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Review

Hypoxia-inducible factor-1alpha: A promising therapeutic target in endometriosis

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ABSTRACT

Endometriosis is a common gynecologic disease defined as the presence of ectopic endometrial tissues on the ovaries and pelvic peritoneum, and it is a significant cause of pelvic pain, dysmenorrhea and infertility of women in their reproductive age. However, the etiology of endometriosis remains obscure. In recent years, a growing body of evidence validated that hypoxia developed a close relationship with endometriosis and the expression of hypoxia-inducible factor-1alpha (HIF-1α) was increased significantly in the development of endometriosis. Furthermore, inhibiting the expression of HIF-1α contributed to suppress endometriosis progression, suggesting HIF-1α plays a critical function in endometriosis. Nevertheless, the mechanisms by which HIF-1α associates with endometriosis are still undefined. In this brief review, we had a general understanding of HIF-1α firstly, and then we tried to sum up the collective knowledge of HIF-1α in endometriosis. Finally, we will discuss kinds of novel therapeutic approaches to endometriosis based on the functions of HIF-1α.

Contents

Abbreviations: ANX, annexin; ANXA2, annexin A2; ARD, arrest defective; Asn, asparagine; ATM, ataxia telangiectasia mutated; bHLH-PAS, basic helix-loop-helix Per/Arnt/Sim; CBP, CREB binding protein; CCAs, clear-cell adenocarcinoma; CDX, caudal-related transcription factor; CHIP, carboxyl terminus of HSP70-interaction protein; CK, casein kinase; COX, cyclooxygenase; CYR61, cysteine-rich angiogenic inducer 61; DFO, desferrioxamine; DNMTs, DNA methyltransferases; DUSP, dual-specificity phosphatase; EGR-1, early growth response protein-1; FIH, factor inhibiting HIF; Glut, glucose transporter; HAF, HIF-associated factor; HDACs, histone deacetylases; HIFs, hypoxia-inducible factors; HIF-1α, hypoxia-inducible factor-1alpha; HIF-1β/ARNT, hypoxia-inducible factor-1β; HSP, heat shock protein; Lys, lysine; MAPK, mitogen-activated protein kinase; MVD, microvessel density; NLS, nuclear localization signals; O_2, oxygen; ODD, O_2-dependent degradation domain; *p*-mTOR, phosphorylated mammalian target of rapamycin; PG, prostaglandins; PGE2, prostaglandin E2; PHD, prolyl-hydroxylase; Pro, proline; SCID, severe combined immune deficiency; Ser, Serine; SIRT, sirtuins; VEGF, vascular endothelial growth factor; VHL, von Hippel–Lindau; vWF, von willebrand factor; WXT, Wenshen Xiaozheng Tang.

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1. Introduction

Endometriosis is a complex, estrogen-dependent disease with the presence of functional uterine glands and stroma outside the uterine cavity, such as ovaries and pelvic peritoneum, rectovaginal septum [1]. Furthermore, endometriosis is one of the most causes of pelvic pain, infertility, dysmenorrhea and dyspareunia, and affects an estimated 10% of the female population of reproductive age [2,3]. Embarrassingly, the pathogenesis of endometriosis is not clear up to now. Sampson's theory of retrograde menstruation is the most widely admitted standpoint, which illustrated that the menstrual debris travels to vagina anterogradely, and to peritoneal cavity retrogradely, and implants in the dependent areas of peritoneum during menstruation [4]. It was accepted that reduced apoptosis could contribute to the survival of refluxed endometrial cells at ectopic sites and estrogen mediated resistance to apoptosis and acceleration of proliferation, nociception and inflammation could be one of the main mechanism of endometriosis formation [5]. Furthermore, the low expressions of progesterone receptors also terminated in apoptosis inhibition in the development of endometriosis, and inhibiting progesterone receptors could be a promising strategy to treat endometriosis [6,7]. Additionally, the high expression of cyclooxygenase 2 (COX-2), angiogenesis related genes and prostaglandins (PG) were proved to be positive with endometriosis development [8–10]. Evidence also showed that the factors including inflammation, immune response and genetic susceptibility played a leading role in endometriosis progression [2]. These findings suggested that the pathogenesis of endometriosis was much more complicated than we known, and it is imperative to explore and get to know the mechanism of endometriosis.

