ABSTRACT

This article is contributed by the COBRE for Reproductive Health. The programmatic and scientific goals of this COBRE support a multidisciplinary, translational, and innovative program in women’s reproductive health. The research projects focus on using pre-clinical and human models to understand mechanisms of preeclampsia, gestational diabetes, preterm birth, IVF pregnancies, and the application of contemporary computational approaches to identify the networks and pathways underlying these devastating pregnancy complications. We discuss how novel observations emanating from the preeclampsia project can be leveraged to understand chronic diseases such as Alzheimer’s disease (AD). Proteinopathy is a hallmark feature of neurodegenerative disorders such as AD. We recently reported that preeclampsia (PE), a severe pregnancy complication, is another prevalent proteinopathy disorder in a younger population. This review provides a comprehensive discussion on shared etiology between PE and AD, establishing a novel blood test for their prediction and diagnosis, and a novel therapeutic option for these disorders.

KEYWORDS: preeclampsia, Alzheimer’s disease, proteinopathy, autophagy, blood test

INTRODUCTION

Diseases rarely manifest in isolation. Instead, most are part of a more complex pathway or “pattern” of connected conditions via underlying biological mechanisms. One common denominator in chronic and complex diseases is the role of inflammation and protein mimicry (misfolding and aggregation), which have gained recognition in several human diseases, including Alzheimer’s disease (AD). Symptoms may emerge across the life course, and large longitudinal databases may help recognize such patterns. Although pregnancy represents a modest portion of the life course, it is now recognized as a window into a woman’s future health. It often unmaskst predispositions to conditions that only become symptomatic decades later. Preeclampsia (PE) is a pregnancy complication that entails both maternal and offspring health consequences. Recent observations suggest that there is an epidemiological connection between PE and AD. Below, we will discuss the biological and clinical aspects of these devastating disorders and provide details that may lead to their early detection and treatment.

PREECLAMPSIA

Preeclampsia (PE) is a severe pregnancy complication with many manifestations for both mother and offspring. It is a multi-factorial and multi-organ pregnancy complication (Figure 1) that affects 3–8% of all pregnant women. It is diagnosed by de novo onset of hypertension and proteinuria at or after 20 weeks of gestation. PE can be diagnosed as an early (<34 weeks gestation) or late (>34 weeks gestation) onset severe complication as well as post-partum. This devastating pregnancy complication is a placenta-specific disease. In normal pregnancy, the placenta develops in a highly choreographed biological environment programmed by post-implantation cross-talk between the developing placenta and the maternal immune system in the deciduated endometrium. The placenta develops a trophoblast layer comprised of inner villous cytotrophoblasts and...
multi-nucleated syncytiotrophoblasts. A subpopulation of cytrophoblasts further differentiate into invading trophoblasts while syncytiotrophoblasts remain in direct contact with the maternal blood and act as a storage hub. A subgroup of invading trophoblasts acquires endovascular properties and migrates into constricted endometrial spiral arteries to remodel them into dilated, resistance-free vessels. These resistance-free arteries allow the free flow of nutrients and blood products from the mother into the intervillous space. After that, nutrients and oxygen can cross the syncytiotrophoblast layer into fetal capillaries inside each villous structure. It has been shown that PE is associated with defective spiral artery remodeling. This creates the onset of local ischemia/hypoxia, oxidative stress, and dysregulated immunity at the maternal-fetal interface. The result is a production of an inflammatory milieu and pathological placental nanoparticles (exosomes) containing misfolded proteins, which are released into the maternal circulation. 

Most importantly, we recently demonstrated that PE is a disease of proteinopathy (e.g., pathologic protein aggregation). We have reported that serum from PE patients can induce PE-like features in pregnant mice. In contrast, depletion of protein aggregates in serum blocks the onset of such features, including elevated blood pressure, proteinuria, glomerular endotheliosis, and fetal growth restriction. In this regard, the question arises on what precipitating events lead to the accumulation of protein aggregates in the placenta. We recently demonstrated that the PE placenta is associated with impaired autophagy. Autophagy is intricate cellular machinery to maintain homeostasis by its ability to clear cells of misfolded, aggregated protein structures and damaged organelles. We proposed that impaired autophagy allows the accumulation of misfolded, aggregated proteins in the PE placenta, causing trophoblast cell death, low differentiation into invading trophoblasts, and defective spiral artery remodeling. Moreover, we have shown that PE is associated with gasdermin D/caspase 3-mediated sterile inflammation in the placenta, a possible trigger for the onset of protein aggregation and trophoblast cell death. We anticipate that impaired autophagy and protein aggregation can be targeted for therapeutic intervention in PE.

