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Survey

A critical role of interleukin-1 in preterm labor

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ABSTRACT

Preterm birth (PTB) is a leading cause of neonatal mortality and morbidity worldwide, and represents a heavy economic and social burden. Despite its broad etiology, PTB has been firmly linked to inflammatory processes. Pro-inflammatory cytokines are produced in gestational tissues in response to stressors and can prematurely induce uterine activation, which precedes the onset of preterm labor. Of all cytokines implicated, interleukin (IL)-1 has been largely studied, revealing a central role in preterm labor. However, currently approved IL-1-targeting therapies have failed to show expected efficacy in pre-clinical studies of preterm labor. Herein, we (a) summarize animal and human studies in which IL-1 or IL-1-targeting therapeutics are implicated with preterm labor, (b) focus on novel IL-1-targeting therapies and diagnostic tests, and (c) develop the case for commercialization and translation means to hasten their development.

Contents

Abbreviations: AF, amniotic fluids; AP-1, activator protein-1; CSAIDs, cytokine suppressive anti-inflammatory drugs; DAMPs, damage-associated molecular patterns; ECM, extracellular matrix; fFN, fetal fibronectin; HPA, hypothalamic-pituitary-adrenal; IKK, IκB kinase; IL, interleukin; IL-1R, interleukin-1 receptor; IL-1Ra, interleukin-1 receptor antagonist; IL-1RAcP, interleukin-1 receptor accessory protein; IRAK, interleukin-1 receptor-activated protein kinase; LMA, leukocyte migration assay; LPS, lipopolysaccharide; LTA, lipoteichoic acid; MAPK, mitogen–activated protein kinases; MMPs, matrix metalloproteinases; MYD88, myeloid differentiation primary response gene 88; NF-κB, nuclear factor-kappa B; NPV, negative prediction value; PAMPs, pathogen-associated molecular patterns; PGHS-2, prostaglandin H synthetase-2; PPV, positive prediction value; PTB, preterm birth; SAPK, stress–associated protein kinases; TIMP, tissue inhibitor of metalloproteinase; TIR, toll- and IL-1R-like; TLRs, toll-like receptors; TRAF, tumor necrosis factor–associated factor; TRP, transient receptor potential canonical; UAPs, uterine activation proteins; VEGF, vascular-endothelial growth factor.

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1. Introduction

Preterm birth (PTB; delivery before 37 weeks of gestation) affects 1 out of 10 newborn and is the second leading cause of infant deaths in the United States and worldwide [1,2]. Major advances have been made in the past decades, but the etiology of PTB remains mostly unknown, and to this date no pharmacological compound has been successful in arresting uterine labor after its onset. Accordingly, the rate of PTB in the United States has increased since 1990 (11.72% in 2011 compared to 10.62% in 1990) suggesting that PTB remains an important clinical challenge despite advances made [2]. Importantly, annual cost of PTB was estimated to $26.2 billion in 2005, and this estimation does not include further health problems that premature infants might suffer [3].

The onset of labor is a gradual process that begins several days before delivery with changes in gestational tissues, culminating in powerful contractions to expulse the conceptus. Term and preterm labor (PTL; labor before term) share a common (patho) physiological process, including activation of the membranes/decidua (detachment of the chorioamniotic membranes from the decidua and rupture of the membrane), uterine contractility (shift from irregular contractions to functional contractions) and cervical ripening (dilatation and effacement of the cervix due to changes in cervical composition and increasing myometrial contractility) [4]. It has been suggested that while term labor is a result of a physiological activation of this pathway, PTL is on the other hand the result of a pathological activation of the same process [5–7]. Many causes of PTB have been identified and include infection, fetal growth disorders, ischemia, uterine over-distension, cervical incompetence, fetal and maternal stress, hemorrhage, and several others [8]. For this reason PTB is not seen as a single disease entity, but is referred to as a syndrome [5,9]. Converging lines of evidences suggest that inflammation plays a significant role in all labors, regardless of the presence of infection, other etiology, or timing of delivery [5,10].

1.1. Inflammatory cascade leading to PTB and role of interleukin-1

Birth reflects transition from a pro-pregnancy state and immunological tolerance towards the fetus allograft to a pro-labor, pro-inflammatory state. Notwithstanding the role of hormones, pro-inflammatory cytokines are thought to orchestrate the on-time synchronization of the aforementioned physiological events characterising labor through the induction of uterine activation proteins (UAPs; including COX-2, prostaglandin $F_{2\alpha}$ receptor, oxytocin receptor, connexin-43, and others) [11–13]. This converging inflammatory pathway precedes the onset of both term and PTL [14–17].

Pathological events leading to PTL are the triggers of inflammatory stimuli consisting in damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs). These molecular pattern entities can activate innate immunity *via* pattern recognition receptors (PRRs), mostly Toll-like receptors (TLRs). TLRs are expressed abundantly in the decidua, placenta and membranes throughout pregnancy, in immune and non-immune cells [18]. Their activation leads to cytokine and chemokine production and initiates an inflammatory response characterised by leukocyte activation and transmigration from peripheral blood to gestational tissues [19]. This leukocyte extravasation has been observed in the decidua, the cervix, the placenta, the fetal membranes and the amniotic fluid (AF) in humans and animal models, and is principally mediated by cytokines and chemokines, including interleukin (IL)-1, IL-6, IL-8 and TNFα [20–27]. As more leukocytes invade the uterus, the inflammatory response is amplified through increased secretion of pro-inflammatory mediators. In this context, pro-inflammatory cytokines can directly trigger the transition from a uterine quiescent state to a subsequent unscheduled activation of the uterus (see Fig. 1 for a representation of the inflammatory cascade leading to PTB, as described above); for this reason, cytokines are sometimes referred to as uterotrophins (uterine activators).

Several studies have correlated the increase in pro-inflammatory cytokines, including IL-1, with the risk of PTB [28–30]. Since the discovery that IL-1 expression rises in term deliveries without infection [31] as well as in preterm deliveries [32], it has been thought that IL-1 overproduction heralds labor. Not only does IL-1 induce labor in various animal species [33,34], but also fetal and maternal carriers of polymorphisms in genes of the IL-1 system are associated with PTB in humans [35–37]. Furthermore, an elevated IL-1β blood concentration in human neonates has been associated with PTB [38]. For these and other reasons (addressed below), IL-1 is now considered a key inducer of inflammation in PTL. This review will focus on the role of IL-1 in PTL, and will discuss the efficacy of IL-1 receptor antagonists in the context of PTB.

2. Overview and mechanism of action of the interleukin-1 system

The interleukin-1 system (illustrated in Fig. 2) is composed of different proteins including IL-1α, IL-1β, IL-1 receptors and the endogenous IL-1 receptor antagonist (IL-1Ra). IL-1α and IL-1β have similar biological effects and bind to the same receptors, but are encoded by different genes [39].

2.1. IL-1α

The IL-1α precursor (which is synthesized in active form unlike IL-1β precursor) is constitutively produced in almost all types of cells in healthy individuals and is released through cell necrosis; this corresponds to a first step in sterile inflammation. Accordingly, IL-1α is described as an alarmin (or DAMP) and is fully active in the