Nature Reviews Drug Discovery | AOP, published online 24 September 2012; doi:10.1038/nrd3852

INFLAMMATORY DISORDERS

Separating good from bad

Agonists of adenosine A_{2A} receptors (A_{2A}Rs) have beneficial anti-inflammatory properties, but their clinical use is prevented by potent vasodilatory effects. Now, a study reported in *Science Translational Medicine* has separated these two physiological effects of A_{2A}R agonists: Schrader and colleagues identified a phosphorylated prodrug A_{2A}R agonist — which was specifically activated by an ectoenzyme expressed on immune cells — that reduced inflammation in a mouse model of arthritis without inducing vasodilatory side effects.

The authors and collaborators had previously synthesized a series of phosphorylated A_{2A}R agonist prodrugs that were activated after being dephosphorylated by the CD73 ectoenzyme that is found on the endothelium and immune cells. In the current study, they investigated the *in vivo* effects of the lead compound, 2-(cyclohexylethylthio)adenosine 5′-monophosphate (chet-AMP).

First, they studied the anti-inflammatory properties of chet-AMP using fluorescent magnetic resonance imaging of a mouse model of collagen-induced arthritis. Chet-AMP (applied by osmotic pump at a dosage of 0.5 μg per kg per minute) for 1 week reduced inflammation by more than 60% in affected knees and hindpaws. Histological studies showed that chet-AMP inhibited proteoglycan depletion and erosion of cartilage matrix, and also increased the relative amount of macrophages and prevented the influx of neutrophils in affected knees of the mice.

Next, the authors showed that expression of CD73 was upregulated on granulocytes, monocytes and macrophages, and A_{2A}R expression was upregulated on granulocytes and monocytes from mice with arthritis. This disease-mediated upregulation of CD73 and A_{2A}R on immune cells probably mediates and amplifies the beneficial effects of the prodrug.

Finally, the vasodilatory effects of chet-AMP in mice were determined by infusing chet-AMP into non-arthritic mice while changes in systemic blood pressure were measured. By relating the measured plasma levels of chet-AMP to changes in blood pressure and immune effects, the authors determined that the plasma concentrations of chet-AMP required to decrease systemic blood pressure were about 100-fold higher than those required for the anti-inflammatory activity.

So this study shows that it is possible to separate the vasodilatory effects of A_{2A}R agonists from the anti-inflammatory effects. Because the upregulation of the CD73–A_{2A}R axis appears to be a general feature of activated immune cells, the authors suggest that an A_{2A}R prodrug might also be useful in other inflammatory disorders.

Charlotte Harrison

ORIGINAL RESEARCH PAPER Flögel, U. *et al.* Selective activation of adenosine A_{2A} receptors on immune cells by a CD73-dependent prodrug suppresses joint inflammation in experimental rheumatoid arthritis. *Sci. Transl. Med.* **4**, 146ra108 (2012)

GETTY