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REVIEW

Threatening biomarkers in lupus pregnancy: Biochemistry and genetic challenges

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OBJECTIVES: Using genetic markers and miRs work strongly beside other sensitive biomarkers in lupus management during sensitive period of pregnancy.
METHOD: PubMed and Google Scholar databases were searched from 2000 to 2017 using the terms "lupus," "lupus pregnancy," "biomarkers," "micro-RNA," "polymorphisms," "anti-phospholipid antibodies," and "cluster differentiation markers."
DISCUSSION: Complement is a valuable biomarker in lupus pregnancy. However, the complement profile has ambiguous meaning because decreased levels of C3 and C4 reflect inflammation and because they are also prognostic biomarkers for abortion. Furthermore, increased C3 and C4 levels indicate hepatic protein synthesis in hepatocytes. Anti-phospholipid (APL) antibodies are present in 25% to 50% of lupus patients, and can lead to thrombotic and obstetric complications in some pregnancies and increase the risk of abortion, especially in a pregnant woman in the active phase of lupus. Several studies have associated APL with HELLP syndrome. However, other pregnancy complications have not been associated with APL. Autoantibodies against the major vault protein and anti-double strand DNA antibodies are valuable biomarkers in evaluating lupus activity. The expression pattern of micro-RNAs (miRs) differs in various diseases. Current studies have demonstrated the potential of miRs as diagnostic and prognostic biomarkers in various diseases; for example, the level of miR-126 is higher in lupus.
CONCLUSION: miR-223-3p and miR-451 are informative biomarkers in estimating disease activity. TWEAK, BAFF, and APOL1 genes, and their polymorphisms are informative in estimating disease activity, especially renal effects, and in monitoring higher-risk pregnant women. Further studies of these genes and their relevant polymorphisms are needed.

Keywords lupus, biomarker, genetic, micro-RNA, anti-phospholipid antibodies

Introduction

Lupus is an immune-mediated disease. In pregnant women, the hormonal and immunological changes that occur can pose a potentially dangerous health challenge to the woman and the fetus. It is essential to control lupus disease activity in pregnancy (Molad et al., 2005). Complications such as preeclampsia, thrombocytopenia, inflammation, and production of anti-phospholipid antibodies (APLs) exacerbate the challenges in a lupus pregnancy (Vinet et al., 2014; Moroni and Ponticelli, 2016; Teh et al., 2016). While the outcomes of pregnancy have improved in women with lupus, pregnancy remains a high-risk situation. Maternal complications and risks remain. For instance, lupus activity flares occur in 25% to 65% of pregnancies in women with lupus (Lateef and Petri, 2017). Risk factors including active lupus in the prior six months or multiple flares in previous years increase lupus-related activities such as arthritis and hematologic diseases such as thrombocytopenia during pregnancy (Ho et al., 2001; Clowse, 2007). Lupus-related pregnancy complications such as intrauterine growth restriction (IUGR) (Sammaritano, 2017) and preterm birth can harm the fetus and increase the risk of mortality (Massenkeil et al., 2016). Preeclampsia in lupus patients can increase blood pressure, which endangers both the pregnant woman and the fetus (e.g., higher risk of stroke) (Lateef and Petri, 2013). Preterm birth and death and exact treatment for preeclampsia is delivery of the pregnancy

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(Chakravarty et al., 2005, 2006). Pregnancy in women with lupus, especially those who have APLs, poses risks of preeclampsia and placenta insufficiency. Detecting pregnancies with poor outcomes could lessen adverse outcomes in women at high risk (Kim et al., 2016b). In anti-phospholipid syndrome (APS), HELLP syndrome seems to be associated with pre-eclampsia/eclampsia and earlier occurrence of eclampsia than in the general population (Le Thi Thuong et al., 2005). Women with thrombotic events have a higher risk of pregnancy complications compared with normal cases. Treatment with aspirin and low molecular weight heparin (LMWH) can improve the outcome in women with a history of miscarriage or early delivery as a result of placental dysfunction (Bramham et al., 2010). To manage all these situations, biomarkers of disease development and the effects of therapy are needed. The erythrocyte sedimentation rate (ESR) is not a reliable biomarker for estimating lupus activity in pregnancy because it also increases significantly in normal pregnancies (Clowse, 2007). In contrast, C-reactive protein (CRP) does not increase in all pregnancies and might be a more reliable biomarker in estimating inflammation in lupus pregnancy (Clowse et al., 2013). Recent studies on microRNAs (miRs) and genetic and cluster of differentiation (CD) markers have indicated the potential of these tools to detect different aspects of lupus and monitor lupus activity, especially in lupus pregnancy.

