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Review Article

The JAK-STAT Signaling Pathway: A Novel Therapeutic Target for Unexplained Recurrent Implantation Failures

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ABSTRACT

Unexplained recurrent implantation failure has become a public health problem especially in the context of a high cost, demand for assisted reproductive therapy and multiple therapy failures. It is attributed to the failure of immunological tolerance between the transferred embryo and the endometrium during assisted reproductive therapy cycles. Cytokines are surrogate mediators of immunological tolerance mechanisms. Since the synergistic interaction between individual cytokines is dynamic, perturbations in the cytokine crosstalk during embryo implantation is considered a major etiology for unexplained recurrent implantation failures. Genome Wide Association Studies suggests that most cytokines initiate their actions through receptor interactions that activate the JAK-STAT signaling pathways. Aberrations in the JAK-STAT signaling pathways have as well been shown to cause perturbations in cytokine crosstalk that result in diseases. We therefore propose the JAK-STAT signaling pathway a potential therapeutic target for unexplained recurrent implantation failures. Currently, many studies have recorded potential therapies in IL-6/JAK/STAT 3 pathway to treat many diseases but limited attention has been paid to unexplained recurrent implantation failures.

Keywords: Unexplained recurrent implantation failures; Cytokines; JAK-STAT pathway; Immunotherapy

INTRODUCTION

Unexplained recurrent implantation failures is defined as the repeated failures of embryos to implant due to a failure of the immunological crosstalk between the transferred embryo and the endometrium in at least three or more assisted reproductive therapy cycles following the transfer of quality embryos in a healthy woman less than 40 years [1,2]. Implantation of the embryo is the rate limiting step in assisted reproductive therapy [3-8]. The mechanism underlying a failed implantation in repeated assisted reproductive therapy cycle could be considered similar to an alloimmune rejection since the embryo is a semi-allograft [9]. Cytokines mediate immune cell interactions during allograft rejections. The embryo during implantation has been described as bathing in a sea of cytokines [10]. Perturbations in the cytokine crosstalk during the window of implantation are therefore considered a major etiology in unexplained recurrent implantation failures. Cytokines has been shown to control the expression of adhesion, anti-adhesion, secretion of endocrine molecules as well as the activation of immune cells at the embryo-endometrial interface during the implantation process [11,12].

SUBJECTS AND METHODS

The JAK-STAT signaling pathway

The Janus kinases (JAK) are part of the tyrosine kinase group of enzymes of which four members have been identified: JAK1, JAK2, JAK3 and TYK2 (Tyrosine kinase 2). The signal transducers and activation of transcription (STAT) on the other hand are family of transcription factors which includes 1-5a, 5b and 6 [13]. The JAK-STAT signaling pathway is a pleiotropic cascade that regulates cytokine function [14]. The current model

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of JAK-STAT signaling holds that the binding of cytokines to their receptors activates JAK which in turn phosphorylates an intracellular domain of the receptor leading to recruitment and phosphorylation of a STAT [14]. Phosphorylated STAT form dimers which then translocate into the nucleus to activate the expression or repression of target genes. The regulation of the JAK/STAT signaling is essential for crosstalk among various cytokine signaling pathways involved in immune cell activation. A crosstalk refers to mutual influences of signals generated from different pathways. Crosstalk occurs at all levels between different immune cells, cytokines and intracellular signaling pathways. The extent of crosstalk during inflammation is not known [15]. JAK function has been shown to be important for the crosstalk of Src-kinase cascade, the Ras-MAP kinase pathway, the P13k-AKT pathway as well as the ERK pathways during an immune response. Aberrations in JAK activity could also lead to perturbations in one or more of the above mentioned pathways resulting in diseases [16].

Cytokines, JAK-STAT signaling and implantation failures

Though cytokines are produced by nearly all immune cells, only a few cytokines particularly the helper T-cell produced cytokines has received prominent importance in our stride to understanding the mechanism of unexplained recurrent implantation failures [17]. This is because the helper T (TH) cells were identified to play a key role of deciding the nature of the immune response as either inflammatory or anti-inflammatory. In effect, if a naïve helper T (THO) cell encounters a paternally derived antigen of the implanting embryo, it undergoes proliferation and differentiation into four distinct populations of cells namely the TH1, TH2, TH17 and Treg cells. Each cell population produces a unique set of cytokines [18,19]. The profile of cytokines produced in response to the implanting embryo determines the nature of the immune response to the embryo as either inflammatory or anti-inflammatory [19]. Based on this, embryo rejection and resultant implantation failures observed in embryo transfer cycles is considered a helper T-cell phenomenon in which the TH1, and TH17 cytokines has an inflammatory effect while the opposing TH2 and Treg cell cytokines exerts an anti-inflammatory effect on the embryo[19,20]. It is therefore proposed that a balance between the antagonist T-cell populations and their respective cytokines is the basis for immunological tolerance failures in embryo implantation process during assisted reproductive therapy cycles. In view of this, unexplained recurrent implantation failures may be considered a T-Cell disorder. Consequently, the role of the JAK-STAT pathway in the regulation of TH cells is well established. STAT 2 and 4 are important for TH1 signaling, STAT 6 is important for TH2 signaling, STAT 3 is important for TH17 signaling while STAT 5 functions in Treg cell signaling (Table 1) [21,22].

