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Preeclampsia: A view through the danger model

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Abstract

Classical thinking suggests that the immune system undergoes activation on the basis of discrimination between ‘self’ and ‘non-self’. Accordingly, the fetus activates the mother’s immune system because the fetus is in part ‘non-self’. Thus, successful pregnancy depends on constraint of maternal immunity. Preeclampsia is an outcome of lost constraint.

Instead, the danger model suggests that normal pregnancy, regardless of the expression of ‘non-self’ antigens, does not activate the maternal immune system unless that pregnancy expresses danger signals. Thus, preeclampsia stems from stress or abnormal cell death in pregnancy-related tissues. This compels expression of specific danger signals and potential activation of anti-fetal immunity, which secondarily feeds the syndrome.

Study of preeclampsia from this perspective may bring forth novel mechanisms and indicators of vascular and metabolic dysfunction during pregnancy.

Keywords

Immunity; Immune tolerance; Pregnancy; Preeclampsia

1. THE EVOLVING DANGER MODEL

The danger model has been proposed as a viable alternative to classical immunology’s model of self/non-self discrimination. Here, I will use the danger model to examine the apparent immune conundrums of normal and pre-eclamptic pregnancies.

Danger model: original elements

The cornerstone of the danger model (Matzinger, 1994) is that the decision to initiate an immune response is not based on discrimination between self and non-self, but instead is based on recognition of ‘danger’ (abnormal cell death, injury or stress). The original danger model focused on adaptive immunity and incorporated elements of classical theory by immunologists such as Bretcher, Cohen and Lafferty. According to the original model:

- Developing T cells die if they recognize antigen (major histocompatibility molecule plus specific peptide) in the thymus. This renders the T cell population tolerant to antigens expressed endogenously by ‘professional’ antigen presenting cells (APC; i.e. dendritic cells).

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- Mature antigen-specific CD8⁺ killers or B cells may see antigen, but will die without help from a helper T cell.
- Helper T cells must both see cognate antigen and receive specific second signals (co-stimulation) to be fully active.
- If naïve helper T cells see antigen without co-stimulation, they die.

Thus, the expression of co-stimulation regulates the outcome of seeing antigen. Furthermore, the model stipulated that:

- Naïve helper T cells must receive co-stimulation from an *activated* professional APC.
- Tissues and cells that are stressed, injured or dying abnormally activate professional APC.
- Normal apoptotic cell death, growth and development, even if through expression of novel antigens, should not activate professional APC.
- Tissues inhibit T cells that see tissue-specific antigens by not elaborating danger signals that activate APC.

Early processing of the danger model increased emphasis on tissues as controllers of immune responses. For example, in infected tissues, danger-activated APCs could process and present *any* tissue antigen, even those belonging to non-infected tissues. However, healthy large or fast growing tissues would resist ‘bystander’ immunity because they would simply ‘outrun’ it. In addition, since effector T cells eventually lose function, and activated APCs are short-lived, continued tissue expression of danger signals would be required for continuous activation. Ultimately, expression of danger signals is a way of *sustaining and directing effector responses in tissues* and non-expression is a way of minimizing the effects of autoimmunity.

Later enhancements of the danger model

Janeway’s model of the immune system was an earlier contemporary of the danger model that incorporated innate immunity. His model differed from the danger model in that APC activation occurred through recognition of evolutionarily conserved, phylogenetically distinct molecular patterns expressed by bacteria and viruses (Janeway, 1992). Although this model significantly encouraged the elucidation of Toll-like receptors, co-receptors and ligands, it did not explain, for example, immunity to transplanted organs.

In response, the danger model was expanded (Matzinger, 1998; Matzinger, 2002) to suggest that:

- Endogenous molecules that indicate damage, stress or necrotic death might bind to the same specific pattern receptors on APC as did conserved molecules on bacteria.
- Infected cells could express these molecules, but so can pathogens in the process of being immobilized and engulfed.

