Comment on Stables et al, page 2950

Another miracle left in aspirin?

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In this issue of Blood, Stables et al provide new insight into how immunoregulation by prostaglandins influences 2 important challenges to human health: severe infections causing sepsis and the rise of antimicrobial drug resistance in bacterial pathogens.1

Bacterial infections are a major cause of morbidity and mortality worldwide. Innovative approaches to their prevention and management are needed. New treatments have focused on discovering antibiotics but this is problematic given the rise of antimicrobial drug resistance in common bacterial pathogens. Recent attention has been placed on identifying immunomodulatory agents that enhance innate and/or adaptive immune defenses of the infected host. The present work by Stables et al advances this immunopharmacology paradigm as it pertains to bacterial infections.1 Their work suggests that one solution may lie within the biology of aspirin.

Stables and collaborators used pharmacologic and genetic techniques to determine whether prostaglandin (PG) synthesis and signaling alters host immune responses to infections caused by either group B Streptococcus (GBS) or Streptococcus pneumoniae. Through elegant human and murine studies, Stables et al found that the inhibition of the PG-synthesizing cyclooxygenase-1 (COX-1) and COX-2 enzymes significantly improved innate immune defenses against common streptococcal pathogens. In so doing, they have brought several previously (and disparately) characterized immunomodulatory actions of PGs together. Their studies characterized several PG receptors and the intracellular signaling molecule (cAMP) involved in suppressing host defenses against infection.

Strengths of the experimental design by Stables et al include the combined use of rodent and human infection models to explore host-microbial interactions.1 Notably, their findings were reproducible when studying either antibiotic-susceptible or -resistant S pneumoniae. This is interesting and important because the class of COX inhibitors used in these studies, the nonsteroidal anti-inflammatory drugs (NSAIDs), is in common clinical use, raising the question of whether such medications might one day be used as adjuvant therapy in the treatment of antibiotic-resistant bacterial infections.

The PGs, oxygenated metabolites of the cell-membrane phospholipid component arachidonic acid, are generated rapidly in the face of physiologic or pathophysiologic perturbation. Unlike proteins, PGs are produced almost immediately upon cell stimulation, without relying on gene transcription and translation. They are important in many non-immune physiologic processes, explaining the utility of aspirin in preventing arterial thrombosis (by reducing platelet thromboxane A2 production) and the adverse effects of NSAIDs such as gastric ulceration and renal toxicity. During infection, PGs have complex actions, both driving and relaxing host responses. PGE2, the archetype immunoregulatory PG, promotes inflammation by inducing endothelial cell–mediated vasodilatation (producing warmth, erythema, and edema), and supporting Th17 adaptive immune responses.3 However, as supported by Stables et al, PGE2 has potent antiinflammatory and immunosuppressive properties including the direct inhibition of: neutrophil chemotaxis and activation; leukocyte reactive oxygen intermediated production; phagocytosis; bacterial killing; and the generation of myriad pro-inflammatory cytokines, chemokines, and lipids.4 Conversely, PGE2 enhances the production of the antiinflammatory cytokine interleukin-10 and stimulates the expression of the suppressor of cytokine signaling-3 protein. In general, the inhibitory effects of PGE2, and the closely related PGI2, result from cAMP-dependent signaling processes triggered by EP2 and EP4 receptor binding, and IP receptor activation for PGI2 (see figure). These immunosuppressive actions of PGs likely evolved to prevent inflammatory tissue damage and promote the resolution of inflammation.5

Aspirin and other NSAIDs have been used in patients with febrile infections for thousands of years, if one considers salicylate-containing botanicals. In 1962, Northover and
get particular PG molecules (or their downstream signaling networks). Previous work has suggested that inhibiting specific EP receptors for PGE2 might be beneficial to host defense and the data from Stables and collaborators drive home this point. They found significant enhancement of leukocyte killing of antibiotic-susceptible and -resistant pneumococci when human whole blood was pretreated with antagonists of the EP2 and IP receptors.1

While much has been learned about the roles of PGs in modulating immune defenses against bacterial infection, more research is needed to identify the ideal pharmacologic targets for clinical use. Perhaps then healthcare providers will urge infected patients to “take 2 EP2 inhibitors and call me in the morning.”

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IMMUNOBIOLOGY

Comment on Ortona et al, page 2960

To the heart of the APS puzzle

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In this issue of Blood, Ortona and colleagues identify the complex between vimentin and cardiolipin as an antigenic target in the APS, and demonstrate that affinity-purified antivimentin/cardiolipin antibodies induce IRAK1 phosphorylation and NF-κB activation in endothelial cells.

The antiphospholipid syndrome (APS) is an autoimmune disease, defined by the presence of so-called antiphospholipid antibodies, in association with clinical manifestations such as thromboembolic events and recurrent abortions and fetal loss. The APS diagnosis strictly relies on the simultaneous identification of clinical manifestations and laboratory findings; the laboratory diagnosis of APS relies on very strict criteria, reached by international consensus.1

Such strict criteria are unavoidable, because antiphospholipid antibodies represent a heterozygous group of antibodies, reactive with several phospholipid-binding plasma proteins. The best-known antigen is β2-glycoprotein I (β2GPI), against which antibodies are found in the majority of APS patients.2 Yet, many more proteins are potential antigen targets in APS, with many implicated in coagulation and anticoagulation regulatory pathways, platelet activation, endothelial cell activation pathways, or in complement activation.1 Another potential mechanism is that APS is characterized by the occurrence of phospholipid-dependent autoimmune antibodies against targets that can trigger different cellular responses, resulting in a variable intensity of clinical manifestations, which, in addition, are determined by antibody specificity and titer. Thromboembolic events and recurrent abortions are the best known manifestations of APS but the clinical symptoms such as neurological and pregnancy complications cannot be explained by thrombotic or ischemic mechanisms.1

Hence, understanding

REFERENCES


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