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COMMENTARY

New drug targets in inflammation: efforts to expand the anti-inflammatory armoury

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Inflammation is a beneficial host response to challenge by foreign bodies or to tissue injury. When this normal physiological process (which is designed to restore normal tissue structure and function), becomes dysregulated, it can become harmful and destructive leading to inflammatory diseases that are a major burden on humanity. Despite some notable successes, there are still major unmet medical needs in the treatment of inflammatory diseases and the development of new anti-inflammatory drugs features prominently in the research portfolios of most pharmaceutical and biotech companies. New insights into inflammatory processes and new anti-inflammatory drug targets were the subjects of a Focus Topic organized for the *Life Sciences 2007* meeting in Glasgow (July 2007). The speakers from this meeting were invited to generate reviews on the basis of their presentations and these reviews contribute to this themed issue and are summarized in this short article.
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The complex process of inflammation protects the body against infection and injury but can itself become dysregulated with deleterious consequences to the host. As such, the inflammatory response can lead to a large number of diseases, the most common of which include rheumatoid arthritis, inflammatory bowel disease, psoriasis and multiple sclerosis. In recent years, it has become clear that inflammation also plays a key role in other widely prevalent diseases not previously considered to have inflammatory aetiologies, such as Alzheimer's disease, cardiovascular disease and cancer.

A range of therapies exists for the treatment of inflammation-driven diseases. The current mainstays of anti-inflammatory therapies such as steroids, non-steroidal anti-inflammatory drugs and anti-histamines are largely based on inhibiting the synthesis or action of inflammatory mediators. The newer biopharmaceuticals (for example, tumour necrosis factor-α-neutralizing therapies, anti-IgE and anti-CD20 antibodies) continue this line of therapeutic intervention (Fleischmann and Yocum, 2004; Holgate and Polosa, 2006), although other biological agents have also been designed to target the recruitment or activation of inflammatory cells that drive the host's response to injury, such as antibodies to integrin-α4β7 and CTLA-4-Ig, which disrupt T-cell activation. However, neither the established therapies nor the newer biopharmaceutical approaches are without their shortcomings (Kremer *et al*., 2003; Edwards *et al*., 2004; Sandborn *et al*., 2005). For example, steroids can cause osteoporosis and impair wound healing, while the ulcerogenic effects of traditional non-steroidal anti-inflammatory drugs, which are COX inhibitors, and the increased risk of coronary thrombosis and stroke associated with the use of selective COX-2 inhibitors are well documented (Wang *et al*., 2005). Moreover, use of biopharmaceuticals such as the tumour necrosis factor-α- and integrin-α4β7-neutralizing therapies have also led to several complications (Kremer *et al*., 2003; Edwards *et al*., 2004; Sandborn *et al*., 2005; Strand *et al*., 2007). Given the limitations of existing small molecule and biopharmaceuticals, there remains a clear need for identification and validation of new anti-inflammatory drug targets (O'Neill, 2006). This was the subject of a Focus Topic organized for the *Life Sciences 2007* meeting in Glasgow (July 2007). The speakers from this meeting were invited to write reviews derived from their lectures and which now contribute to this themed issue and are summarized in this article.

Under normal conditions, the resolution phase of the inflammatory response ensures that the inflammatory response is self-limiting and its *raison d'etre* is to return the damaged tissue to its original homeostatic state. Resolution of inflammation is a highly coordinated and active process that is controlled by pro-resolving mediators that terminate leukocyte trafficking to the inflamed site, reverse vasodilation

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and vascular permeability and ensure removal of inflammatory leukocytes, exudates and fibrin. In the absence of effective resolution, scarring can occur and/or the tissue will progress to a chronic inflammatory state and even to fibrosis (Gilroy *et al*., 2004). Detailed characterization of the biochemical pathways leading to resolution might therefore lead to the identification of novel targets that can be exploited for future anti-inflammatory drug discovery. This is currently a major topic of investigation in the search for anti-inflammatory therapies, and is reflected in the topics covered within the accompanying review articles. Charles Serhan (Serhan and Chiang, 2008) focuses on new families of local chemical mediators that are generated endogenously in exudates collected during the resolution phase. These are termed resolvins and protectins to represent their ability to control both the duration and magnitude of inflammation in animal models of complex diseases. These pro-resolving mediators are generated from the major Ω-3 polyunsaturated fatty acids, eicosapentaenoic acid and docosahexaenoic acid. These mediators, along with Ω-6 polyunsaturated fatty acid arachidonic acid-derived lipoxins, are described as resolution agonists. Interestingly, aspirin triggers formation of these mediators, providing a novel mechanism underlying aspirin's clinical benefits, in addition to its long-recognized ability to inhibit the biosynthesis of pro-inflammatory prostaglandins. Given that the precursors to resolvins and protectins are Ω-3 fatty acids, this fits well with the widely appreciated notion that Ω-3 fatty acid diet supplementation reduces inflammatory disease and brings about an anti-inflammatory state. The reader is left in no doubt that endogenous pro-resolving mediators, their mimetics and stable analogues have an exciting future in drug development for inflammatory diseases.

In the second review, Chris Buckley and colleagues (Flavell *et al*., 2008) propose that stromal cells such as fibroblasts are active components of tissue-specific microenvironments. As such, these cells actively contribute to cytokine and inflammatory chemokine networks, which result in immune cell recruitment and activation. However, an exciting role of stromal cells has been demonstrated with regard to the inappropriate expression of constitutive, housekeeping chemokines. These contribute to the persistence of inflammation by actively blocking its resolution. The recognition that fibroblasts are able to determine the type and persistence of inflammatory infiltrates has opened up new horizons in research and highlighted these cells as possible therapeutic targets in inflammation.

Finally, Pettipher (2008) focuses on allergic inflammation and the roles of the prostaglandin D_2 receptor DP1 and CRTH2. Pharmacological studies using recently discovered DP1 and CRTH2 antagonists combined with genetic analysis support the view that these receptors play key roles in mediating aspects of allergic diseases that are resistant to current therapy. The emerging roles of DP1 and CRTH2 in acute and chronic aspects of allergic diseases are considered, and it is proposed that these receptors have complementary roles in the initiation and maintenance of the allergy state.

Together, these articles provide a compelling, exciting and cutting-edge insight into current understanding of the inflammation processes and strategies to identify new drug targets. While we may dream of an aspirin of the twenty-first century, the discovery of a range of new therapeutic tools will broaden and extend the anti-inflammatory armoury. The availability of a diverse arsenal of therapeutic weapons, with a repertoire of targets tailored towards specific therapeutic needs, seems a more achievable goal.

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