Journal of Cytokine Biology
ISSN: 2576-3881
Ogbuabor et al., J Cytokine Biol 2019, 4:1
Mini Review
Open Access

The Cytokine Network: An Integrated Approach to Understanding the Mechanism of Unexplained Recurrent Implantation Failures

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Received date: October 07, 2019; **Accepted date**: October 23, 2019; **Published date**: October 30, 2019

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 interactions between individual cytokines is dynamic, perturbations in the cytokine network during implantation is considered a major etiology for unexplained recurrent implantation failures. So far reproductive immunologists have not elucidated a comprehensive picture of the cytokine network in patients with unexplained recurrent implantation failures. This is a major factor limiting our understanding of the mechanism of unexplained recurrent implantation failures. The cytokine network appears to be a good toolkit to understanding the mechanism of unexplained recurrent implantation failures. We present an overview on cytokine interactions during embryo implantation using the cytokine network. Suggestions are put forward for future approach that may significantly improve our understanding of the cytokine network in unexplained recurrent implantation failures.

Keywords: Unexplained recurrent implantation failures; Assisted reproductive therapy; Cytokines; Cytokine network

Introduction

Unexplained recurrent implantation failures is defined as the repeated failures of embryos to implant due to a failure of the immunological tolerance 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 network 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].

Cytokines, Immune cells and Implantation Failure

Immune cells interact with uterine endometrium and trophoblast cells during implantation to provoke rejection of the fetal allograft. The function, activation and differentiation of these cells are regulated by the local microenvironment determined by cytokines [13,14]. An abnormal network in cytokines has been postulated to bring about recurrent implantation failures through the activation of potent antigen presenting cells such as the local decidual macrophages and dendritic cells which secretes cytokines that stimulate specific antigen dependent responses by B-cells, T-cells and uterine natural killer (uNk) cells [15,16].

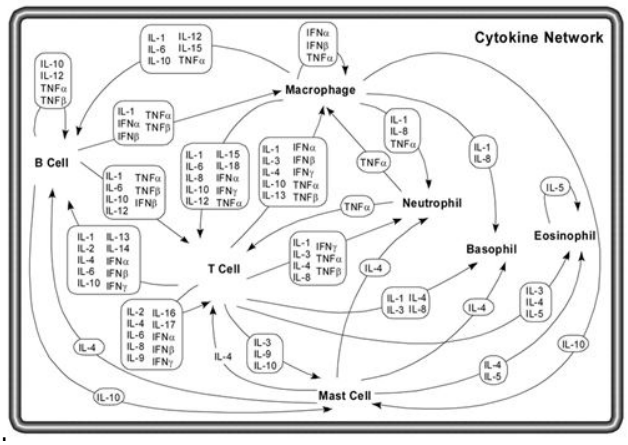

Figure 1: The cytokine network during an immune response [17].

Macrophages being potent antigen presenting cells secrete cytokines that stimulate specific antigen dependent responses by B and T cells

and on specific responses by other cells such as NK cells. The proliferation and activation of neutrophils, basophils and eosinophils are cytokine dependent.

Once trophoblast invasion begins, an array of cytokines (IL-1, IL-6, IL-8, IL-10, IL-12, IL-15, IL-18, IFNα, IFNY, TNFα etc.) produced by an activated macrophage (Figure 1) stimulates cellular differentiation of uterine glandular cells, stromal fibroblasts and eventually decidual cells (decidual basalis and decidual parietalis). This triggers the trafficking of leukocytes (Mast cells, Basophils, Neutrophils, Eosinophils, B-cells, T-cells) and a cascade secretion of various cytokines by the decidual cells which activates multiple signaling network that act in concert on the trophoblast producing a strong TH1 environment for rejection of the implanting embryo [18].

