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Review

The complement system and adverse pregnancy outcomes

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ABSTRACT

Adverse pregnancy outcomes significantly contribute to morbidity and mortality for mother and child, with lifelong health consequences for both. The innate and adaptive immune system must be regulated to insure survival of the fetal allograft, and the complement system is no exception. An intact complement system optimizes placental development and function and is essential to maintain host defense and fetal survival. Complement regulation is apparent at the placental interface from early pregnancy with some degree of complement activation occurring normally throughout gestation. However, a number of pregnancy complications including early pregnancy loss, fetal growth restriction, hypertensive disorders of pregnancy and preterm birth are associated with excessive or misdirected complement activation, and are more frequent in women with inherited or acquired complement system disorders or complement gene mutations. Clinical studies employing complement biomarkers in plasma and urine implicate dysregulated complement activation in components of each of the adverse pregnancy outcomes. In addition, mechanistic studies in rat and mouse models of adverse pregnancy outcomes address the complement pathways or activation products of importance and allow critical analysis of the pathophysiology. Targeted complement therapeutics are already in use to control adverse pregnancy outcomes in select situations. A clearer understanding of the role of the complement system in both normal pregnancy and complicated or failed pregnancy will allow a rational approach to future therapeutic strategies for manipulating complement with the goal of mitigating adverse pregnancy outcomes, preserving host defense, and improving long term outcomes for both mother and child.

1. Introduction

Pregnancy is a complex process with incredible changes occurring in the cardiovascular and immune system of the mother to insure a successful birth. More than 4 million births occur in the United States alone each year with the majority of them being uneventful (but no less miraculous). Despite modern medicine and the advancements that have been made in prenatal care, adverse pregnancy outcomes still occur at a disturbing rate, including spontaneous abortion and early pregnancy loss, preterm labor, preterm birth, fetal growth restriction and gestational hypertension including preeclampsia and HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count). Preterm birth rates have increased during the last 20 years, with up to 12% of births in the United States occurring before 37 weeks of a normal 40 week gestation. Preeclampsia is characterized by new onset high blood pressure and often protein in the urine after 20 weeks of gestation (ACOG, 2013) and affects 3–6% of all pregnancies (Ananth et al., 2013). In the 1990s, preeclampsia accounted for 15% of maternal deaths in pregnancy (NHLBI, 2000). The maternal mortality has improved, with 9% mortality attributable to hypertensive disorders of pregnancy in 2010 (Creanga et al., 2015), yet the only clear treatment for preeclampsia is delivery of the placenta. Adverse pregnancy outcomes take a severe toll on quality of life with long-term adverse cardiovascular and respiratory sequelea in both mother and child. Survivors of fetal growth restriction and preterm birth have increased risk of cardiovascular disease as adults

Abbreviations: aHUS, atypical hemolytic uremic syndrome; aPL, antiphospholipid; APLAS, antiphospholipid antibody syndrome; AT1-AA, agonistic autoantibodies to the angiotensin II type 1 receptor; CH50, complement hemolytic activity; C1-INH, C1 esterase inhibitor; CR1, complement receptor 1; Crry, complement receptor 1-related gene protein y; C4BP, C4 binding protein; DAF, decay accelerating factor, CD55; HELLP, hemolysis, elevated liver enzymes, low platelet count; HSPC, hematopoietic stem-like progenitor cells; MASP, mannose associated serine protease; MCP, membrane cofactor protein, CD46; MBL, mannose binding lectin; MMP, matrix metalloprotease; PlGF, placental growth factor; PNH, paroxysmal nocturnal hemoglobinuria; RUPP, reduced utero-placental perfusion pressure; sFlt-1, soluble fms-like tyrosine kinase-1; SLE, systemic lupus erythematosus; VEGF, vascular endothelial growth factor.

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(Lewandowski et al., 2014; Lewandowski and Leeson, 2014) as well as metabolic and respiratory complications and developmental delays (Saigal and Doyle, 2008). An increased lifetime risk for cardiovascular disease is also associated with mothers who experienced hypertension in pregnancy (Bellamy et al., 2007; Veerbeek et al., 2015).

Significant adaptations of the immune system occur in pregnancy, both in the innate and adaptive arms, to insure survival of the fetal allograft and maintenance of an immune system to defend the mother and fetus from invaders. The complement system is no exception with marked changes apparent to protect the fetus from complement system attack. In addition, newer evidence indicates the importance of the complement system in orchestrating normal development (Kolev et al., 2014), not just protecting from infection. We will first review the changes in the complement system and its regulators that occur to insure a successful normal pregnancy and then discuss studies demonstrating dysregulation of the complement system in adverse pregnancy outcomes, consequences of that dysregulation, and potential therapeutic strategies.

