Review

MOLECULAR METABOLISM

An intracrine view of sex steroids, immunity, and metabolic regulation

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ABSTRACT

Background: Over the past two decades, parallel recognition has grown of the importance of both sex steroids and immune activity in metabolic regulation. More recently, these discrete areas have been integrated in studies examining the metabolic effects of sex steroid immunomodulation. Implicit in these studies has been a traditional, endocrine model of sex steroid delivery from the gonads to target cells, including immune cells. Thus, research to date has focused on the metabolic effects of sex steroid receptor signaling in immune cells. This endocrine model, however, overlooks the extensive capacity of immune cells to generate and metabolize sex steroids, enabling the production of sex steroids for intracrine signaling — that is, sex steroid production for signaling within the cell of origin. Intracrine function allows highly cell-autonomous regulation of sex steroid exposure, and sex steroid secretion by immune cells could confer paracrine signaling effects in neighboring cells within metabolic tissues. In this review, immune cell intracrinology will denote sex steroid production within immune cells for either intracrine or paracrine signaling. This intracrine capacity of immune cells has been well established, and prior work has supported its importance in autoimmune disorders, trauma, and cancer. The potential relevance of immune cell intracrine function to the regulation of energy balance, body weight, body composition, and insulin sensitivity has yet to be explored.

Scope of review: The following review will detail findings to date regarding the steroidogenic and steroid metabolizing capacity of immune cells, the regulation of immune cell intracrine function, and the biological effects of immune-derived sex steroids, including the clinical relevance of immune cell intracrinology in fields other than metabolism. These findings will serve as the basis for a proposed model of immune cell intracrinology constituting a new frontier in metabolism research.

Major conclusions: The development of highly sensitive mass spectrometric methods for sex steroid measurement and quantitation of metabolic flux now allows unprecedented ability to interrogate sex steroid production, metabolism and secretion by immune cells. Immune cell intracrinology could reveal key mechanisms underlying immune cell-mediated metabolic regulation.

Keywords Macrophages; Lymphocytes; Estrogens; Androgens; Intracrine; Metabolism

1. INTRODUCTION

The term ‘intracrinology’ first was used almost 30 years ago to describe androgen synthesis in peripheral tissues in orchiectomized rats, denoting sex steroid production and signaling that occurred within the same cell [1]. Intracrinology, therefore, introduced unprecedented autonomy of peripheral cells and tissues to regulate sex steroid production locally, independent of gonadal sex steroid production. Tissue intracrinology long has been a central focus of research in rheumatology and oncology and has generated key insights into the pathogenesis of diseases including rheumatoid arthritis, breast cancer, and prostate cancer [2—4]. The steroidogenic or intracrine capacity of peripheral tissues now also has become an emergent area of interest in metabolism research [5,6], as metabolic tissues including brain, liver, adipose tissue, and skeletal muscle all possess steroidogenic capacity. These metabolic tissues are enriched in sex steroids [5], and androgens and estrogens have well established roles in the regulation of energy metabolism, appetite, adipogenesis, and insulin sensitivity [7—11]. Importantly, clinical data consistently demonstrate a lack of uniform association between plasma and tissue-specific sex steroid concentrations, suggesting that altered sex steroid production within metabolic tissues may contribute to the evolution of obesity and associated metabolic disorders [5,12—14]. Thus, identifying the mechanisms whereby local sex steroid production and metabolism are regulated within metabolic tissues could provide critical insight into the pathophysiology of metabolic disease.

Immune cell populations are present in all metabolic tissues, and steroidogenic capacity has been identified in immune cells, particularly in macrophages and T lymphocytes. Tissue immune cells, therefore, could be a key source of local sex steroid production, and immune cell-derived sex steroids may play important intracrine and paracrine roles, with signaling effects conferred both in the cell of origin and in surrounding cells. The metabolic significance of immune cell steroidogenesis remains almost wholly unexplored to date. Immune cell intracrinology is a novel facet of metabolism research that may prove essential for comprehensive elucidation of the mechanisms through which sex steroids and immunity regulate metabolic health.

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Review

2. BACKGROUND: POTENTIAL RELEVANCE OF IMMUNE CELL SEX STEROID PRODUCTION TO METABOLIC REGULATION

2.1. A conceptual shift from endocrinology to intracrinology

The classic, endocrine view of sex steroid biology is that sex steroids are produced in the gonads and secreted into circulation for conveyance to target tissues. Whereas an endocrine view assumes that circulating sex steroid concentrations determine sex steroid exposure for peripheral cells, an intracrine view requires attention to local, cell- or tissue-specific regulation of sex steroid production and metabolism. These locally produced sex steroids are primarily generated from circulating, adrenal-derived steroid precursors, and, strikingly, some data suggest that the majority of all androgens and estrogens may be produced in peripheral tissues rather than the gonads in both males and females [15]. In contrast to a traditional, endocrine model, intracrinology recognizes the extensive capacity of virtually all cell types to both generate and metabolize sex steroids and thereby tightly regulate sex steroid signaling in cell-autonomous fashion. In strict definition, intracrine signaling is specific to mediators that signal through cytosolic or nuclear receptors, as they can confer signaling effects without first being secreted from the cell of origin. Local mediators that are secreted into the extracellular space instead confer autocrine or paracrine effects, signaling through receptors on the plasma membrane of the cell of origin or on neighboring cells, respectively (Figure 1). In this review, immune cell intracrinology will refer to the capacity of immune cells to synthesize, modify, and metabolize sex steroids. These sex steroids and their derivatives - generated through intracrine pathways - may confer either intracrine, autocrine, or paracrine signaling effects. Thus, an intracrine view underscores the importance of interrogating local, tissue-specific regulation of sex steroid production and metabolism.