In this review, we discuss several biomarkers that may have an impact on pregnancies occurring in women with lupus as well as genetic and classic biomarkers that are used in lupus management.

The challenge of classic biomarkers

Complement

There is no clear profile for complement level, mainly C3 and C4, in lupus pregnancy because in inflammatory level, these criteria decrease and can be prognostic biomarker for pregnancy lose in women with higher lupus activity, however increase in complement levels reflect the level of hepatic protein synthesis in hepatocytes (Pickering and Walport, 2000; Ho et al., 2001). Recent data suggest that lupus anticoagulant is the best predictor of pregnancy loss in the first trimester and that decreased levels of complement proteins is another informative biomarker for pregnancy loss (Mankee et al., 2015). In the second trimester of pregnancy, low complement has been associated with the rates of pregnancy loss and preterm birth (Clowse et al., 2011). The complement activity test (Ch50) and detection of antibody to double-stranded DNA (dsDNA) are two valuable tests in predicting lupus pregnancy outcome (Shimada et al., 2017). Lupus patients generally have low levels of C3 and C4, which could be a diagnostic criterion of lupus. However, in pregnancy, the levels of C3 and C4 are increased as a result of the influence of estrogen on the liver. Thus, normal levels of C3 and C4 do not exclude disease activity in lupus pregnancy (Keisa et al., 2016).

APLs

APLs are present in 25% to 50% of lupus patients. The antibodies lead to thrombotic and obstetric complications in some lupus pregnancies and increase the risk of abortion, especially in women in the active phase of lupus (Ünlü et al., 2016; Lateef and Petri, 2017). Three notable APLs are lupus anticoagulant (LAC), anti-cardiolipin (a-CL), and anti-Beta2 glycoprotein (aβ2GPI); they should be considered in evaluating lupus activity in pregnancy in order to predict the pregnancy outcome (Lazzaroni et al., 2017). However, a recent study suggested that LAC, but not aCL and aβ2GPI, is an indicator for the poor outcome of pregnancy (Yelnik et al., 2016). APL is also a good biomarker in estimating therapeutic response to LMWH and low dose aspirin (LDA) during pregnancy, and the patient may show a more severe type of the disease (Lazzaroni et al., 2016). LAC may be associated with the risk of thrombosis recurrence in lupus pregnancy, and hence it is an important biomarker in pregnancy management of lupus patients (Medina et al., 2015). Several studies suggested an association of APL HELLP syndrome, although other pregnancy complications are not associated with APL (Blomjous et al., 2017).

Anti-dsDNA antibody

Anti-dsDNA antibody is a sensitive biomarker for predicting lupus and lupus activity, especially in renal problems (Linnik et al., 2005). Anti-dsDNA antibody isotypes (IgG/IgM ratio of anti-dsDNA antibodies) are associated with disease activity such as nephritis, and they can be used as prognostic biomarkers (Förger et al., 2004). The antibodies are an indicator of increased pro-atherothrombotic activity in lupus patients (Perez-Sanchez et al., 2017). Autoantibodies against major vault protein and anti-dsDNA antibodies are strong biomarkers in evaluating lupus activity (Budde et al., 2017). In anti-dsDNA antibody-negative patients, evaluation of anti-Smith (anti-Sm) antibody) is a valuable biomarker for lupus (Flechsig et al., 2017). An increase in anti-dsDNA level exceeding 20% is an alerting biomarker in lupus (de Leeuw et al., 2017). Anti-dsDNA IgG antibody downregulates miR-10a expression in human mesenchymal cells, similar to what occurs in inflammation (Tangtanatakul et al., 2017).

Anti-SSA/SSB/U1RNA antibodies

Neonatal lupus is a rare autoimmune disease that appears as a result of maternal immunoglobulin G in the fetus. RO/SSA and La/SSB are the two main antibodies in neonatal lupus (Heelan et al., 2013). Maternal anti-SSA/Ro antibody can cross the placenta and affect the fetus (Mendez et al., 2014).

SSA/Ro and/or SSB/La ribonucleoprotein complex antibodies in lupus pregnancy can alert to heart blockage without structural changes; neonatal lupus has also been reported with anti-U1RNP antibody that may also be associated to heart blockage (Izmirly et al., 2017). Neonatal lupus syndrome occurs in babies born from mothers with rheumatic systemic lupus erythematosus, Sjögren's disease, immune-mediated thrombocytopenia, thyroiditis, and undifferentiated autoimmune syndromes (Nasef et al., 2014). Generally, the fetuses of pregnant women who develop these antibodies are at increased risk of congenital heart block as well as hematologic and hepatic abnormalities (Boh, 2004).

