Role of Nuclear Factor KappaB Signaling in Endometrium

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The superfamily of nuclear factor kappaB (NF-κB) proteins consists of five known members: protein RelA of NF-κB superfamily (RelA (p65)), protein RelB of NF-κB superfamily (RelB), protein cRel of NF-κB superfamily (cRel), protein NF-κB1 of NF-κB superfamily (NF-κB1 (p50/p105)), and protein NF-κB2 (NF-κB2 (p52/p100)). Each of the five NF-κB members interacts with suitable inhibitory factors belonging to the family of inhibitors of κB (IκB) (IκBα, IκBβ, IκBε, or Bcl-3) or the C-terminal sequences of the NF-κB precursor proteins (p105 and p100). The RelA, RelB, and cRel proteins share a homology domain Rel, which is a transcription activation domain, allowing control of the transcription of DNA molecules, whereas NF-κB1 and NF-κB2 proteins are precursor proteins, which need proteolytic activation and forming dimers with suitable Rel protein.

NF-κB endometrosis hormone

1. Introduction

The nuclear factor kappaB (NF-κB) is one of the transcription factors responsible for cellular chemoresistance [1]. The NF-κB signaling pathway controls the expression of genes of proinflammatory chemokines and cytokines, adhesion molecules, chemoattractants for inflammatory cells, and antigen receptors on immune cells [2]. It remains a critical regulator of immune systems in most multicellular organisms. It can be found in most animal cell types, involved in multiple cellular responses [3][4][5]. Proinflammatory chemokines and cytokines act under both physiological conditions and pathological processes, and their aberrant production leads to immune system dysregulation, which plays a role in some endometrial diseases' initiation and progression [6]. In the case of endometritis, NF-κB is strongly involved in the activation of proinflammatory genes which are critical for uterine response to infection and inflammation [7]. In the case of endometriosis, NF-κB stimulates the expression of genes that regulate endometriotic cell adhesion, migration, and proliferation, as well as extracellular matrix (ECM) remodeling and inflammation intensity in ectopic endometrium [1][6], whereas in the case of endometrosis, NF-κB seems to take part in the mediation of the expression of genes that stimulate proinflammatory chemokines and inhibit anti-inflammatory cytokine in fibrotic endometrium, as well as stimulating ECM remodeling and chemotaxis [8][9]. Moreover, NF-κB is also associated with chronic inflammation in neoplastic development, as well as with the mediation of insensitivity to growth inhibitory signals, avoidance of apoptosis, angiogenesis, and metastasis [10]. As the endometrium undergoes cyclic changes in all species, its cells have to be constantly supplied with signal molecules, which can lead to increased susceptibility to actions of the NF-κB pathway [11].

2. Regulation of NF-κB Signaling in Endometrium

It has been evidenced that the hormone-dependent immune system dysregulation in response to the aberrant production of chemokines and cytokines plays a role in the initiation and progression of endometrial diseases, such as endometritis [7][12], endometriosis [1][6], endometrosis [11], and endometrial carcinoma [13]. In both humans and animals, hormonal therapies, based on the creation of hypoestrogenic (GnRH agonists), hyperandrogenic (danazol and gestrinone), or hyperprogestogenic (progesterone and progestins) environments are commonly used [6][14][15], often causing systemic side effects due to the suppression of endometrial cell proliferation and endogenous steroid hormone concentrations [6][16]. Therefore, the hormone-dependent regulation of NF-κB signaling in the endometrium is summarized here to highlight the hormone-NF-κB interaction.

2.1. Progesterone's Regulation

In both, humans [17][18] and livestock animals [7], the uterus is resistant to infections with decreasing blood progesterone concentration and is susceptible to infections with increasing blood progesterone concentration. In human endometrium, progesterone was proven to inhibit TLR4 expression, NF-κB activation, as well as IL-6 and IL-8 productions, limiting the effectiveness of inflammation in response to bacterial infection [12]. Similarly, in bovine endometrium, progesterone was found to decrease the expressions of IL-1β, IL-6, IL-8, and TNF-α via the NF-κB and MAPK signaling pathways [7]. The progesterone-related suppression of the NF-κB pathway was observed in endometrial cells with high progesterone receptors (PR) expression, contrary to weak PR expression, suggesting the PR-mediated action [12]. Moreover, it has been proven that NF-κB (RelA (p65)) and PR can repress each other through direct contact [19].

