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Uncovering Novel Roles for Matrix Metalloproteinases in Preeclampsia

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One of the main risk factors for the development of Cardiovascular disease (CVD) is hypertension. According to the American Heart Association, CVD is the leading cause of death in the US, with almost 1 in 3 deaths attributable to it. Remodeling of the vasculature, is one of the first detectable changes that occurs early on during the development/progression of hypertension and is a risk factor for subsequent cardiovascular events (19, 23). In fact, recent reports suggest that vascular remodeling and, in particular vascular stiffening, precedes the development of hypertension, and is itself a primary risk factor for CVD (2, 25). Vascular remodeling is primarily characterized by the presence of structural changes in the vascular wall that modify the passive lumenal diameter of blood vessels in the absence or presence of changes to the amount of wall material (17). We and others have demonstrated that both inward (the structural reduction in passive luminal diameter of blood vessels) and outward (the structural increase in passive luminal diameter) involves the production and activation of matrix metalloproteinases (MMPs), primarily MMP 2 and 9 (6, 10, 18). MMPs are a family of enzymes that degrade components of the extracellular matrix that comprise the vessel wall to which vascular cells attach. The activity of these enzymes during vascular remodeling promotes multiple processes that facilitate the structural modification of the vascular wall including the detachment, repositioning and migration of vascular smooth muscle cells, as well as the formation of new extracellular matrix proteins and the production of inflammatory cytokines by different cells of the vascular wall.

A prominent physiological process that involves one of the most rapid and greatest changes in vascular remodeling is pregnancy. In both pregnant humans and rodent animal models, vascular remodeling allows for uterine blood flow to increase significantly in order to provide the nutrients and environment for the proper development of the growing embryo and fetus. This occurs in association with a blood volume increase over the course of pregnancy. Concomitantly, vascular resistance is reduced via the outward remodeling of spiral arteries and the reduction in vascular tone that takes place as the placenta is being formed. In particular, cytotrophoblast invasion into decidualized endometrium and myometrium is posited to play an important role in the outward remodeling of spiral arteries within the uterine vasculature, by transforming them into conduit arteries of low resistance (15). In normal pregnancies, increased MMP-9 activity is implicated in trophoblast invasion (1), and both MMP 2 and MMP 9 are implicated in endometrial tissue and vascular remodeling. During this time, maternal blood pressure remains at pre-pregnancy levels or is marginally decreased (20).

A common pregnancy-related disorder that endangers the proper development of the embryo-fetus as well as the health of the mother is preeclampsia, a pathological condition in which vascular resistance is aberrantly increased and leads to maternal hypertension. Preeclampsia is associated with restricted fetal development and blunted uterine growth/expansion, and although the underlying causal mechanisms leading to preeclampsia have not been fully elucidated, it is postulated that reduced uteroplacental perfusion pressure (RUPP) and the subsequent placental ischemia/hypoxia play a role in increasing maternal vascular resistance. In this volume of AJP, Li et al. publish a research article in which they tested the

hypothesis that placental ischemia could modulate the expression and activity of MMPs through an inflammatory cytokine-mediated mechanism. They demonstrate that the presence of MMP-1 and MMP-7 is increased not only in the uterus and placenta of a RUPP animal model of preeclampsia, but also in the aortae of the dams. Furthermore, they demonstrate that presence of these MMPs in the uterus, placenta and maternal vasculature is associated with an increased production of collagen type I in those tissues. This suggests that an increased activity of multiple MMPs in the maternal circulation may be responsible for inducing maternal vascular remodeling processes that prompt the development of preeclampsia. Moreover, as Li et al. discovered that exposure of tissues from RUPP rats to a TNFα antagonist reduced their content of MMP-1 and MMP-7, their results further suggest that increased circulating levels of that inflammatory cytokine may be responsible for inducing the remodeling of maternal blood vessels and for prompting the development of preeclampsia.