Thus, even innate responses are not predicated on self/non-self discrimination, but on the detection of danger, in the form of endogenous molecules made in response to stress, damage and non-apoptotic cell death.

The nature of danger signals

The finding that necrotic cells (Gallucci et al., 1999) activate dendritic cells supported the danger model and drove the search to identify specific danger signals. Because they are released by stressed cells and can stimulate dendritic cells, several molecules are now considered in this

group of signals, including DNA, hyaluronan, heat shock proteins, uric acid, heparan sulfate, oxidized LDL and TNF (Seong and Matzinger, 2004).

Recent thinking about danger signals has produced predictions about their molecular nature, receptors and functional capabilities. For example, because hydrophobicity of molecules must be tightly regulated in healthy cells, it was postulated that the sudden exposure of the hydrophobic portions (HYPPOs) of molecules would be an indication of damage and stress. Depending on their aggregate configurations, HYPPOs could be immunostimulatory through binding to specific receptors on APCs and thus constitute danger signals (Seong and Matzinger, 2004). Because HYPPOs, such as the lipid portion of LPS, can be exposed on all life forms, and because many of the pathogen-associated-molecular-patterns (PAMPS) found in bacteria are lipids, it was suggested that they could constitute a universal set of damage-associated-molecular-patterns (DAMPs) that use an evolutionarily related set of receptors (the TLRs). This view unifies the Janeway and the danger models.

Danger signals are now also predicted to be:

- Present as pure initiators or as initiator/feedback-enhancers of APC activation
- Used by cells to induce both normal repair and defense
- Functionally regulated by their cellular localization
- Ligands for receptors that are also regulated by tissues

By these criteria, the recently studied High Mobility Group Box Protein-1 (HMGBP-1) (Harris and Raucchi, 2006) might be a danger signal. HMGBP-1 is a transcription factor in healthy cells. It is retained in the nucleus of apoptotic cells and released from necrotic cells. It binds to TLR 2 and 4, thereby activating dendritic cells, and is actively secreted from inflammatory cells (positive feedback?). Blocking its activity ameliorates septic shock and autoimmune disease.

Class of the immune response

Key to the danger model is that the decision of whether or not to respond precedes and is separate from the decision of how to respond, i.e. class of response. Usually 'class' constitutes different subtypes of antibodies, effector cell functions and supporting T cell responses. Class as a decision made by the immune system is still 'under construction' in the danger model (Matzinger, 2007). Consistent with the original model, the prediction is that this decision is dictated by tissues, and not specific antigens.

2. NORMAL PREGNANCY VIEWED THROUGH THE DANGER MODEL

Key points

Classic models of self/non-self discrimination have suggested that, since the fetus is non-self, the maternal immune system should respond to it and that successful pregnancy relies upon mechanisms that constrain maternal immunity. In contrast, the danger model posits that the maternal immune system's decision does not depend on the fetus's foreignness but rather on whether it is in trouble and sends danger signals. From this model, it follows that:

- The presence of paternal antigens should not induce APC activation under normal conditions.
- T cells that see these antigens in normal tissues will die due to absence of co-stimulation.
- Maternal immune suppression is not critical for normal pregnancy.

If there is stress, necrosis, infection, or altered metabolism etc, at the maternal-fetal interface, there will be an increased expression of DAMPs and, in turn, the activation of APCs. Presentation of paternal antigens and activation of anti-paternal T cells would follow. If the elaboration of DAMPs continues, the ensuing response can cause fetal loss. However, because the function of activated immune effector cells is short-lived, a *temporary* loss of fetal health will generate a time-limited immune response that should end when the fetus heals, and should not result in significant harm.