Progesterone has two isoforms of PRs (PR isoform A and PR isoform B) encoded by the same gene, whereas PR isoform A is predominant in the uterus and ovaries [20][21]. In endometrial epithelium and stroma, progesterone passes through the cells and binds to an intranuclear receptor, then regulates cell development and differentiation by inducing multiple genes transcription [21][22]. Progesterone binds to PR isoform A and acts as an antagonist for estrogen-induced epithelial cell proliferation. Moreover, progesterone downregulates PR expression, and thus regulates both its biological effects and receptor abundance [23][24]. In human endometrium, these biological alterations during the ovarian cycle are also regulated via NF-κB (RelA (p65))/PR repression [25]; however, in animals, the NF-κB-PR interaction in the ovarian cycle requires confirmation. So far, in equine endometrium, no correlations were found between genes expression of RelA (p65), NF-kB1, NF-kB2, and PR in both the follicular and luteal phases of the ovarian cycle [11]. In human endometrium, the NF-κB-PR interaction was suggested to be involved in pathophysiologic processes, such as irregular uterine bleeding [26] and endometriosis [1][27][28]. In the case of recurrence of ovarian endometriosis, both inverse [27] and direct [28] relations between RelA (p65) and PR were reported; however, both researchers considered PR isoform B as predominant [27][28]. In equine endometrium, the initial signs of NF-κB-PR interaction were indicated in mild endometrosis by the strong positive correlation between RelA and PR genes transcription [11]. In the case of endometrial carcinoma, progesterone exertion was suspected to inhibit anti-inflammatory cytokines production, which was confirmed for IL-10 [18] and excluded for IL-

37 [13]. The recent result suggests some signs of hormone-dependent immune system dysregulation in endometrial carcinogenesis. However, regarding the role of the NF-κB-PR interaction, this requires further research.

2.2. Estrogen's Regulation

Contrary to the blood progesterone concentration in both humans [17][18] and livestock animals [7], the uterus is susceptible to infections with the decreasing of blood estrogen concentration and is resistant to infections with the increasing of blood estrogen concentration. In endometrial epithelium and stroma, estrogen passes through the cells, binds to an intranuclear receptor, and regulates cell development and differentiation by inducing multiple genes transcription [21][22]. In the canonical pathway, estrogen has two specific estrogen receptors (ERs) (ER-α and ER-ß) encoded by different genes. ER-α is predominant in the uterus [21][29]. The binding of estradiol to ER-α and ER-ß has contradictory uterotrophic effects. The activation of ER-α stimulates the proliferation of the epithelial cells and stromal cells, whereas the activation of ER- ß inhibits it. Moreover, the activation of ER-α upregulates PR expression, whereas the activation of ER- ß downregulates it [23][24]. In healthy human endometrium, the negative crosstalk between ER-α and NF-κB was confirmed as a part of the regulatory process of normal physiological responses [30]. In horses, the NF-κB-ER-α interaction has not been confirmed so far, since no correlations were found between genes expression of RelA (p65), NF-kB1, NF-kB2, and ER-α and ER-ß in both phases of the ovarian cycle [31]. Considering endometriosis as an estrogen-dependent disease, the NF-κB-ER interaction was suggested to be involved in its pathogenesis. It can be observed that estrogen promotes the implantation of endometrial tissue to ectopic foci, and thus is necessary but not sufficient for sustaining endometriosis [32]. In the ectopic endometrial cells, ER-α and ER-β were reported as able to increase NF-κB activity [33] by activating several proinflammatory pathways (CXCL12/CXCR4, PI3K/Akt), and thus promote the viability and proliferation of endometriotic cells [34]. In other studies on endometriosis, the inhibitory effect of estrogen signaling on NF-κB has been reported [35][36]. Estrogen was able to reduce the expression of a gene that encodes the angiotensin II receptor (AGTR1), and thus activates NF-κB signaling [36]. Moreover, in the eutopic endometrium, ER-β was able to downregulate TNFα/NF-κB signaling [35]. Therefore, the effects of estrogen signaling on NF-κB in endometriosis are controversial [1]. In equine endometrium, the initial signs of NF-κB-ER interaction were indicated in inactive nondestructive, active nondestructive, and active destructive types of endometrosis by moderate to strong negative correlations between RelA, NF-kB1, and ER-β genes transcription [11]. In the case of endometrial carcinoma, estradiol action was suspected to inhibit IL-10 [18], but not IL-37 [13] anti-inflammatory cytokines production. Moreover, in the endometrial carcinoma model, the NF-κB activity was induced by different concentrations of estradiol in a rapid, non-genomic, and non-receptor manner. It was confirmed that activation of NF-κB plays a role in estradiol-induced angiogenesis by up-regulator basic fibroblast growth factor (bFGF) and VEGF, a major angiogenic factor that induces endothelial cell proliferation and thus promotes tumor-induced angiogenesis [37]. Therefore, the role of the NF-κB–estrogen interaction, both receptor and non-receptor, in the hormone-dependent immune system dysregulation in endometrial diseases requires further research.

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