

SUMO-wrestling the pre-eclamptic placenta

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Preeclampsia (PE), which complicates ~14% of pregnancies worldwide (Peters & Flack, 2004), can lead to significant maternal morbidity, fetal and neonatal morbidity and premature birth. Despite the burden PE plays to society, the specific etiology for the initial onset and progression of PE is not fully understood. The central hypothesis concerning the development of PE involves an initial reduction in trophoblast invasion into the uterus, leading to a decrease in placental perfusion and reduced vascularization at the placental site, which activates a maternal inflammatory response. Finally, as the disease progresses, there is a generalized maternal endothelial dysfunction, release of excessive anti-angiogenic factors from the placenta and trophoblast debris in the maternal bloodstream (Purswani *et al.*, 2017).

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An emerging area of research has investigated the potential of pro-translational modifications that may play a role in the progression of PE. Small ubiquitin-like modifiers (SUMOs) modulate key cellular processes including DNA repair, cell cycle progression and protein localisation (Baczyk *et al.*, 2013). SUMOylation is reversible, and occurs mainly in the nucleus (Baczyk *et al.*, 2013), but also the plasma membrane and cytosol (Lomeli & Vazquez, 2011). In contrast to ubiquitination, SUMOylation is not a mechanism to tag proteins for degradation. Altered SUMOylation can be involved in the progression of a number of diseases including cancer and Alzheimers disease. Mammals express 4 SUMO isoforms (SUMO1-4), with SUMO-2 and SUMO-3 often described as SUMO 2/3 due to their high (97%) sequence similarity. SUMO proteins are covalently conjugated to target proteins via an activating enzyme E1, conjugating enzyme E2 and at times, a SUMO ligase E3 (Baczyk *et al.*, 2013). Despite the redundancy of some of the SUMO proteins (Lomeli & Vazquez, 2011), individual SUMO proteins may control specific downstream targets under normal conditions. The SUMO pathway is likely to play a diverse and important role in modulating cellular function as a recently developed human SUMO proteomics database identified 3,617 proteins that are SUMOylated across 7,327 SUMOylation sites (Hendriks & Vertegaal, 2016).

In this issue of the Journal of Physiology, Baczyk *et al.* (2018) investigate the SUMO pathway and its potential role in the development of PE through the localisation of SUMO proteins in human placentas, as well as their distribution in response to oxidative stress, similar to the conditions associated with PE. The authors found that placental expression of SUMO proteins demonstrated spatiotemporal differences. SUMO-1 and SUMO-4 were localised to villous cytotrophoblast in the first trimester and migrated to the syncytium that forms the maternal-facing surface of human placenta, by term. Conversely, SUMO-2/3 was identified as being evenly distributed throughout cytotrophoblasts and the syncytiotrophoblast across gestation. The unique spatiotemporal distribution of SUMO proteins may be critical for their function within a normal placenta during pregnancy.

Baczyk *et al.* (2018) also demonstrated that under oxidative stress conditions, which mimic the placenta compromised by PE, hyperSUMOylation of SUMO-1 and SUMO-4 was induced as well as translocation of SUMO-2/3 to the nuclear region (Baczyk *et al.*, 2018). In placentas compromised by PE, as well as normal placental explants exposed to oxidative stress, SUMO-1 and SUMO-4 protein expression were increased in the cytoplasm. As a downstream, target of SUMOylation is keratin, the

authors suggested that the SUMO pathway in PE may impair the stability of cytoskeleton filaments and thus promote trophoblast shedding into the maternal circulation that occurs late in the progression of the disease. However, it is likely that the SUMO pathway modulates numerous proteins involved in the progression of PE, as SUMOylation also modifies transcription factors that are dysfunctional in PE, namely glial cell missing-1 (GCM-1), downstream regulatory element antagonist modulator (DREAM), hypoxia inducible factor-1 α (HIF-1 α) and the downstream product placenta growth factor (PIGF). What currently remains unknown is the role of dysfunctional SUMOylation in the initial development of PE. Further, as SUMOylation is a dynamic and rapid process, what is yet to be determined is the sustainability of this modification in PE. Simply, is SUMOylation a long-term effect of the oxidative stress associated with PE or are these responses simply occurring due to an acute cellular stress?

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