The challenge to recent biomarkers

miRs

The expression pattern of miRs differs in various diseases. Contemporary studies have demonstrated the potential of miRs as diagnostic and prognostic biomarkers in various diseases. For example, miR-126 is higher in the blood of lupus patients and miRs may be associated with the pathogenesis of lupus (Wang et al., 2012b). Recent data indicated that miR-146a and miR-155 play different roles in immune response (Testa et al., 2017). Several miRs can affect DNA hydroxymethylation; they may potently hypomethylate DNA in lupus ad decrease lupus development (Zhang et al., 2013). Several miRs associated with lupus and lupus activities are summarized in Table 1.

Cluster of differentiation (CD) markers

CD markers are used to identify, count, study, purify, destroy, or participate in some other way with, leukocytes (Zola and Swart, 2016). CD markers constitute a classification system for monoclonal antibodies against surface molecules of leukocytes and other cells. $CD3^+$, $CD34^+$, $Bcl\text{-}2^+$, and $CD20^+$ are significantly higher in lupus patients (Ramezani et al., 2017). CD40/CD40L markers play important roles in T cell/B cell functional interactions, such as T cell-dependent humoral immune response and T cell activation of antigen presenting cells, are elevated in nephritic damage, and predict thrombotic events (Chamberlain et al., 2017; Kim et al., 2017). CD27 is a receptor present on most T cells. This marker is also increased in lupus patient serum and is related to disease activity, as its' elevation is the first reflection of T cell activation (Font et al., 1996). Recent studies on the CD70 B cell costimulatory ligand reported that hypomethylation and overexpression of CD70 on T cells elevates B cell costimulation and induces immunoglobulin overproduction (Ray et al., 2016). This epigenic change of CD70 may be associated with lupus severity (Ray et al., 2016). It also reflects disease activity in lupus patients (Balada et al., 2014). Recent evidence revealed that therapy targeting CD11a can be a useful lupus treatment method that acts by downregulating CD11a expression by the histone demethylase, JMJD3 (Yin and Lu, 2014).

Inflammatory cytokines

Interferon, tumor necrosis factor-alpha (TNF-α), and specific inflammatory interleukin (IL) such as IL-6 are elevated in lupus due to the activation of Toll-like receptors in response to clumping of apoptotic bodies (Lyn-Cook et al., 2014). IL-17A and IL-17A/IL-17F are notable biomarkers in lupus because they reflect T helper17 (Th17) flare-up in blood circulation (Brkic et al., 2014). A study in a Caucasian

Table 1 miRs associated with lupus and lupus activities

miR	Upregulation	Downregulation	Role	Reference
miR-21	*		Increased plasma miR-21 levels are associated with C3 and C4 levels in LN.	Guo et al., 2016
miR-451	*		Overexpression of miR-451 attenuates glomerular damage.	Sun et al., 2016
miR-223-3p	*		Correlates with lupus anticoagulant	Kim et al., 2016a
miR-16	*		Associated with primary Sjögren's syndrome	Papp et al., 2017
miR-125a-3p	*	*	Disease activity, treatment response	Zeng et al., 2017
miR-155		*	Pathophysiology of lupus; might be used as a biomarker. Urinary level can be a potent biomarker for disease activity and therapeutic responses.	Wang et al., 2010, 2012a; Testa et al., 2017
miR-210	*		Regulating the expression of HIF-1α and the differentiation of Th17 may be involved in the development and function of the immune response.	Huang et al., 2017
miR-146a		*	Increases phagocytic activity and suppresses inflammatory cytokine production. Urinary level can be a potent biomarker for disease activity and therapeutic responses. Disease severity	Pauley et al., 2011; Lu et al., 2012; Wang et al., 2012a
miR-185	*		Contributes to DNA hypomethylation of CD4 + T cells in pregnancies. miR-185 may represent a potential therapeutic target in lupus.	Liu et al., 2016
miR-26a, miR- 30b, miR-4286		*	Decrease in lupus nephritis	Costa Reis et al., 2014

Abbreviations: Lupus nephritis: LN; Complement protein 3 and 4: C3 and C4; hypoxia-inducing factor-1α: HIF-1α; T helper 17: Th17

population suggested that IL-12p70 is associated with renal damage in lupus patients (McCarthy et al., 2014). IL-6 is another notable inflammatory biomarker; the serum level of IL-6 is increased in flare-up of arthritis in lupus patients (Ball et al., 2014). The levels of IL-12 and IL-10 are higher in lupus patients, while that of IL-4 is decreased (Guimarães et al., 2017). We suggest that a profile of cytokines can help clarify lupus activity during pregnancy. Further studies focused on the influence of inflammatory cytokines on pregnancy are needed.

