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Rapid regulatory actions of sex steroids on cell movement through the actin cytoskeleton

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ABSTRACT

Cell movement is required in relevant physiological processes such as embryonic development, tissue and organ differentiation, inflammation, immune response and wound healing, along with pathological phenomena, such as cancer metastatic spread. Cell motility is tightly controlled by a complex and often redundant array of intracellular signaling pathways largely devoted to the dynamic regulation of the actin cytoskeletal network and of its relationship with the cell membrane and the extracellular matrix. Sex steroids, particularly estrogen and progesterone, are effective regulators of cell migration and tissue organization, and recent evidence indicates that this is in part obtained through the regulation of the cytoskeleton. Intriguingly, many of these regulatory actions related to cell movement are achieved through rapid, non-classical signaling of sex steroid receptors to kinase cascades, independently from nuclear alteration of gene expression or protein synthesis. The identification of the mechanistic basis for these rapid actions on cell cytoskeleton and cell movement has special relevance for the characterization of the effects of sex steroids in physiological conditions, such their role in the control of inflammation, brain or vascular cell remodelling, angiogenesis or wound healing, as well as in the context of pathological conditions such as steroid-sensitive cancer cell invasion and metastasis. This review highlights the physiological and clinical conditions where the regulatory effects on the cytoskeleton and cell movement of sex steroids might have a special importance, as well as the recent advances in the characterization of the mechanisms, providing insights and working hypotheses on possible clinical applications for the modulation of these pathways.

1. Introduction

Cell movement is a highly integrated molecular process that plays a central role in a wide variety of biological phenomena, representing a key aspect of many normal and abnormal processes [1]. In embryogenesis, cell migration is a recurring phenomenon in important morphogenic events ranging from gastrulation to the development of the nervous system [2]. Cell motility is also prominent in the adult organism, in physiological and pathological conditions. For example, cell movement is required in the inflammatory and immune response for leukocytes or lymphocytes to migrate into tissues [3]. Wound healing requires fibroblast and vascular endothelial cell movement to achieve tissue repair. Angiogenesis

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requires movement of vascular cells, as well. Even more importantly, cell movement is the basis for local cancer invasion and distant metastasis, which represent the main reason of morbidity and mortality for malignancies [4].

Although the cellular mechanisms behind cell movement are extremely complex, a critical role in the generation of motility force is played by the dynamic remodelling of the actin cytoskeleton, which forms the backbone of every cell [5]. In addition to this, dynamic changes of the cytoskeleton are related to the ability of the cell to respond to external signals from the surrounding environment and result in the recruitment of specific intracellular signaling cascades.

In this context, sex steroid receptors, particularly estrogen and progesterone receptors, have been recently identified to work along with growth factor receptors, cytokine or integrins receptors in an integrated system that orchestrates cell migration. Interestingly, these actions of sex steroid receptors seem to be mainly plaid through rapid, non-classical, signaling actions activated independently from the traditional nuclear effects of these receptors [6], but rather requiring the recruitment and activation of kinase cascades within the cytoplasm or at the cell membrane [7,8].

In the recent years significant advances have been made in the characterization of these rapid signaling cascades recruited by sex steroids, showing that these hormones turn into rapid activation of tyrosine kinases, c-Src, G proteins, phosphatidylinositol 3-OH kinase/Akt and mitogen-activated protein kinases [7,8] some of which have been proved to play a relevant role for the regulation of cell movement.

The aim of this review is to discuss the role of sex steroids on the regulation of cell movement in physiology and disease, and to present the most recent evidence on the molecular mechanisms behind these processes, particularly focusing on the influence of sex steroid signaling to the actin cytoskeleton in different cell types (Fig. 1).

2. Sex steroids and cell movement: physiological relevance

2.1. *Motility of spermatozoa and of ciliated fallopian tube cells*

Spermatozoa are produced in the testis and progressively acquire the ability to swim during their transit through the epididymis [9]. In many species, sperm also undergoes a further maturation process, termed capacitation, which is required for successful egg fertilization. This is a two-step process, with a first acrosomal reaction (AR) followed by the acquisition of a “whiplash” motility also known as “hyperactivated motility” [10]. This process can be recruited by fluid aspirated from human ovarian follicles [11]. Activation of cyclic nucleotides production as well as modifications of Ca^{2+} and intracellular pH are implicated in the progressive acquisition of motility and with capacitation, including the change to ‘whiplash’ hyperactivated motility [12]. Progesterone is thought to be one of the agents present in follicular fluid responsible for the trigger of the acrosomal reaction human sperms [13,14]. This is supported by the observation that progesterone induces increases in intracellular free calcium into either capacitated or non-capacitated human sperm cells [13], possibly linked to the recruitment of a putative progesterone plasma membrane receptor [15]. Progesterone effect on sperm motility is dose-related but not abolished by inhibitors of the classical progesterone nuclear receptors [15].

Less is known about estrogen effects on sperm motility, although estradiol has been shown to recruit rapid non-genomic cascades in these cells [16]. Older evidence indicates that estradiol stimulates sperm movement from asthenospermic patients [17] and increases human sperm movement in vitro [18] whereas the non-steroidal estrogen receptor (ER) antagonist tamoxifen seems to reduce sperm motility both in vivo [19] and in vitro [17]. The renewed interest on these phenomena might possibly increase our knowledge on the importance of sex steroids in the area of fertility, sterility, and contraception at the level of the sperm [13].

In addition to possibly altering the motility of sperm cells, sex steroids may also facilitate their transport to the site of fertilization through the regulation of Fallopian tube cilia motion. Indeed, the epithelium of Fallopian tubes undergoes cyclical functional and morphological changes during the different stages of menstrual cycle [20]. To this extent, it has been reported that rising progesterone levels in the secretory phase, along with an estrogen-rich environment, might stimulate ciliary beat frequency (CBF) through an enhanced release of ATP into ciliated cells and an increased interaction between the microtubules that constitute the cilia and allow ciliary motility [21].

2.2. *Angiogenesis*

Angiogenesis represents an interesting process where the characterization of how sex steroids interfere with vascular cell motility might result in relevant clinical applications. Growing evidence suggests that estrogen may affect angiogenesis via direct effects on endothelial cell migration [22], largely mediated through rapid signaling pathways. In the adult organism, angiogenesis is virtually absent under normal conditions, except in the female reproductive tract. At this level, physiological changes in new vessel formation ensue during the menstrual cycle, characterized by synchronized endometrial neovascularization induced by steroid hormones [23]. The formation of these uterine vessels depends on the proliferation and migration of fully differentiated endothelial cells from pre-existing neighbour vessels [24] and on the homing and differentiation of circulating, bone-marrow derived, endothelial progenitor cells (EPCs). To this extent, effects of sex steroids on bone marrow-derived precursor cells have been established long since [25] and have been recently shown to be involved in endometrial and corpus luteum neoangiogenesis [26]. In addition, a visible recruitment of macrophages and other nucleated cells takes place in the endometrium in the second part of the menstrual cycle under the control of sex steroids [27,28]. While there are strong indications that estrogen regulates this leukocyte trafficking, the greatest variations in the number of these cells occur in parallel with the changes of progesterone concentration, with an increase of endometrial cell influx being maximal immediately prior to menstruation, suggesting that both sex steroids are powerful regulators of these events [29].