Cytokines are Biological Molecules with Special Properties

Cytokines has been defined as multifunctional cell signaling molecules produced by immune cells which play the crucial roles of initiation, development, regulation of the intensity and duration of the immune response [17,19]. They are essentially proteins or glycoproteins with small molecular weights ranging from 8-30KDa which are produced through the mitogen activated protein kinase pathway [20]. They bind to specific receptors thereby activating intracellular messengers which regulate gene transcription for physiological functions. Cytokines participate in cell mediated immune response to the implanting trophoblast through a mediation of immune cell interactions. Cytokines has been proved to possess some specialized properties which enables them control biological process such as embryo implantation. Such properties includes

(a) Autocrine action (cytokines may act on the cells that produced them)

(b) Paracrine action (cytokines may act on nearby cells

(c) Endocrine action (cytokines may act on distant cells

(d) Pleiotropic action (a single cytokine can produce different effects on different cells)

(e) Redundancy (different cytokines can have the same effects)

(f) Crosstalk (the effect of a cytokine can be synergized by another)

(g) Antagonism (the effect of a cytokine can be reduced or blocked by another)

(h) Potency (cytokines act in the range of nanomolar to femtomolar concentrations).

Specific Cytokines has been implicated in Unexplained Recurrent 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. 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 Treq cells. Each cell population produces a unique set of cytokines [21,22]. 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 [22]. Based on this, embryo rejection and resultant implantation failures observed in embryo transfer cycles was recognized as a helper T-cell phenomenon in which the TH1 and TH17 cytokine has an inflammatory effect while the opposing TH2 and Treq cell cytokines exerts an anti-inflammatory effect on the embryo [22,23]. It is therefore proposed that a balance between the antagonistic T cell populations and their respective cytokines is the basis for immunological tolerance failures in embryo implantation process during assisted reproductive therapy cycles. Currently, members of the gp130 cytokines have been implicated in the implantation process. The gp130 cytokines describes the various cytokines that utilizes the gp130 signaling pathway. This includes the leukemia inhibitory factor (LIF), 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). The LIF, IL-6 and IL-11 in particular have been identified as candidate biomarkers during the window of implantation. Besides, the importance of the gp130 in the JAK/STAT signal-transduction pathway in embryo implantation has been demonstrated [24].

In view of the complexities of the above system there is need to develop a proteomic model that will enable scientists understand the complexities of cytokine interactions in patients with unexplained recurrent implantation failures. So far, proteomics has not elucidated a comprehensive picture of the cytokine network in patients with unexplained recurrent implantation failures. This is because the individual components of the cytokine network exhibit an overlapping nonlinear behaviour during their interaction (Figure 1). A major property of a nonlinear interaction is that a minor perturbation can immediately be amplified to magnitudes that can affect a network as whole. It is therefore possible that complex immunological changes can emanate from few cytokine interactions suggesting that minor changes in single cytokine concentrations or expression during the window of implantation can result to overlapping effects on other cytokines within the network [25].

Conclusion

Evidence has shown that the study of biological networks provides insights into the mechanism of diseases. The cytokine network appears to be a better toolkit to understanding the framework of cytokine-cytokine interactions and cytokine-immune cells interactions in unexplained recurrent implantation failures. Application of a system biology approach to the study of the cytokine network during the window of implantation is therefore necessary to help elucidate the mechanism of unexplained recurrent implantation failures. System biology provides a network analysis of immune regulatory circuits for biological processes. A proteomic analysis of the cytokine network during embryo implantation will help elucidate the specific concentrations, structures, modifications and mode of interaction of individual cytokines with one another and immune cells in patients with unexplained recurrent implantation failure. Such insights will surely stimulate clinical applications that can translate to therapeutic solutions.