Table 1: Signal transducer and activator of transcription (STAT) for different cytokine signaling.

Type	Cytokines
STAT 1	Type I, type II and type III interferons (IFNs)
STAT 2	Type 1, type II and type III IFNs
STAT 3	IL-6 (IL-6, IL-II, IL-31, LIF, CNTF, CLC/CLF, NP, CT1 and OSM) and IL-10 (IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26) families, G-CSF, Leptin, IL-21, and IL-27
STAT 4	IL-12
STAT 5A and STAT 5B	IL-3 family (IL-3, IL-5, and Gm-CSF), IL-2 family (IL-2, IL-7, TSLP, IL-9, IL-15 and IL-21), growth hormone, EPO (erythropoientin) and TPO (thrombopoietin)
STAT 6	IL-4 and Il-13

IL-6/JAK/STAT 3: A therapy target model

Members of the gp130 signaling cytokines have been implicated in implantation failures through their interactions with interleukin 6 (IL-6). The gp130 cytokines describes the various cytokines that utilizes the gp130 signaling pathway. This includes Interleukin-6 (IL-6), Interleukin-11(IL-11), Cardiotrophin (CT) 1, Ciliary Neutropic Factor (CNTF), Oncostatin M (OSM) and Cardiotropin-Like Cytokine/ Cytokine-Like Factor (CLC-CLF) [23]. IL-6 binds to the IL-6R on target cells, the IL-6/IL-6R complex activates the gp130 triggering its dimerization and subsequent activation of STAT 3 phosphorylation by JAK [24]. This classical signaling pathway is activated during early immune response and may be responsible for the activation of various immune cells that act locally at the maternal-conceptus interface during the window of implantation. In view of the above system, we suggest that a therapeutic strategy targeting the IL-6/JAK/STAT 3 pathway using their inhibitors may stimulate the development of a suitable therapy for unexplained recurrent implantation failures. A major challenge to this will be a stimulation of adverse effects unrelated to the target therapeutic actions by the JAK-STAT inhibitors. However, the generation of a selective inhibitor of JAK 3 will be an effective approach to addressing this. This is because studies has shown that patients with JAK 3-SCID remain healthy after successful transplantation. This implies that

JAK 3 deficiency results in mere immunodeficiency but not diverse immunological defects [25]. A highly specific JAK3 inhibitor will surely have very limited side effect. Many JAK inhibitors (JAKinhibs) and STAT inhibitors (STATinhibs) are currently under preclinical evaluations while some are passing clinical trials and FDA approval (Table 2).

Table 2: A number of JAK and STAT inhibitors are explored for treatment of diseases.

Drug	Target	Disease	Status
Ruxolitinib (INC 424)	JAK 1, JAK 2	Polycythemia, Psoriasis (topical), myelofibrosis varius cancers	FDA approved
Tofacitinib	JAK 3>JAK 1>>(JAK2)	RA, Psoriasis, spondyloarthropathy, Transphant rejection, ulcerative colitis	FDA approved
Oclacitinib	JAK 1	Canine allergic dermatitis	FDA approved
Baricitinib	JAK1, JAK2	RA, Psoriasis, diabetic nephropathy, SLE, Atopic dermatitis	Phase III Phase II
Momelitinib	JAK1, JAK2	Myelofibrosis	Phase III
Peficitinib	JAK1, JAK3	RA, Psoriasis	Phase III Phase II
IINCB 039110	JAK1, JAK2	Psoriasis, RA	Phase II
AZD 1480	JAK1, JAK2	Myeloproliferative diseases, various cancers	Phase I
ISIS-STAT 3 Rx (AZD 9150)	STAT 3	Various cancers	Phase II
OPB-31121	STAT 3	Various cancers	Phase I

CONCLUSION

JAK-STAT pathway has a critical role in the regulation of the immune system particularly cytokine crosstalk. Since perturbations in the JAK-STAT pathway and their regulators may lead to unexplained recurrent implantation failures, targeting their signaling may lead to development of novel strategies for the treatment of unexplained recurrent implantation failures.

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