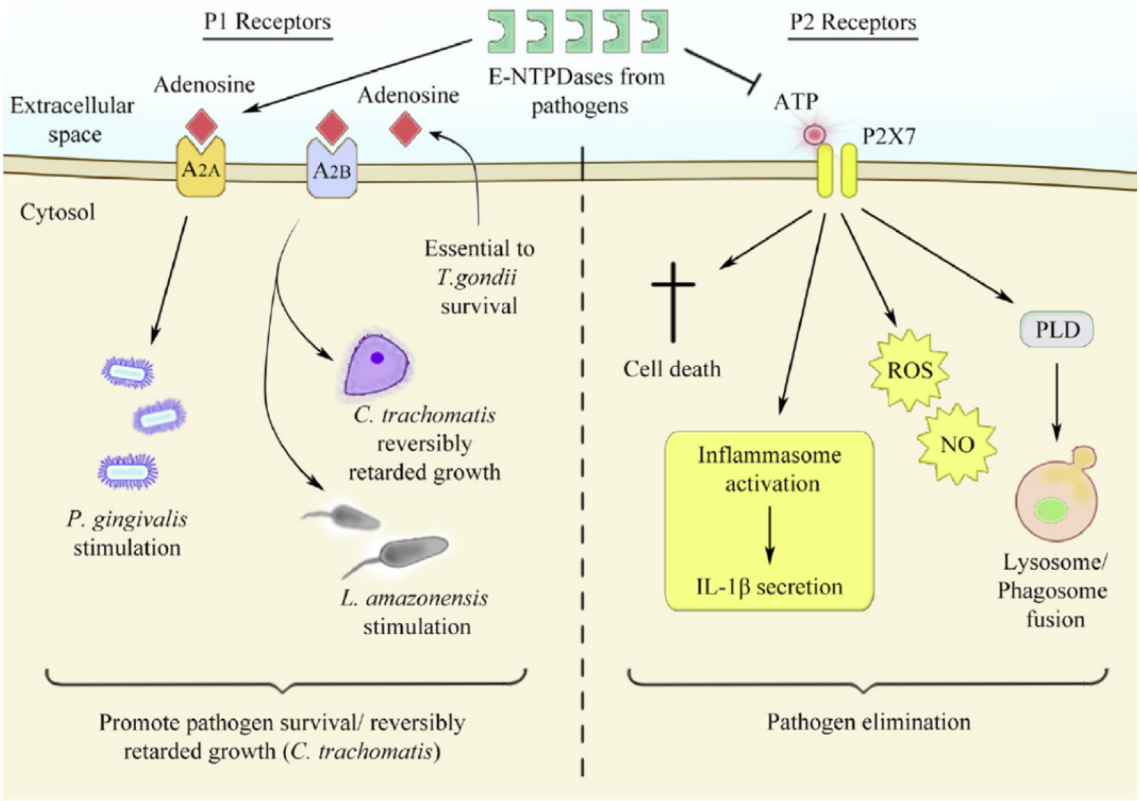

Fig. 1 – Several pathogens express ecto-nucleotidases (E-NTPDases) which reduce extracellular levels of ATP while promoting the accumulation of extracellular adenosine. This in turn inhibits signaling through P2 receptors and promotes signaling through P1 receptors, leading to the evasion of immune responses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

(EBV). In this issue of the *Biomedical Journal*, Chang et al. [21] shed light on its aggressive tendency and the role of EBV-encoded proteins.

EBV is a household name among cell biologists, known widely as the virus capable of transforming the humble B cell into an ever propagating immortalized lymphoblastoid cell line. In the human body however, EBV is usually a harmless passenger residing in the B cells of around 90% of the population worldwide [22]. Yet, under some circumstances, EBV may create favorable conditions for the development of certain cancers, notably lymphoma but also NPC, a disease which is particularly endemic in Southern China and Taiwan [23].

Latent membrane protein 1 (LMP1) is the primary transforming gene product of EBV and has been linked with NPC [24]. LMP1 is a transmembrane protein that mimics the TNFR family member CD40, and activates several signaling pathways promoting morphological and phenotypic alterations epithelial cells [25]. A key and deadly property however of LMP1 in the pathogenesis of NCP is its ability to promote metastasis. The N-LMP1 variant, which was isolated from Taiwanese patients with NPC [26], downregulates the expression of cell adhesion molecules while upregulating that of matrix metalloproteases [27,28]. However, little is known about the dynamics of LMP1-driven metastasis and whether LMP1 alone is sufficient to drive metastasis in immunocompetent hosts.