Supporting data

Although debated, there is increasing evidence that apoptosis is more critical than necrosis for implantation, placental development and placental homeostasis (Huppertz et al., 2006). By the danger model, then, suppression of maternal immunity is not necessary for pregnancy success. This idea is supported by emerging data that expression of molecules such as Fas ligand on trophoblast is not critical to limit the effects of fetal antigen-specific T cells (Chaouat and Clark, 2001). Moreover, TH-2 cytokines that support deviation of immune responses away from cytotoxicity, are expendable (Bonney, 2001). Anti-fetal responses, however, can be generated during pregnancy (Bonney and Matzinger, 1997) without loss of the fetus, supporting the idea that danger in tissues is required for tissue immunity. In addition, infection (Clark et al., 2004) or altered vascularity (Dixon et al., 2006) at the maternal-fetal interface can lead to abnormal pregnancy.

Immunity at the maternal-fetal interface

Classic models have compelled researchers to explain how fetal antigen recognition sometimes generates a diminished response to allow trophoblast invasion and prevent pregnancy loss, but otherwise generates an *enhanced* response that constrains trophoblast invasion and avoids disorders such as placenta accreta. The difficulty of this apparent dichotomy is avoided by the danger model. Recognition of fetal antigens in the absence of danger may lead to death for some immune cells. For others, it may lead to the adequate elaboration of helpful substances, such as γ IFN from uterine NK cells (Ashkar, et al., 2003), that support the development of placental blood supply. Consistent with this are the data suggesting that trophoblast can attract appropriate NK cells to the maternal-fetal interface (decidua and invading trophoblast) via chemokine and receptor expression (Hanna et al., 2003). Thus, the danger model removes recognition of fetal antigens as the prime focus of immune modulation at the maternal-fetal interface, and replaces it with recognition of damage, injury or stress. It suggests also a search for developmental functions for locally expressed immune modulating substances, whether they are 'pro-inflammatory' or 'anti-inflammatory'.

Normal pregnancy and the danger model: tissue control of class

The danger model continues to address the issue of class in immune responses to stress or pathogens. In this model, the tissue is key - not the particular pathogen (Matzinger, 2002). The placenta and related tissues may exhibit inherent tendencies towards specific types of response. However, the model asserts that these tendencies, and their underlying mechanisms, may be shared by disparate tissues and are not governed by expression of 'non self' antigens. Consistent with this idea is the presence of specialized populations of both T cells (i.e. $\gamma\delta$) and antigen-presenting cells in various tissues.

3. A VIEW OF PREECLAMPSIA THROUGH THE DANGER MODEL

Is immune system involvement central to preeclampsia?

Because of epidemiologic evidence suggesting that preeclampsia is modified by exposure to paternal or fetal cells, it has been suggested that preeclampsia may be an immune system-

mediated disease. Although T cell reactivity may be important in both the initial poor placentation disorder and in the maternal hypertensive/proteinuric response, existing experimental evidence to support this idea is tentative. Data exist suggesting that administration of IL-2 and IL-12-activated T cells (Zenclussen, 2006) or LPS (Faas et al., 2000) causes proteinuria and hypertension in animal models. However, it is not clear from these studies that the implicated T cell populations are antigen-specific due to, for example, lack of comparison between syngeneic and allogeneic pregnancies. Moreover, it is not clear the activated T cells involved specifically traffic to the tissues, such as the kidney, that are most affected by the disease. Further work is needed to carefully document the presence of anti-fetal or endothelial antigen-specific T cells in women with preeclampsia or in animal models.

It has been suggested that the poor placentation and the maternal syndrome related to preeclampsia stems from altered immune regulation of NK cells (for example, Borzychowski et al., 2005). However, before concluding that the disease is related to deficient suppression of NK cell activity, we should consider the evidence that NK cells are involved in some non-immune aspects of proper placentation (Ashkar et al., 2003). Should these be defective, or should trophoblast fail to elaborate adequate NK-trophic signals, the resulting stress- or damage-related signals could initiate immune responses secondarily. Consistent with this are data suggesting a predominantly non-activating KIR haplotype is associated with preeclampsia (Hiby et al., 2004).