The results from Li et al., provide new insights on our limited understanding of the mechanisms that cause preeclampsia and introduce a novel link between the role that RUPP may have on the regulation of MMP-1 and MMP-7 expression in maternal tissues during pregnancy and how the inflammatory cytokine, TNFα, may regulate that expression and the development of vascular remodeling/fibrosis and preeclampsia. Although novel and exciting, the study of Li et al. has a number of limitations that allow for the development of important questions that remain unanswered and should be addressed with additional research. For instance, it remains to be determined how TNFα exert its influence on the expression of MMP-1 and MMP-7, and whether that effect is limited to those MMPs only. It also remains to be determined whether the increased presence of MMP-1 and MMP-7 is indeed associated with an increased tissular activity of those enzymes. Moreover, it must be found if an increased activity of MMP-1 and MMP-7 is truly responsible for inducing maternal vascular remodeling/stiffening, increased vascular resistance and hypertension during the development of preeclampsia. Further research should also determine if the dysregulation of MMP-1 and MMP-7 presence/activity in preeclampsia affects the outward remodeling of the uterine vasculature directly, or if the effect is indirect. For example, the activity of multiple MMPs is implicated in the cytotrophoblast switch to an invasive phenotype, thus dysregulation of MMPs may lead to reduced infiltration of cytrophoblasts and a subsequent reduction in spiral artery transformation. Inadequate spiral artery transformation is a common feature of preeclampsia (26). There are reports that periarterial trophoblast cell expression of MMP-7 is reduced in early onset preeclamptic patients compared to healthy women (21) and that MMP-1 and -7 gene expression in decidua basalis tissue from preeclamptic patients is downregulated and MMP-1 protein levels are reduced in trophoblasts from the same tissue (14). These reports demonstrating a reduction in MMP-1 and -7 in trophoblasts suggest that the elevated MMP-1 and -7 levels in tissue from RUPP rats observed by Li et al may be exerting effects independently of modulating the trophoblast invasion phenotype in preeclamptic pregnancies.

As mentioned above, results by Li et al. demonstrate that the inflammatory cytokine, TNFα, plays a role in the upregulation of MMP-1 and MMP-7 expression, but the mechanisms by which TNFα may upregulates MMP-1 and MMP-7 in preeclampsia are not known. Serum TNFα levels are reported to be elevated during pregnancy in humans (13), though it would appear that the levels of TNFα change over the course of pregnancy. In a large longitudinal study, maternal plasma TNFα is reported to progressively decrease from the first, second and third trimesters in healthy pregnancies (9). In preeclamptic patients, plasma TNFα levels are reported to be higher than those in normotensive women in the third trimester of pregnancy (11,

12), suggesting that failure to attenuate TNFα signaling, may play a role in the development of preeclampsia, through the aberrant overexpression of MMPs.

TNFα is a cell surface molecule activated by ectodomain shedding. Pro-TNFα is tethered to the membrane via a transmembrane domain that is cleaved by a number of MMPs to generate the soluble, active form of the cytokine. The main sheddase implicated in the release of soluble TNFα into the circulatory system is ADAM17, also referred to as TNFα converting enzyme or TACE (4). One possible source for increased TNFα in preeclamptic pregnancies could be the placenta, which is subjected to hypoxia/oxidative stress as a consequence of reduced uteroplacental perfusion pressure (8). Oxidative stress is a known activator of ADAM17 (5). Lipid peroxides (24), a byproduct of oxidative stress, are increased in preeclamptic placentas as is ADAM17 expression (7)(16). It therefore follows that TNFα levels are also elevated in placentas from preeclamptic pregnancies (22, 24). It would appear that hypoxia/oxidative stress plays a role in this increase, as exposing placental tissue explants, harvested from normal pregnancies, to low oxygen or cobalt chloride to mimic the hypoxic response significantly increases the release of TNFα (3). Thus, a plausible model emerges in which hypoxia/oxidative stress in the placenta activates ADAM17, leading to the shedding and activation of TNFα and the subsequent increased expression-activity of MMP-1, -7, and likely other MMPs that impairs vascular remodeling and promotes preeclampsia (Figure).