To examine the metastatic potential of LMP1, Chang and colleagues used their previously developed model of EBV-driven NPC in which tumor formation is induced in BALB/c mice by 3T3 cells expressing N-LMP1 [29]. Using PCR, they detected N-LMP1 DNA in the draining lymph nodes of mice as early as 7 days following tumor formation. To follow metastasis in real time in living animals, they used a bioluminescent assay in which N-LMP1 was coupled to a luciferase reporter gene. Luciferase activity was detected primarily in the lungs, surprisingly, even before the rapid growth of the primary tumor.

These results not only show that oncogenic LMP1 alone is capable of inducing metastasis in an immunocompetent host, they also strongly suggest that systemic cancer cell dissemination is an early event, that can occur before aggressive growth at the primary site. Thus, early treatment with LMP1-based therapies will be essential to stop the expansion and spread of NPC tumors.

Also in this issue:

Original articles

Neurotrophic factor linked to bipolar mania

Brain-derived neurotrophic factor (BDNF) is the most abundant growth factor in the central nervous system and is essential for brain development and plasticity. Imbalance in BDNF levels – which can be measured directly in the blood since BDNF crosses freely the blood–brain barrier – has been linked to several neuropsychiatric disorders [30], in particular bipolar disorder, although not all studies have been conclusive [31] and many have failed to analyze patients according to mood state (mania, depressive, euthymic). Lin et al. [32] measure serum BDNF protein and mRNA levels in 30 patients with bipolar mania and 30 healthy controls. Their findings suggest that BDNF levels are low patients with bipolar mania, although a larger sample size is needed to confirm these findings.

Visualizing cellular changes in patients with coronary heart disease

Ischemic heart disease (IHD, also called coronary heart disease) is the leading cause of mortality worldwide, accounting for 12.7% of deaths in 2008 [33]. Despite the major burden of the disease, the damage that occurs to the myocardium on a cellular level mostly been studied in animal models or post-mortum. Abuderman et al. [34] use light and electron microscopy on biopsies taken from 75 patients undergoing coronary bypass surgery to study the morphological changes occurring *in vivo* during the disease in humans. Fortunately, their findings are consistent with those in animals, including increased vascular density and increased arteriole wall to lumen ratio in patients with IHD.

Unassisted central venous catheterization: safe in most cases but not ideal

Central venous catheterization (central line placement) is a time-honored technique that is essential for the treatment of many hospitalized patients. Nowadays, it is normally performed under ultrasound guidance to reduce the risk of complications. However, in developing countries point-of-care ultrasound may not be available and the line must be placed unassisted. To investigate the safety of this approach, Rathi et al. [35] analyzed 233 attempts at unassisted internal jugular vein catheterization in patients undergoing hemodialysis at their center in India. Unassisted catheterization was associated with a slightly higher complication rate than that typical of ultrasound-guided catheterization, but long term outcomes were comparable; thus, this alternative method is acceptable, but only if imaging is not available.

Possible link between parasite and recurrent urinary tract infection

The protozoan parasite *Trichomonas vaginalis* (TV) causes the most common non-viral sexually-transmitted infection in women, and potentially the most neglected, with 80% of cases being asymptomatic [13]. Its prevalence is highest among women in their 50s [36], which incidentally coincides with the prevalence of another less inconspicuous condition, recurrent urinary tract infection (UTI) [37]. Noting this curious trend, Chang et al. [38] investigated the prevalence of TV in Taiwanese women with recurrent UTI. In total, 16.9% of the 65 women studied had TV. This prevalence is two to eight times higher than that reported in other populations, suggesting that patients with recurrent UTIs are at risk of TV infections.

Brief communication

An unusual case of gout

Wu et al. [39] report a rare case of gout affecting the nasal region and leading to nasal obstruction and bone destruction. This case highlights the importance of taking a detailed medical history, especially since gout can mimic malignancy, unrelated diseases and infection.

Conflicts of interest

Authors declare no conflicts of interest.

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