Adenosine receptors in the response to sepsis: what do receptor-specific knockouts tell us?

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IN THIS ISSUE Dr. Lee and colleagues (8a) demonstrate that the A3 adenosine receptor subtype (A3R) protects against a septic challenge. In this regard, the A3R joins the A1R and A2AR in similar investigations. Although the focus of their investigation was the A3R, Dr. Lee and colleagues directly compared their results to responses in A1R and A2AR knockout mice. The authors clearly show that A3R activation is protective against a septic challenge, but also confirm reports from other labs that similar statements can be made regarding the A1R and that the A2AR also plays a role in sepsis, although the specific role is less clear. Previously, Gallos et al. (6) demonstrated increased mortality after cecal ligation and puncture (CLP) sepsis in A1R knockout mice. In contrast, Nemeth et al. (12) demonstrated reduced mortality in A2AR knockout mice, which agrees with the results presented by Lee et al. (8a). However, Sullivan et al. (16) found that an A2AR agonist improved survival from CLP sepsis, and Nemeth et al. (12) suggested that an A2AR antagonist improved survival only when administered in a delayed fashion. These results render the role of the A2AR in sepsis less clear and may be dependent on the time course of the pathology.

Beneficial effects of adenosine in sepsis have been suggested in other studies. Inhibition of the rephosphorylation of adenosine by adenosine kinase (5) or its degradation by adenosine deaminase (2, 3, 8) improves survival from sepsis in various models. All of these studies suggest that endogenous adenosine acts as an immunomodulating agent, regardless of the receptor involved. Recent evidence from our laboratory lends credence to this. In primary macrophages, all adenosine receptor agonists inhibit LPS-mediated TNF production, but all agonists used in tandem appear to exert additive or synergistic effects. Ablation of a single adenosine receptor can provide insights into the physiological role of the receptor, but the diffuse, complex, and myriad physiological actions of adenosine provide an impetus for caution in overstating the therapeutic potential of individual receptors. It would serve us well to remember the history of adenosine research in this regard. Most of the papers looking at this phenomenon have focused on immune function or markers (such as cytokines) or have used indexes of oxysterol-mediated tissue damage or blood markers of organ function. Yet, adenosine was first recognized for its cardiac and vascular effects (1), actions that are not easily indexed by a single molecule nor readily studied in vitro. During sepsis, adenosine clearly plays a role in the perfusion redistribution that occurs (10, 11, 14, 15). Vascular effects of adenosine are typically attributed to the A2AR, although other receptors are more likely to play a role in the vascular responses in other tissues and organs. The A1 and A3 receptors are known to have significant influence on cardiodynamic responses. In total, the cardiovascular effects of adenosine can impact every organ system and cell type in an organism. In addition, adenosine is known to influence hemostasis, neural function, metabolism, and pulmonary function (to name a few), all of which may impact survival during a septic crisis. It is important that we remember these phenomena to understand the important findings by Lee et al. (8a) in their appropriate context.

There are at least four subtypes of adenosine receptor, all of which are hepta-spanning transmembrane G protein-coupled receptors. Three of the adenosine receptor subtypes (A1, A2A, and A2B) demonstrate 80–95% sequence homology across a wide evolutionary range of species. In contrast, the A3 receptors demonstrate significant species variation. Signal transduction by the adenosine receptors varies, not only among the subtypes, but also for a particular subtype between different cell sources. A1 receptors were originally characterized as coupled to pertussis toxin-inhibited Gi-coupled signal transduction, but in some cells, they are directly associated with, and act through, ion channels. The A2 receptor subtypes (A2A and A2B) are typically coupled to G1-linked receptors. The prototypic response to adenosine (vasodilation) is effected in this way via stimulation of adenylyl cyclase. In some tissues, A1 adenosine receptor-mediated inhibition and A2A receptor-mediated stimulation of adenylyl cyclase appear to coexist and be counterregulatory (13). Furthermore, A2A receptors that do not stimulate adenylyl cyclase have been identified in heart tissue (7), so alternative signaling mechanisms may be associated with this receptor subtype, as well. Because of the ubiquitous and plurieffective nature of adenosine receptor-mediated actions, these receptors have often been targeted for the development of pharmacologically active agonists and antagonists or genetic manipulation. However, the various systems upon which adenosine receptors exert influence can also be a hindrance to such pharmacological approaches, and undesirable side effects in nontarget systems are readily seen.

We must also remember the dynamic nature of adenosine receptors after a septic challenge. Cells can express as few as one adenosine receptor subtype, or combinations of the four adenosine receptor subtypes, and the specific receptor(s) expressed change with physiological stimuli. A relevant example of this is in monocytes. Among the changes that have been shown to occur as monocytes differentiate into macrophages are adenosine receptor subtype profile changes (4). Further complicating this is the distinct differentiation related to the final tissue residence of the macrophages. Isozyme profiles of PKC, one of the signaling pathways used by adenosine receptor signaling, has been shown to vary between alveolar and peritoneal macrophages (9).

The work by Lee et al. (8a) is pivotal not only in demonstrating a role for the third class of adenosine reactors in the response to sepsis, but also in providing in a single publication verification of roles for involvement of nearly all of the adenosine receptors in the response to sepsis. It is important that we do not expand our interpretation of associated phenom-
ena, such as changes in cytokines or liver enzymes, into conclusions about causality. In this regard, Lee and colleagues have tempered their interpretation appropriately with context. Due to the complexity of adenosine signaling throughout mammalian systems and the vast array of physiological systems influenced, this nucleoside represents a true challenge to the integration of genomic, transcriptomic, proteomic, and metabolomic approaches needed to truly understand, and perhaps, to yield viable therapeutic modalities.

REFERENCES