COMMENTARY

Exploiting Endogenous Anti-Inflammatory Pathways as a Therapeutic Approach to Multiorgan Inflammatory Disease

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It is not uncommon for patients to be afflicted simultaneously with inflammatory diseases of multiple organ systems. For example, many patients with inflammatory bowel disease also experience rheumatoid arthritis, uveitis, ankylosing spondylitis, or various inflammatory disorders of the skin. Treatment of these co-existing disorders can sometimes be challenging (eg, nonsteroidal anti-inflammatory drugs commonly used to reduce the symptoms of arthritis can exacerbate inflammatory bowel disease). Use of multiple types of anti-inflammatory drugs to treat co-existing inflammatory disorders can lead to a range of adverse effects, including an increased susceptibility to opportunistic infections. There is a need, therefore, for broader-acting anti-inflammatory therapies that can safely exert beneficial effects against several types of inflammatory diseases.

In this issue of The American Journal of Pathology, Montero-Melendez et al describe studies of an experimental drug that is effective in reducing, in the same animal, the symptoms and severity of experimental rheumatoid arthritis and periodontitis, disorders that are known to co-occur in humans. DTrp—γ-melanocyte stimulating hormone (DTrp) is an agonist of melanocortin receptor 3 (MC3), one of the five melanocortin receptors that have been shown to modulate a wide range of important biological functions. Adrenocorticotropic hormone has long been recognized to exert cortisol-independent anti-inflammatory effects, specifically in rheumatoid arthritis and gout, produced at least in part through activation of MC3. Montero-Melendez et al demonstrate important roles for MC3 in modulating periodontal status in both health and disease; thus, mice genetically deficient of MC3 exhibited increased alveolar bone loss compared with healthy wild-type mice. Induction of rheumatoid arthritis in mice with K/BxN serum was accompanied by the development of significant periodontitis, mimicking what can occur in humans. Effects on bone resorption in the maxillae and substantial infiltration of immunocytes mirrored the destructive changes in the joints during rheumatoid arthritis, and the accompanying infiltration of inflammatory cells. Treatment of the mice with DTrp resulted in significant reductions in the severity of both the periodontal and joint diseases. In contrast, treatment with dexamethasone provided a beneficial anti-inflammatory effect in the joints, but significantly worsened alveolar bone loss. Of course, prolonged glucocorticoid use is also associated with marked reductions in bone density and increased risk of fractures.

On the other hand, another drug tested as a positive control (calcitonin) protected against alveolar bone loss, but had minimal beneficial effect on the joint inflammation. DTrp has also been shown to be effective in treating experimental gout. Montero-Melendez et al proposed that MC receptor agonists selective for MC3 may “represent a novel class of anti-artritic therapeutics able to target joint disease without aggravating unwanted effects on distant organs and tissues.” Moreover, DTrp could be viewed as a starting point for a new class of bone-sparing anti-artritic agents.

Many pharmaceutical companies are increasingly focusing on monoclonal antibody-based therapeutics, driven to a significant extent by the large profit margins for these compounds and by the substantially increased obstacles to the development of generic substitutes (biosimilars). Although effective in certain disorders, some monoclonal antibody therapies carry significant risks for serious adverse effects. The study by Montero-Melendez et al highlights the continued value of simpler and cheaper (for both the maker and the end user) approaches to drug development.

Disclosure: J.L.W. is a founder and officer of Antibe Therapeutics Inc., a company developing anti-inflammatory drugs.

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harnessing the potential of endogenous anti-inflammatory mechanisms. Such approaches are being used for drug development on the basis of several endogenous anti-inflammatory substances in addition to MC3, including resolvins, hydrogen sulfide, and annexin-1. All of these mediators participate in the active process of resolution of inflammation, limiting tissue injury and promoting a return to homeostasis after an inflammatory episode. In general, they produce a wide range of anti-inflammatory effects, as well as promoting the healing of tissue injury. They are chemically diverse: resolvins are lipids, annexin-1 is a protein, and hydrogen sulfide is a gas. Being endogenous, physiological substances, there are few adverse effects associated with their use as drugs. They also hold significant promise for safely treating a wide range of inflammatory disorders, including co-existing inflammatory diseases in the same patient (like MC3 agonists).

References