ALZHEIMER’S AND RELATED NEURODEGENERATIVE DISEASES

The pathological hallmark of AD and its related neurodegenerative diseases is the accumulation of hyperphosphorylated tau as intracellular tangles and amyloid-β as extracellular plaques in AD and its prodromal condition, mild cognitive impairment (MCI). α-Synuclein accumulates as aggregated protein in Lewy bodies in AD and Parkinson’s disease, and other distinct proteins in other neurodegenerative diseases. Like PE, protein misfolding, aggregation, and impaired autophagy are also intertwined in AD. Tau can manifest in diverse isoforms stemming from distinct phosphorylation patterns and sites, imbalanced isomerization involving trans and cis configurations, and the preponderance of C-terminal microtubule-binding peptide region. Tau aggregates without amyloid-β involvement are also present in frontotemporal dementia and corticobasal degeneration. Although pathological protein misfolding and aggregation in neurodegenerative diseases have been accepted for a long time now, it has been difficult to leverage these findings for prediction or therapeutic intervention. To date, no well-defined, cost-effective, non-invasive blood test has been developed to diagnose AD. The widely used tests currently rely on cerebrospinal fluid protein analysis and positron emission tomography (PET) imaging, which are invasive and expensive. Recently, efforts have focused on blood tests for AD and MCI. However, they still depend on the identification of a single, non-aggregated protein with pre-evaluation manipulation of plasma samples.

DO THE SAME PROTEINS UNDERGO AGGREGATION IN PE, AD, AND MCI?

An important question that is often asked is whether we have access to pathological markers or a blood test that can enable diagnosis in much larger populations at a pre-AD age. Similarly, this argument can also be made for PE. We took advantage of our observations of impaired autophagy and protein aggregation in PE. We hypothesized that autophagy-deficient trophoblasts would not clear protein aggregates, and the accumulated aggregated structures can then be identified by an immunofluorescence probe. We have established an autophagy deficient human extravillous trophoblast cell line by stably transfecting a mutant autophagy gene that blocks the assembly of autophagosomes and reduces lysosomal expression machinery proteins. Our novel blood test for detecting serum protein aggregates depends on the exposure of autophagy-deficient trophoblasts to serum for 12–24 hours, fixing the cells, and then staining with an immunofluorescence dye for estimation of total protein aggregates. With specific antibodies, we can co-localize and identify individual proteins. Our data suggest that transthyretin, 

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Figure 2. Identification of protein components of serum aggregates from patients with preeclampsia, Alzheimer’s disease, and mild cognitive impairment.
amyloid-β, and hyperphosphorylated tau are common in the protein aggregates among PE, AD, and MCI. In contrast, the protein aggregates in AD, and MCI also contain α-synuclein [Figure 2]. This suggests that PE and AD share etiological biomarkers, and these observations may suggest a common therapeutic option(s) for both disorders.

**CAN IMPAIRED AUTOPHAGY AND PROTEIN AGGREGATION BE USED AS THERAPEUTIC TARGETS FOR PE AND AD?: COMMON THERAPEUTIC OPTIONS FOR PE AND AD**

To date, no effective therapy is clinically available for PE. The most effective treatment is the delivery of the placenta and fetus. PE is accompanied by severe health consequences not only during pregnancy but also in later life. PE patients are at higher risk of developing cardiovascular disease, diabetes, and possibly AD as suggested by our lab and that of others. Our group’s preliminary data are innovative in their support of a predictive assay for PE and investigation of a small, non-mammalian disaccharide molecule targeting autophagy and proteinopathy. This molecule can reverse the cellular and pathological events associated with PE. Our preclinical model for screening possible therapeutic options is a novel approach that is likely to lead to novel therapeutic options for PE.

Since both PE and AD share impaired autophagy and protein aggregation as key pathological factors, it is fair to predict that a drug that targets these cellular pathways may have therapeutic potential to prevent and/or treat these devastating conditions. We plan a similar therapeutic approach to prevent or treat the onset of AD-like symptoms. The disaccharide drug blocks appearance of AD-like pathology in h-tau AD transgenic mice. In in vitro experiments, this drug is quite potent in restoring autophagy and blocking protein aggregation in response to endoplasmic stress inducers such as hypoxia. The drug entails no detrimental effects in non-pregnant, pregnant, or wild-type mice. Notably, the offspring born to disaccharide-treated mothers were of normal weight and showed no ill effects through a few months of their life. As described above, the novel blood test and the disaccharide drug have become the focus of our recent efforts for planning pilot prediction and clinical trials for PE and AD.

**CONCLUSIONS**

A syndrome of younger age can rarely provide mechanistic and therapeutic insights for devastating chronic diseases such as AD, which entail a huge socio-economic burden on the healthcare systems. Diagnosis and treatment of such conditions have suffered from a lack of appropriate animal models, non-invasive blood tests, and target-based therapies. Thus, it is clinically important that a well-defined treatment modality be pursued that may eventually lead to randomized clinical trials. We discuss here that a pregnancy complication, preeclampsia, share etiological and therapeutic insights with AD and its prodromal MCI condition.

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**References**