Preeclampsia as a response to danger

The danger model suggests that, if preeclampsia is an immune disease, the initiating factor is not fetal antigen recognition, but rather recognition of DAMPS generated as the result of poor placentation, oxidative stress (Hubel, 1999), endothelial cell dysfunction (Levine et al., 2006), altered glucose metabolism (Paine et al., 2006) or many other incompatibilities at the gene or protein level. By the danger model, generation of specific anti-fetal T cells, if it occurs, is a *secondary* event that could subsequently feed the syndrome, but would end when danger ceases to be communicated. A placenta without a fetus (as in a molar pregnancy) is not normal, and would also be expected to generate stress-related danger signals. In the presence of danger signals, immune responses may be generated to any cellular component, including pregnancy-specific elements expressed in the placenta and on endothelial cells in important vascular beds (i.e. kidney).

The evidence that TLR-4 is upregulated in the placenta of women with preeclampsia has caused investigators to draw the link between DAMPS or DAMP receptors and preeclampsia (Kim et al., 2005). Potential DAMPs expressed in the placenta of women with preeclampsia include HSPs (Geisler et al., 2004) and TNF (Pijnenborg et al., 1998). These may be 'positive feedback' DAMPS, since these studies are necessarily begun after the disease develops. Potential DAMPs up-regulated in the blood or urine of pregnant women with preeclampsia include molecules such as Fetal DNA (Zhong et al., 2006), hyaluronan (Osmers et al., 1998), HSPs (Bloschinskaya and Davidovich, 2003) and Oxidized LDL (Uotila et al., 1998). A potential DAMP shown recently to be up-regulated in preeclampsia is long pentraxin-3 (Rovere-Querini et al., 2006). This molecule is recruited to sites of tissue damage and repair, but prevents presentation of antigen from apoptotic cells. It is increased by TNF-alpha and IL-1beta, and thus could be a 'positive feedback' DAMP. It is constitutively expressed in normal placental tissues, yet is released into the serum of women with preeclampsia. It is likely that several other DAMPS may be found associated with preeclampsia.

Culture of human placental explants under normoxic conditions produces syncytiotrophoblast apoptosis, a normal mechanism which is thought to maintain the trophoblast syncytium. However, hypoxia in this system leads to syncytiotrophoblast necrosis and separation from the underlying cytotrophoblast (Huppertz et al., 2003). Preeclampsia is associated with increased

syncytiotrophoblast membrane microvesicles in uterine veins (Knight, et al., 1998). In light of the danger model, these findings together raise the interesting possibility that disrupted physiology favoring necrosis and increased circulatory release of the wrong cell type may both signal danger at the maternal-fetal interface and feed the disease. The expression of DAMPS and the state of released syncytiotrophoblast vesicles (necrotic, aponecrotic or apoptotic) found in preeclamptic women has yet to be fully elucidated.

Testing the danger model: preeclampsia and first pregnancies

Early discussions of preeclampsia emphasized its occurrence in young women in their first pregnancy. A potential explanation is that inherent, genetic incompatibilities between mother and fetus could lead to metabolic stress and DAMP expression. Another is that poor adaptation to pregnancy, for example intolerance to volume expansion (Bernstein et al., 1998), may lead to DAMP expression and immune activation. Such factors may be modifiable with subsequent pregnancies, and account for more mild disease.

Preeclampsia: sex and danger

There is significant evidence that length of cohabitation (Robillard et al., 1994), lack of condom use and oral sex with swallowing of semen (Koelman et al., 2000) decreases risk of preeclampsia. Current thinking is that these practices allow for tolerance against paternal antigens. The danger model, however, emphasizes that 'danger' and not 'foreign' is the primary focus of the immune system's decision to respond. Accordingly, if preeclampsia is related to stimulation of an immune response because of danger signals, it is possible to get anti-paternal immunity as a second and modifying effect. However, if anti-paternal T cells have previously seen antigen in the absence of danger, they would be deleted and not be available for a subsequent response. This tolerance would be short-lived as (particularly in young women) new T cells leave the thymus on a regular basis, and a proportion of these would be reactive to paternal antigens. Thus, not only the length of cohabitation but the frequency and timing of sexual acts would be important elements of epidemiologic study.

