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Editorial

Steroids: Modulators of inflammation and immunity

The study of steroids started in the first half of the last century. Following the discoveries of sex steroids and then glucocorticoids between the 1920s and 1940s, they rapidly made their way into the clinic. From the beginning, glucocorticoids proved themselves to be potent anti-inflammatory agents and they remain the most effective therapy for many allergic and chronic inflammatory diseases, although their use, especially at high pharmacological dose, is limited by their diverse side effects. Endogenous steroids are important modulators of the immune system. It is well known that men and women differ in their immunity, with women being more susceptible to auto-immune disease, but less susceptible to infections. Sex steroids modulate immunity and inflammation – some of these effects may be indirect, but the presence of oestrogen and androgen receptors within immune cells highlights the important and direct effects they have. Recently, the involvement of other steroids in immunity has attracted attention, in particular the role of noncalcemic actions of vitamin D in immune cells (especially T cells), and there is considerable promise in the use of vitamin D to treat some allergic diseases. Some immunomodulatory steroids, the prime example being dehydroepiandrosterone (DHEA) and its sulfated form, DHEAS, do not even bind to members of the nuclear receptor family. The exact mechanism how DHEA exerts its effects still remains unknown.

This special issue of the *Journal of Steroid Biochemistry and Molecular Biology* highlights the effects of these steroids upon inflammation and immunity. Inflammation is, of course, a normal process, being a host defence mechanism activated in response to injury or infection that serves to control and eliminate invading pathogens and promote the repair of damaged tissues. Many normal body processes harness aspects of the inflammatory response, a prime example of this being the female reproductive system, with its cycles of tissue damage and repair - follicular rupture and release of the oocyte from the ovary, shedding of the endometrium at menstruation with subsequent repair and regeneration ready for the next cycle. It is when the inflammatory response goes awry or the initial stimulus persists that problems set in and chronic inflammation ensues. Administered therapeutically, glucocorticoids are immuno-suppressive and anti-inflammatory and are widely used to control chronic inflammatory diseases such as asthma, rheumatoid arthritis and dermatitis. Endogenous glucocorticoids are immunomodulatory rather than simply immunosuppressive (some of their actions can be considered pro-inflammatory) and exert their effects through two members of the nuclear receptor superfamily. Under some circumstances the mineralocorticoid receptor (MR) acts as a high affinity glucocorticoid receptor, and may be responsible for some of the pro-inflammatory effects of glucocorticoids, particularly within the vasculature. However, most glucocorticoid actions are mediated by the glucocorticoid receptor (GR) which is expressed almost ubiquitously, including in immune cells. Its mechanism of action has been extensively investigated, although exactly how and where it exerts its anti-inflammatory effects *in vivo* remains the subject of some debate. In the first paper in this volume, Baschant and Tuckermann describe the use of conditional GR knock-out and GR function-selective mouse models to elucidate the cell-specific roles of GR in modulating inflammation and immunity. A major clinical problem is glucocorticoid resistance, whereby patients are (or become) non-responsive to glucocorticoids. Understanding the cellular mechanisms that give rise to glucocorticoid resistance is key to improving therapy. These mechanisms are reviewed in the paper from Barnes, together with potential treatments to reverse or by-pass glucocorticoid resistance. A key target in the development of glucocorticoid resistance may be regulatory T cells (Treg cells). Regulatory T cells are critical to maintain "tolerance" and prevent inappropriate immune activation in response to ubiquitous non-harmful allergens. Induction of regulatory T cells in patients may be an effective therapy to treat allergic disease, especially in glucocorticoid resistant patients. The influences of steroids on regulatory T cell induction and function is discussed by Dimeloe et al. This is followed by a paper from De Bosscher who describes the development of novel selective glucocorticoid receptor modulators; compounds which maintain the therapeutically useful anti-inflammatory actions of glucocorticoids, without the detrimental metabolic side effects. Some of these drugs are showing promise and may soon reach the clinic.

The levels of circulating sex steroids decline in later life, with loss of the cardio-protective effects of oestrogen following menopause in women, although whether this is reversed with hormone replacement therapy remains controversial. This topic is covered by Gilliver, who has reviewed the effects of sex steroids upon immune cell function. This is an area that will be increasingly important to understand and exploit to our advantage as we move towards an increasingly elderly population. Normal inflammatory and anti-inflammatory effects of sex steroids in the human reproductive system are reviewed by King and Critchley, who also highlight the important role played by steroid metabolising enzymes in the modulation of intracellular steroid access to receptors. As well as sex steroids, levels of some other steroids also decline during later life. DHEA and DHEAS, precursors to sex steroids, are abundant in plasma in young adults, but decline thereafter. There is popular interest in the use of DHEA as a supplement to counter the many effects of aging including those associated with immune senes-

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cence, but the evidence as to whether and how it exerts these effects has been debated. In the final review article, Hazeldine et al. look at the evidence regarding the immunomodulatory effects of DHEA and DHEAS, and speculate on the mechanisms by which these steroids may act.

The subject of this volume is large and the papers included here by no means offer comprehensive coverage of the field, but they do give a flavour of the current state of the field and highlight exciting and promising avenues for future research.

We would like to thank all the Authors who have contributed manuscripts to this special issue. We would also like to thank all the Reviewers who have given their time and effort to evaluating the manuscript submissions. Last, but not least, thank you to the editorial staff at Elsevier, especially Lijuan Wang and Malini Sangeneni for keeping us on track and to time with this issue.

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