Correspondence for

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Caveats and cautions for the therapeutic targeting of the anti-inflammatory A2 adenosine receptors

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Dear Editor,

Jacobson and Gao recently published an excellent overview of adenosine receptors as therapeutic targets[1]. In this commentary, we would like to identify some caveats in pre-clinical development of promising novel approaches to manipulating inflammation via targeting of the A2 adenosine receptor-mediated natural anti-inflammatory pathway.

The important roles of A2A and A2B adenosine receptors in functioning or protection of major organs[2–5] have long been appreciated and have led to extensive efforts to develop selective agonists and antagonists of adenosine receptors[1–6]. The therapeutic targeting of A2 adenosine receptors to manipulate inflammation has became even more appealing and feasible due to the discovery of their critical and non-redundant role in protecting tissues from inflammatory damage during the anti-pathogen immune response[7]. These findings have been subsequently confirmed in different models of inflammation[8–13]. Further incentive to target A2 adenosine receptors was provided by the *in vivo* genetic evidence that tissue-protecting effects of local tissue hypoxia are due to extracellular adenosine initiating A2AR/A2BR signalling[9].

Indeed, A2AR agonists attenuated neuronal damage and improved functional outcome after experimental traumatic spinal cord injury[10,11] or renal ischemia–reperfusion injury[12] or gastric mucosal inflammation[13]. A2AR agonists have also been shown to suppress inflammatory activation after myocardial infarction[14], and may be advantageous in the treatment of sepsis15 because A2A-receptor-mediated signalling physiologically attenuates proinflammatory transcription in vivo16. In addition, important and promising clinical applications of A2A antagonists have been suggested by studies of Parkinson's disease[17–19] and liver cirrhosis[20,21].

However, although the development and clinical applications of A2 receptor ligands are very promising, and may lead to breakthroughs in the treatment of many diseases, the often-used comparison of inflammation to a 'double-edged sword' should be kept in mind when considering the therapeutic use of A2A and A2B adenosine receptor ligands. Failure to do so may lead to the unintended tissue damage and/or abnormal tissue remodelling if, for example, A2 receptor agonists are used during the resolution of inflammation, since activation of the A2A adenosine receptor may be responsible for hepatic collagen production[20].

It is important to tailor the timing of adenosinergic treatment to the specific disease pathogenesis, the tissue microenvironment, and the stage of inflammation. Special caution is required in choosing an agonist or an antagonist of A2A or A2B adenosine receptors in order to accomplish the desired therapeutic effect and to avoid unintended tissue damage. There is an acute need for reliable biomarkers of different stages of inflammation.

The consideration of the use of A2 receptor ligands in the treatment of the systemic inflammatory response syndrome (SIRS) versus the compensatory anti-inflammatory response syndrome (CARS) stages of sepsis illustrates when to use and not to use A2 receptor agonists and antagonists. Many sepsis patients suffer either because of multiple organ failure due to myeloid cell-mediated tissue damage during SIRS and/or because of nosocomial or opportunistic infections due to the weakened anti-pathogen response during CARS[22,23]. Agonists of A2A adenosine receptors could be used to prevent inflammatory damage during SIRS[15], whereas A2AR/A2BR antagonists may increase the inflammatory anti-pathogen response and survival during CARS, as the disengagement of hypoxia-driven and A2AR/A2BR-mediated pathways results in an increase in levels of inflammatory mediators[9]. We caution, however, that although A2AR agonists are anti-inflammatory during the acute inflammation stage, they may be harmful and promote organ disfunction if added at the later inflammatio-resolution stage. Similarly, although A2AR antagonists could exacerbate the collateral inflammatory damage during SIRS, they may also de-inhibit the inflammatory pathogen destruction and thereby improve bacterial sepsis and survival at the CARS stage.

So, we propose first, that A2AR agonists should be used to prevent collateral damage (by for example, TNF-α-producing overactive immune cells) at early stages of acute inflammation; and second, that A2AR agonists should not be used at later stages of inflammation to avoid A2AR-mediated tissue damage by other, yet-to-be-identified cAMP-regulated mediators of inflammation. By contrast, antagonists of A2ARs should not be used at the acute inflammation stage to avoid the tissue-damaging effects of increasing levels of immune cells-produced inflammatory mediators. However, antagonists of A2ARs should be tested to 'de-inhibit' activated immune cells during, for example, the CARS stage of sepsis. It is expected that A2AR antagonists will prolong and strengthen the anti-pathogen immune response, increase levels of anti-bacterial inflammatory mediators, and improve bacteria destruction and sepsis survival if added during the CARS stage of sepsis.

The availability of reliable biomarkers indicating the transition from the 'acute' to 'chronic' inflammation will allow the timely recruitment of an immunosuppressive pathway with A2AR agonists and thereby prevent inflammatory organ damage during SIRS. In an opposite, but as important application of biomarkers of inflammation, it will be possible to enhance the pathogen destruction using A2AR/A2BR antagonists during CARS.

Finally, of relevance for pre-clinical studies, it is important to emphasize that attempts to engineer inflammation by targeting the A2ARs should take into account the 'infectious past' of experimental animals. This is because A2AR expression is activation-depended and in 'naïve' animals that are kept in pathogen-free conditions, the effects of antagonists in short-term assays will not be observed. It may be beneficial to model the inflammatory and counter-inflammatory responses in animals that have been pre-exposed to, for example, endotoxin, in order to mimic the real-life immune system.

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