Preeclampsia and the danger model: reproductive technology

It has been suggested that Assisted Reproductive Technology (ARTS) using surgically obtained sperm, in the relative absence of prior specific semen exposure, increases the risk of preeclampsia (Wang et al., 2002). It is said that lack of tolerance to paternal antigens is the cause. Although pregnancy that progresses to term and delivery is a reasonably common outcome of ART, concerns have been raised about increases in disease experienced by offspring (Sutcliffe et al., 2006). Moreover variations in methods related to handling of egg, sperm and early embryos leads to different outcomes. It is not hard to imagine, then, that an ART pregnancy might be stressed, even though it goes to completion. It is also possible that such a pregnancy is deficient in ways we do not now recognize and eventually expresses DAMPS that lead to immune responsiveness and the syndromes seen. Again, the focus is not that the developing fetal-placental unit is foreign, but whether it expresses danger signals. Perhaps, a comparison of embryo transferred and normal syngeneic and allogeneic pregnancies in mouse models of preeclampsia might shed light on this issue.

Preeclampsia as seen through the danger model: the effect of previous pregnancy where the syndrome did not develop

If a previous pregnancy occurred in the absence of danger signals being generated, it is possible that any T cells seeing paternal or other pregnancy-specific antigen would be deleted. The preeclampsia that develops in a subsequent pregnancy could be relatively mild, provided it occurs before new T cells are generated in the thymus, and provided T cell activation is an important factor in the overall response.

Preeclampsia as seen through the danger model: the effect of previous pregnancy where the syndrome did develop

In this situation, clinicians have observed two main outcomes: the syndrome is ameliorated when the subsequent pregnancy occurs soon after, or with same partner, while the syndrome recurs or is worse when the subsequent pregnancy occurs later or with a new partner. Current literature reflects controversy about whether second pregnancy effects are more appropriately linked with pregnancy interval (Skjaerven et al., 2002) or paternity (Robillard et al., 1999). However, the danger model does not need to make this distinction. Since the prime focus is danger and not paternal antigens, either scenario is possibly explained.

For example, the model might suggest that the expression of danger signals could be modified by time (i.e. vascular adaptation to volume expansion) alone, without immune system involvement. In contrast, if the immune system is central to these findings, a possible explanation is that, although certain TH-2 cytokines are not critical to normal pregnancy (Bonney, 2001), there may be a *tendency* towards 'TH-2 like' responses in the placenta and related tissues. During a first *abnormal* pregnancy, what is expressed as danger at the maternal-fetal interface could be translated initially to a 'wrong' class of response, leading to preeclampsia, but post- delivery this may shift to the 'appropriate' class. The idea that there might be a change in the class of response generated in preeclampsia is consistent with the gestational timing and severity of disease (rare at less than 20 weeks gestation, severe at weeks 20–34, less severe at greater than 34 weeks till term), but such timing is difficult to explain on purely self/non-self grounds.

Since antigen-specific tolerance is difficult to achieve once an immune response is generated, apparently less severe preeclampsia in a subsequent pregnancy could be related to a change in the *class* of the response by the relevant T cells. If the next pregnancy is with the same partner or close in time, incompatibilities or stresses could generate an *enhanced*, switched response and milder disease. This is consistent with data that memory, as compared to naïve, immune responses are enhanced.

With time, the class-switched T cell pool shrinks (memory cells have limited life spans) and, with a new pregnancy, the repertoire of danger signals may change (due to distinct incompatibilities and stresses). This may produce a syndrome that appears similar to the initial one, thus accounting for the increased severity in a next pregnancy after a long interval or with changed paternity.