References

1. Timeva T, Atanas S, Stanimir K (2014) Recurrent implantation failure: The role of the endometrium. J Reprod Infertil 15: 173- 183.
2. Siristatids C, Vogiatzi P, Branchnis N, Liassiduo A, Illiodromit Z, et al. (2015) Micro RNAs in assisted reproduction and their potential role in IVF failure. In Vivo 29: 169-175.
3. Comins BA, Garcia SA, Prado DNN, Fuente DL, Alonso J, et al. (2016) Evidence-based update: Immunological evaluation of recurrent implantation failure. Reprod Immunol Open Acc 1: 1-8.
4. LY KD, Aziz N, Safi J, Agarwal A (2010) Evidence-based management of infertile couples with repeated implantation failures following IVF. Curr Women's Health Rev 6: 200-218.
5. Koot YEM, Hoof VSR, Boomsma MC, Leenen VD, Koerkamp MJAG, et al. (2016) An endometrial gene expressionsignature accurately predicts recurrent implantation failrues after IVF. Sci Rep 6: 1-12.
6. Khalife D, Ghazeeri G (2018) Recurrent implantation failure and low molecular weight heparin. Open J Obstet Gynecol 8: 146-162.
7. Bakshi R, Jha B, Prakash (2016) The impact of endometrial scratching on the outcome of in vitro fertilization cycles: A prospective study. Fertil Sci Res 3: 8-86.
8. Shufaro Y, Schenker JG (2011) Implantation failure, etiology, diagnosis and treatment. IJIFM 2: 1-7.
9. Nakagawa K, Kwak KJ, Ota K, Kuroda K, Hisano M, et al. (2015) Immunosuppression with tracrolimus improved reproductive outcome of women with repeated implantation failure and elevated peripheral blood Th1/Th2 cell ratios. Am J Reprod Immunol 73: 353-361.
10. Wegmann TG, Lin H, Guilbert L, Mosmann TR (1993) Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon? Immunol Today 14: 353-356.
11. Simon CJ, Martin C, Pellicer A (2000) Paracrine regulators of implantation. Baillieres Best Pract Res clin Obstet Gynecol 14: 815-826.
12. Bowen JM, Chamley L, Mitchel MD, Keel JA (2002) Cytokines of the placenta and extra placental membranes: Biosynthesis, secretion and roles in establishment of pregnancy in women. Placenta 23: 239-256.
13. Lee JY, Lee M, Lee SK (2011) Role of endometrial immune cells in implantation. Clin exp Reprod Med 38: 119-125.
14. Schumacher A, Sharkey DJ, Robertson SA, Zenclussen AC (2018) Immune cells at the fetomaternal interface: How the microenvironment modulates immune cells to foster fetal development. J Immunol 201: 325-334.
15. Herberts C, Melgert B, Laan JWVD, Faaas M (2010) New adjuvanted vaccines in pregnancy: What is known about their safety? Expert Rev Vaccines 9: 1411-1422.
16. Andrea OO, Pilar FE, Ismael MH, Rodrigo VS, Lorenza D, et al.(2019) Innate immune cells and Toll-like receptor-dependent responses at the maternal fetal interface. Int J Mol Sci 20: 3654.
17. Zhang J, An J (2007) Cytokines, inflammation and pain. Int Anesthesiol Clin 45: 27-37.
18. Mori M, Boddan A, Balassa T, Csabai T, Julia SB (2016) The decidua-the maternal bed embracing the embryo-maintains the pregnancy. Semin Immunopathol 38: 635-649.
19. Shao R, Liu X, Ding Y, Chen X, Gao R, et al. (2012) Characterization of IK cytokine expression in mouse endometrium during early pregnancy and its significance on implantation. IJMM 30: 615-621.
20. Oliveira CMB, Sakata RK, Issy TSAAM, Gerola LR, Salomao R (2011) Cytokines and pain. Rev Bras De Anestesiol 61: 255-265.
21. Wang T, Secombes CJ (2013) The cytokine networks of adaptive immunity in fish. Fish Shellfish Immunol 35: 1703-1718.
22. Ginsburg ES, Xiao L, Gargiulo RA, Kung F, Politch JA (2005) Successful in vitro fertilization embryo transfer. Fertile and Steril 83: 1-6.
23. Azad M, Sara K, Bahia NJ, Zahra K, Gharesi FB (2017) T helper cell subsets and related cytokines in infertile women undergoing in vitro fertilization before and after seminal plasma exposure. Clin Exp Reprod Med 44: 214-223.
24. Dimitriads E, White CA, Jones RL, Salamonsen LA (2005) Cytokines, chemokines and growth factors in endometrium related to implantation. Human Reprod Update 11: 613-630.
25. Callard R, George AJT, Stark J (1999) Cytokines, chaos and complexity. Immunity 11: 507-513.