2.2. Sex steroid biosynthesis

Sex steroids are synthesized from cholesterol through sequential enzymatic steps (Figure 2). The rate limiting step of *de novo* steroidogenesis from cholesterol is thought to be mediated by steroidogenic acute regulatory protein (StAR), which transports cholesterol to the inner mitochondrial membrane. Cholesterol is then converted to pregnenolone by CYP11A1 (side chain cleavage enzyme). Pregnenolone, in turn, can be converted to progesterone or to the weak androgen dehydroepiandrosterone (DHEA). DHEA subsequently can be converted to more potent androgens including testosterone. Testosterone can undergo conversion either to 17β-estradiol through aromatization or to dihydrotestosterone (DHT) through 5α-reductase activity.

In addition to estrogens and androgens, steroid precursors derived principally from the adrenal glands circulate in high concentrations, the most abundant of which is DHEA sulfate (DHEA-S). These precursors can undergo conversion to more potent androgens or estrogens in peripheral tissues, enabling local concentrations of sex steroids to be determined in highly tissue-specific fashion. Thus, it has been estimated that nearly half of total androgens and the vast majority of estrogens in men are formed in peripheral tissues, with most androgens and ~75% of total estrogens similarly attributed to peripheral formation in premenopausal women [15–17]. In postmenopausal women, essentially all estrogens and androgens are synthesized within peripheral tissues [15]. Some peripheral cells have the capacity not only for steroid conversion but also for the production of sex steroids *de novo* from cholesterol. Whereas *de novo* steroidogenesis was once believed to be exclusive to the gonads and adrenal glands, *de novo* sex steroid production now has been identified in numerous other tissues and cell types, including kidney, neurons, astrocytes and other glial cells, keratinocytes, adipocytes, and placental trophoblasts [18–23]. Furthermore, sex steroid synthesis in brain and peripheral tissues involves steroidogenic pathways and enzymes that are not found in the gonads and adrenal glands; for example, peripheral tissues have been shown to generate 17β-estradiol and DHT through pathways that do not require testosterone as an intermediate [24]. These findings collectively underscore the intricacy of local sex steroid regulation and highlight the importance of understanding sex steroid production, signaling, and metabolism within a single cell or tissue [15].

2.3. Sex steroids may influence energy metabolism through immunomodulatory effects

The importance of sex steroids as key regulators of metabolic health has been well established in both men and women. In men, androgen

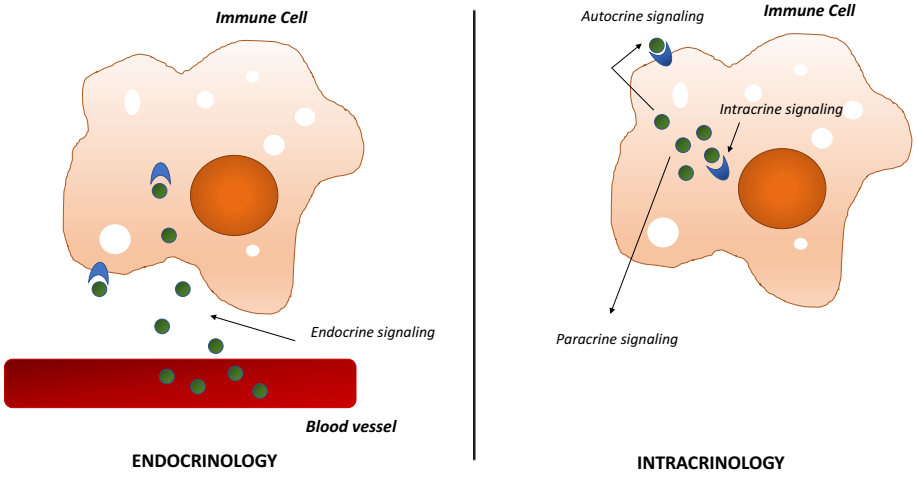

Figure 1: Immune cell intracrinology. In an endocrine model of sex steroid biology, sex steroids are synthesized in classically steroidogenic tissues and disseminated to target cells through the circulation. In contrast, immune cell intracrinology denotes the capacity of immune cells to synthesize, modify, and metabolize sex steroids. Sex steroids signal through nuclear receptors, and a membrane receptor (GPR30) also has been identified for estrogen signaling. Therefore, intracrine function in immune cells can generate sex steroids and their derivatives that mediate intracrine, autocrine, and paracrine effects.