Genetic and epigenetic influences

Genetics and epigenetics play important roles in many aspects of lupus. Recent data indicate that the profile of DNA methylation changes or histone modifications can be helpful in estimating disease activity. Change in cytokine-mediated methylation of genes such as INF can be a diagnostic biomarker (Wang et al., 2017). Other changes that include PTPN22 polymorphisms such as rs1217414 and rs3811021 have been associated with decreased risk of lupus in a Chinese population, although polymorphisms such as rs3765598 increase the risk of lupus among these individuals (La Paglia et al., 2017). Genetic-epigenetic studies suggest that the genetic risk and T cell DNA demethylation are correlated with disease severity and flare-up, and also suggest that gender affects lupus flare-up, with males being at a higher risk (Sawalha et al., 2012). Another study revealed that factor V Leiden and mutation of the prothrombin gene can be responsible for thrombotic events in APL negative patients (Palatinus and Adams, 2009). TNFSF7 gene expression induces the synthesis of auto-reactive antibodies in lupus (Araki and Mimura, 2017). FcR polymorphisms also play a role in autoimmune disease pathogenesis (Kaifu and Nakamura, 2017). The collective results indicate the value of genetic analysis in case lupus and in the management of lupus pregnancy at different stages. We categorize the involved genes and relevant polymorphisms in Table 2.

Conclusions and future perspectives

Pregnancy is a challenging situation that becomes more complicated if the pregnant woman also has lupus. Hormonal changes due to pregnancy can lead to disease flare-up. Disease activity is a challenging subject in lupus pregnancy. Selecting the right biomarkers to predict different situations of lupus is important in lupus management. Tests for Ch50, APL, anti-dsDNA antibody, and anti-SSA/SSB/U1RNA antibodies are essential in estimating disease activity. Sensitivity of anti-dsDNA antibody testing has been proven and the value of this test is clear in lupus diagnosis and evaluating lupus activity. In case of neonatal lupus, especially when a heart defect is suspected, checking for anti-U1RNP and SSA/Ro and/or SSB/La ribonucleoprotein complex antibodies are informative in determining whether a fetus has a heart defect.

Recent genetic and miR findings can expand our vision of lupus and lupus activity, and will be beneficial in the prognosis and prediction of future events in lupus pregnancy. Urinary levels of miR-155 and miR-146a can be informative biomarkers in estimating disease activity. miR-223-3p has been associated with LAC, and miR-451 is an informative biomarker in glomerular damages. TWEAK, BAFF, and APOL1 genes and their polymorphisms are informative in estimating disease activity, especially in cases of renal effects, and they are important in monitoring and increasing the care for high-risk pregnant women.

Table 2 Genes and polymorphisms associated with lupus and lupus activities

Gene	Polymorphism	Role	Reference
ANKRD44	rs1429411	Primary disease pathogenesis, involved in INF-α production, have a high correlation with European INF-α	Kariuki et al., 2015; Qian and Nan, 2017
PLEKHF2	rs297573	Associated with DC and NK cell function, involved in INF-α production, primary pathogenesis, associated with IFN-α (however, secondary to the serological association)	Kariuki et al., 2015; Qian and Nan, 2017
Ox40 &Ox40L	rs4810485	Ox40 &Ox40 ligand (Ox40L) are associated with lupus risk, and the NL phenotype	Perricone et al., 2016; Sitrin et al., 2017
APOL1	G1/G2 alleles	LN who progress ESRD in African-American population	Freedman et al., 2014
BAFF	insertion–deletion variant, GCTGT→A (in which A is the risk allele) Increase lupus risk	Abnormal form of BAFF may also be a pathogenic factor lupus & NL.	Kang et al., 2017; Mackay, 2017; Steri et al., 2017
TWEAK	TWEAK/Fn14	Increased risk of atherosclerosis and activation was found in the lesion of CLE.	Badawi et al., 2017; Liu et al., 2017
HER2	-	Increase in LN	Reis et al., 2017

Abbreviations: Lupus Nephritis: LN; end-stage renal disease: ESRD; lupus erythematosus (CLE); dendritic cells: DCs; natural killer: NK

More genome-wide studies are needed in different populations to highlight alerting polymorphisms among them. Studies on PLEKHF2 and ANKRD44 polymorphisms in various populations are important because these genes encode INF-α production and are associated with primary pathogenesis. Hence, using multiple biomarkers, especially genetic markers and miRs, work strongly beside other sensitive biomarkers in lupus management during sensitive period of pregnancy and expand our choice in test ordering. However, there are lots of valuable biomarkers which reflect a plenty of information about body situation in lupus pregnant patient, the choice is yours. Find out what you are looking to know in patient situation and then go ahead.

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Compliance with ethical standards

The authors declare no conflict of interest. This article does not contain any studies with human participants or animals performed by any of the authors.

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