Of special note is that hypoxia-inducible factor-1alpha (HIF-1α) was found to be crucially associated with endometriosis in a multitude of studies during the past years. For example, an *in vitro* study reported that the expression of HIF-1α in stromal cells isolated from ectopic lesions of endometriosis patients was higher than that in stromal cells derived from eutopic endometria of disease-free women [11]. Furthermore, it was convincingly displayed that the elevated level of HIF-1α played a major role in promoting angiogenesis related gene expression in endometriosis, such as vascular endothelial growth factor (VEGF), leptin, early growth response protein-1 (EGR-1), osteopontin, cysteine-rich angiogenic inducer 61 (CYR61), dual-specificity phosphatase-2 (DUSP2) and IL-8 [11–14]. In addition, inhibiting HIF-1α expression could be conducive to the treatment of endometriosis [15,16]. These significance results indicated that HIF-1α was crucially associated with endometriosis, and HIF-1α may become a potential therapeutic target of endometriosis. However, the precise mechanism underlying HIF-1α implicated in development of endometriosis development is still not fully clarified till now. The aim of this review is to integrate the knowledge of HIF-1α in endometriosis.

2. Overview of HIF-1α

Oxygen (O_2) concentrations were intimately involved in cell division and angiogenesis. It has been illustrated that hypoxia was associated with a wide diversity of diseases [17–19]. Studies have been focused on the mechanisms by which hypoxic stress alter its transcriptional profiles to modulate glycolysis, cell proliferation, survival and invasion [20,21]. It is worth noting that the hypoxia-inducible factors (HIFs) are the most pivotal mediator which responses to hypoxic stress [22]. The HIFs are heterodimeric complexes that are composed of an O_2-labile α subunit (HIF-1α, HIF-2α and HIF-3α) and a constitutively stabilized β subunit (HIF-1β/ARNT) [23]. Furthermore, HIF1, which consists of HIF-1α and HIF-1β subunits, is the best characterized HIFs and found to be expressed in nearly all cell type [24]. Noteworthily, HIF1 activity is primarily dependent upon the viability of the HIF-1α subunit.

2.1. The regulation of HIF-1α stability

HIF-1α was first identified by Semenza et al., in 1995 and revealed as a member of the basic helix-loop-helix Per/Arnt/Sim (bHLH-PAS) transcription factors [25]. The structure of HIF-1α was shown in (Fig. 1a) [26]: the bHLH and PAS domains, which were required for dimerisation and DNA-binding activities, the N-terminal (N-TAD) and C-terminal (C-TAD) transactivation domains, the O_2-dependent degradation domain (ODD), which partly overlaps with N-TAD, and the two bipartite nuclear localization signals (NLS). The regulation of these domains controlled HIF-1α stability, and the regulation could proceed with O_2-dependent and O_2-independent way.

In normoxic conditions, HIF-1α was degraded by the following manner. The oxygen-dependent enzymes, prolyl-hydroxylase (PHD) and factor inhibiting HIF (FIH) were activated by oxygen firstly. PHD would lead to hydroxylation on HIF-1α Pro402/564 and acetylation on HIF-1α Lys532 (ODD), and FIH would lead to hydroxylation on HIF-1α Asn803 (C-TAD) [27–29]. Then the E3 ubiquitin ligase complex, von Hippel–Lindau (VHL) tumour suppressor protein bound and caused HIF-1α ubiquitination which finally led to HIF-1α degradation [30]. Importantly, the FIH-dependent Asn803 residue hydroxylation was implicated in the interaction between HIF-1α and the transcriptional co-activators p300 and CREB binding protein (CBP), suppression of FIH-dependent Asn803 residue hydroxylation could facilitate the integration of HIF-1α with p300 and CBP and lead HIF-1α activation [31,32]. FIH also interacted with VHL and functioned as a co-repressor to inhibit transactivation by recruiting histone deacetylases (HDACs) [33]. While in hypoxic conditions, the PHD and FIH were inhibited and the hydroxylation or acetylation reactions decreased, and VHL could not contribute to the ubiquitination mediated HIF-1α degradation [22]. These outstanding results indicated that normoxic-dependent HIF-1α degradation was crucially related with VHL mediated amino acid residues hydroxylation and acetylation controlled by PDH and FIH, and the hypoxia