4. SUMMARY

The danger model

- Shifts control of immune responses to tissues
- Separates the question of whether to respond from the questions of how to respond and how to protect without destroying tissues
- Suggests that normal pregnancy does not require limitation of maternal immunity
- Predicts that placental damage or stress, not loss of tolerance to fetal antigens, is the primary mechanism underlying preeclampsia
- Potentially explains the clinical findings associated with preeclampsia, and encourages specific studies in women
- Supports examination of novel preeclampsia-related DAMPs, cellular circuits, antigen-specific T cell responses and tissue effects on the class of immune response

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References

- Ashkar AA, et al. Assessment of requirements for IL-15 and IFN regulatory factors in uterine NK cell differentiation and function during pregnancy. *J Immunol* 2003;171:2937–2944. [PubMed: 12960317]
- Bernstein IM, et al. Intolerance to volume expansion: A theorized mechanism for the development of preeclampsia. *Obstet Gynecol* 1998;92:306–308. [PubMed: 9699772]
- Bloshchinskaya IA, Davidovich IM. Nitric oxide and HSP 70 proteins during normal pregnancy, gestosis, and preclinical gestosis. *Bull Exp Biol Med* 2003;135:241–243. [PubMed: 12802391]
- Bonney EA. Maternal tolerance is not critically dependent on interleukin-4. *Immunol* 2001;103:382–389.
- Bonney EA, Matzinger P. The maternal immune system's interaction with circulating fetal cells. *J Immunol* 1997;158:40–47. [PubMed: 8977173]
- Borzychowski AM, et al. Changes in systemic Type 1 and Type 2 immunity in normal pregnancy and pre-eclampsia may be mediated by natural killer cells. *Eur J Immunol* 2005;35:3054–3063. [PubMed: 16134082]
- Chaouat G, Clark DA. Fas/Fas ligand interaction at the placental interface is not required for the success of allogeneic pregnancy in anti-paternal mhc preimmunized mice. *Am J Reprod Immunol* 2001;45:108–115. [PubMed: 11216873]
- Clark DA, et al. Ecology of danger-dependent cytokine-boosted spontaneous abortion in the CBA x DBA/2 mouse model. I Synergistic effect of LPS and (TNF-alpha + IFN-gamma) on pregnancy loss. *Am J Reprod Immunol* 2004;52:370–378. [PubMed: 15663602]
- Dixon ME, et al. Failure of decidual arteriolar remodeling in the CBA/J x DBA/2 murine model of recurrent pregnancy loss is linked to increased expression of tissue inhibitor of metalloproteinase 2 (TIMP-2). *Am J Obstet Gynecol* 2006;194:113–119. [PubMed: 16389019]
- Faas MM, et al. Activation of peripheral leukocytes in rat pregnancy and experimental preeclampsia. *Am J Obstet Gynecol* 2000;182:351–357. [PubMed: 10694336]
- Gallucci S, et al. Natural adjuvants: Endogenous activators of dendritic cells. *Nature Med* 1999;5:1249–1255. [PubMed: 10545990]
- Geisler JP, et al. Heat shock protein 27 in the placentas of women with and without severe preeclampsia. *Clin Expt Obstet Gynecol* 2004;31:12–14.
- Hanna J, et al. CXCL12 expression by invasive trophoblasts induces the specific migration of cd16–human natural killer cells. *Blood* 2003;102:1569–1577. [PubMed: 12730110]
- Harris HE, Raucci A. Alarmin(g) news about danger: Workshop on innate danger signals and HMGB-1. *EMBO Reports* 2006;7:774–778. [PubMed: 16858429]
- Hiby SE, et al. Combinations of maternal KIR and fetal HLA-C genes influence the risk of preeclampsia and reproductive success. *J Exp Med* 2004;200:957–965. [PubMed: 15477349]
- Hubel CA. Oxidative stress in the pathogenesis of preeclampsia. *Proc Soc Expt Biol Med* 1999;222:222–235.
- Huppertz B, et al. Apoptosis and its role in the trophoblast. *Am J Obstet Gynecol* 2006;195:29–39. [PubMed: 16579915]
- Huppertz B, et al. Hypoxia favours necrotic versus apoptotic shedding of placental syncytiotrophoblast into the maternal circulation. *Placenta* 2003;24:181–190. [PubMed: 12566245]
- Janeway CA Jr. The immune system evolved to discriminate infectious nonself from noninfectious self. *Immunol Today* 1992;13:11–16. [PubMed: 1739426]
- Kim YM, et al. Toll-like receptor 4: A potential link between 'danger signals', the innate immune system, and preeclampsia? *Am J Obstet Gynecol* 2005;193(3 Pt 2):921–927. [PubMed: 16157088]
- Knight M, et al. Shedding of syncytiotrophoblast microvilli into the maternal circulation in pre-eclamptic pregnancies. *Brit J Obstet Gynecol* 1998;105:632–640.