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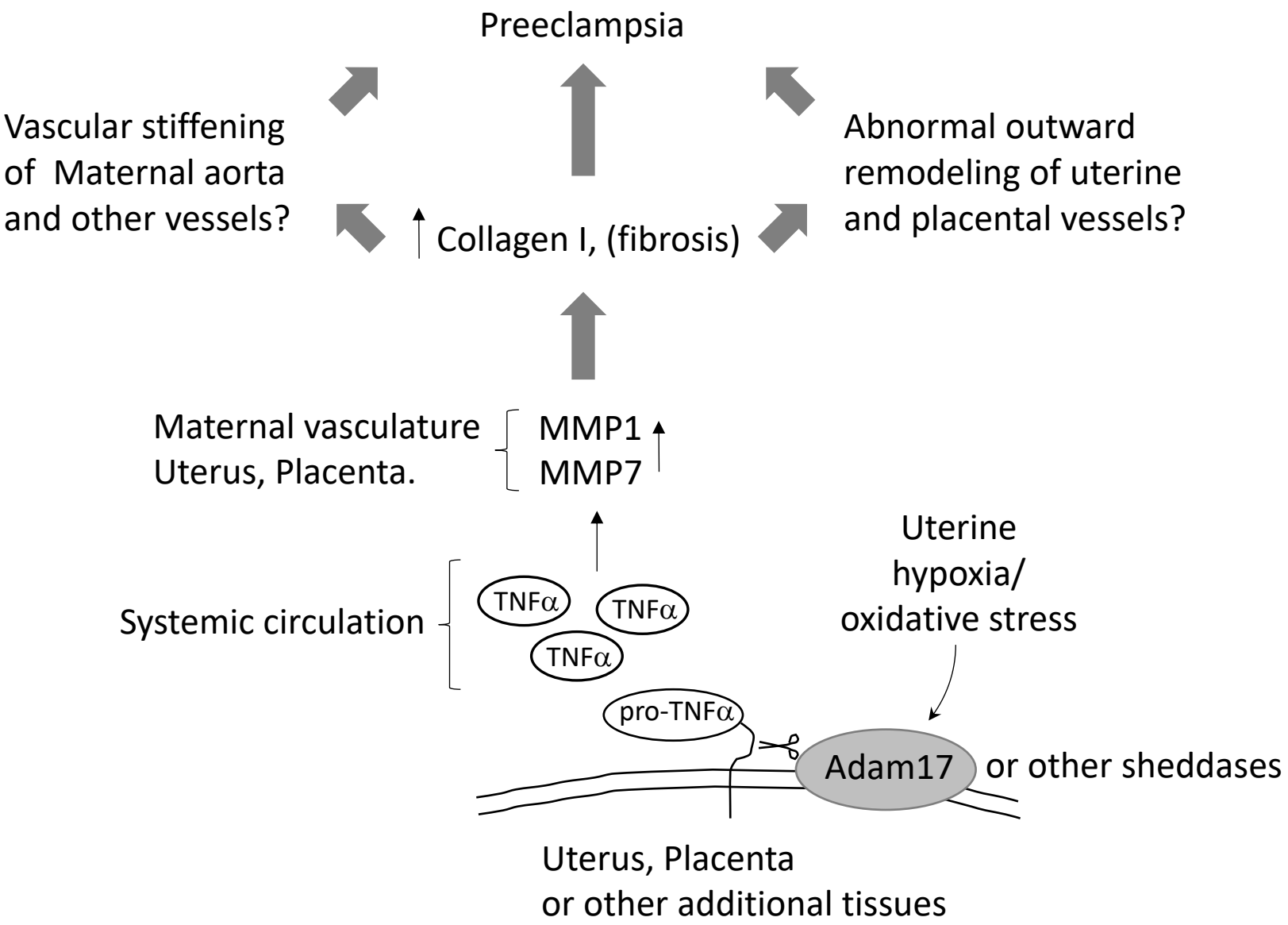
Preeclampsia
Vascular stiffening of Maternal aorta and other vessels?
Abnormal outward remodeling of uterine and placental vessels?
Collagen I, (fibrosis)
Maternal vasculature Uterus, Placenta.
MMP1
MMP7
Systemic circulation
TNFα
TNFα
TNFα
Uterine hypoxia/ oxidative stress
pro-TNFα
Adam17
or other sheddases
Uterus, Placenta
or other additional tissues