2. Complement system and normal pregnancy

2.1. Complement system

The complement system is comprised of more than 50 proteins and normally operates at a low steady state level of activation. However, the complement cascade may be amplified by one or more of three activation pathways; classical, lectin or alternative (Fig. 1). Activation through C3 can result in covalent binding of the C3b fragment to invaders or self, i.e. C3 deposition. Activation through C9 can lead to lysis of target cells and is a prominent host defense mechanism for many microorganisms. C3a and C5a are fluid phase activation products that interact with G protein coupled receptors on numerous cell types to elicit inflammation and immune cell activation. C5b-9 forms a membrane pore resulting in cell lysis. Sublytic concentrations of the Membrane Attack Complex C5b-9 can stimulate cells and upregulate adhesion molecules. Also, a cytolytically inactive C5b-9 complex that is soluble (sC5b-9) and is detectable in plasma or serum can also be formed and initiate cytokine synthesis and vascular leakage in endothelial cells (Tedesco et al., 1997). Complement activation is controlled by soluble and membrane bound inhibitors, primarily at C3 and C5b-9 (Fig. 1). C1-INH inhibits both C1r and C1s of the classical pathway and the mannose associated serine proteases (MASP) of the MBL pathway. Factor H and C4 binding protein (C4BP) are soluble plasma regulators that target C3 and C4, respectively, to limit activation. Complement receptor 1 (CR1), CD55 (DAF; decay accelerating factor), CD46 (MCP, membrane cofactor protein) and CD59 are membrane-associated regulators that limit activation on self. In contrast to widespread expression in humans, in mice and rats the CD46 molecule is exclusively expressed in testis. Mice and rats also have complement receptor 1-related gene protein y (Crry) that regulates C3 activation and has CD46 and CD55 like activity (Naik et al., 2013).

2.2. Placental development

The fetus and the placenta express paternal antigens and thus present as foreign to the maternal immune system. This semi-allogeneic graft requires special protection from the maternal immune system and the exact mechanism of protected status of the fetus is under continuing investigation. The human placenta (as well as that of rabbit, guinea pig, mouse and rat) is a hemichorial structure meaning that maternal blood is in direct contact with the fetal chorion. The placental villi are fetal structures that bridge the uterus and the fetal chorion and carry the fetal vasculature (Fig. 2A). The maternal blood pours into the intervillous space bathing placental villi to provide nutrients and oxygen for active transport or diffusion into the fetal blood vessels. Maternal IgG antibodies are transported by endocytosis to reach the fetal circulation. In the human, the regions are often designated as extravillous and villous, whereas in the rodent, the placental layers are designated as the labyrinth and trophospongium or junctional layer. The trophospongium layer is both fetal and maternal with fetal trophoblasts invading to remodel maternal spiral arteries. The villous or labyrinth space is of fetal origin with villous structures carrying fetal blood vessels into the intervillous space for exchange of oxygen and nutrients. The placental villi and the intervillous space are lined by fetal trophoblasts, the outermost epithelial like cell layer of the developing fetus. The trophoblasts differentiate with the task of invading the maternal uterine decidua to remodel spiral arteries and establish a high flow low resistance source of maternal blood that enters the intervillous space and bathes the placental villi. The different trophoblast cell types are depicted in Fig. 2B. The interstitial and endovascular trophoblasts invade maternal decidua to direct remodeling of maternal spiral arteries to a low resistance blood vessel that can provide adequate maternal blood to the intervillous space. The villous cytotrophoblasts differentiate into the outer syncytiotrophoblast layer on the placental villi in contact with the intervillous space with maternal blood and complement. The fetal trophoblast on the outermost layer of the embryonic placental villi is the syncytiotrophoblast that establishes the interface between maternal blood and the fetus. It is formed by fusion of the underlying layer of villous cytotrophoblasts and lacks gaps for immune cell penetration. The fetal derived trophoblast is the only cell in contact with the maternal blood so this is an important site for control of complement activation by endogenous complement regulators. Complement system activation at the syncytiotrophoblast must be carefully controlled so the fetus is not harmed by the mothers innate immune complement system. In addition, a functioning intact complement system is of critical importance in maintaining host defense to protect the fetus and mother from infection.

2.3. Complement and placental development

Complement is very important in a normal pregnancy for development of placenta and consequently for normal development of the fetus. At initial stages of pregnancy, the uterine wall undergoes changes and transforms into decidual tissue that is important for implantation. Inflammation accompanies the trophoblast invasion of the decidual tissue and successful embryo implantation. Numerous changes in the adaptive immune response are also important in success of this process, but we will concentrate primarily on the role of the complement system in successful trophoblast invasion and fetal development. Activated C3 participates in normal phagocytic activity of the mouse trophoblast in vitro suggesting that C3 may assist in trophoblast invasion of the decidua and endometrial blood vessels (Albieri et al., 1999). Some trophoblasts invade the uterine decidua as endovascular trophoblasts and migrate up the uterine spiral artery to replace the endothelial cells and result in vascular remodeling and a high flow, low resistance vessel. Normally endothelial cells do not synthesize complement components. However, Bulla et al. (2008) demonstrated that endothelial cells in decidual tissue secrete C1q during pregnancy and C1q is seen at contact sites between endovascular trophoblasts invading the spiral arteries and decidual endothelial cells. No C4 is detected co-localized with C1q suggesting that C1q does not initiate complement activation at this location. In vitro studies suggest that C1q is likely a bridge allowing adherence of decidual endothelial cells and the endovascular trophoblast. MBL is known to inhibit this interaction (Agostinis et al., 2012). Moreover, MBL is increased in