- Koelman CA, et al. Correlation between oral sex and a low incidence of preeclampsia: a role for soluble HLA in seminal fluid? *J Reprod Immunol* 2000;46:155–166. [PubMed: 10706945]
- Levine RJ, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. *N Engl J Med* 2006;355:992–1005. [PubMed: 16957146]
- Matzinger P. Tolerance, danger, and the extended family. *Ann Rev Immunol* 1994;12:991–1045. [PubMed: 8011301]
- Matzinger P. An innate sense of danger. *Sem Immunol* 1998;10:399–415.
- Matzinger P. The danger model: A renewed sense of self. *Science* 2002;296:301–305. [PubMed: 11951032]
- Matzinger P. Friendly and dangerous signals: Is the tissue in control? *Nature Immunol* 2007;8:11–13. [PubMed: 17179963]
- Osmers RG, et al. Increased serum levels of hyaluronic acid in pregnancies complicated by preeclampsia or hemolysis, elevated liver enzymes, and low platelets syndrome. *Am J Obstet Gynecol* 1998;178:341–345. [PubMed: 9500497]
- Paine MA, et al. P-type inositol phosphoglycans in serum and amniotic fluid in active pre-eclampsia. *J Reprod Immunol* 2006;69:165–179. [PubMed: 16384607]
- Pijnenborg R, et al. Immunolocalization of tumour necrosis factor-alpha (TNF-alpha) in the placental bed of normotensive and hypertensive human pregnancies. *Placenta* 1998;19:231–239. [PubMed: 9639318]
- Robillard PY, et al. Revisiting the epidemiological standard of preeclampsia: Primigravidity or primipaternity? *Eur J Obstet Gynecol Reprod Biol* 1999;84:37–41. [PubMed: 10413224]
- Robillard PY, et al. Association of pregnancy-induced hypertension with duration of sexual cohabitation before conception. *Lancet* 1994;344:973–975. [PubMed: 7934427]
- Rovere-Querini P, et al. Plasma and tissue expression of the long pentraxin 3 during normal pregnancy and preeclampsia. *Obstet Gynecol* 2006;108:148–155. [PubMed: 16816069]
- Seong SY, Matzinger P. Hydrophobicity: An ancient damage-associated molecular pattern that initiates innate immune responses. *Nature Rev Immunol* 2004;4:469–478. [PubMed: 15173835]
- Skjaerven R, et al. The interval between pregnancies and the risk of preeclampsia. *N Engl J Med* 2002;346:33–38. [PubMed: 11778000]
- Sutcliffe AG, et al. Assisted reproductive therapies and imprinting disorders--a preliminary british survey. *Hum Reprod* 2006;21:1009–1011. [PubMed: 16361294]
- Uotila J, et al. Antibodies against copper-oxidised and malondialdehyde-modified low density lipoproteins in pre-eclampsia pregnancies. *Brit J Obstet Gynecol* 1998;105:1113–1117.
- Wang JX, et al. Surgically obtained sperm, and risk of gestational hypertension and pre-eclampsia. *Lancet* 2002;359:673–674. [PubMed: 11879865]
- Zenclussen AC. A novel mouse model for preeclampsia by transferring activated th1 cells into normal pregnant mice. *Meth Mol Med* 2006;122:401–412.
- Zhong XY, et al. Minimal alteration in the ratio of circulatory fetal DNA to fetal corticotropin-releasing hormone mRNA level in preeclampsia. *Fet Diag Ther* 2006;21:246–249.