Physiological Smooth Muscle Cell Apoptosis Contributes to the Uterine Vascular Remodeling in Human Early Pregnancy

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Although equipped with the entire machinery driving cell proliferation and cell death, the turnover of the vascular smooth muscle cell (VSMC) layer within the vascular wall is quite low throughout the adult normal body. Vascular wall remodeling with VSMC apoptosis is routinely considered as associated with vascular diseases. This includes the development and regression of vascular thickening in hypertension, in advanced atherosclerotic plaques where VSMC apoptosis promotes plaque rupture, after angioplasty-induced arterial injury, as well as in arterial aneurysm where apoptosis is responsible for excessive slackening and rupture of the vessel media. Furthermore, in several animal studies, early pregnancy is a physiological situation where vessel wall remodeling plays a vital role. Indeed, in the first trimester of human pregnancy, vascular wall remodeling through degenerative changes converts the uterine spiral arteries located within the decidua basalis into toneless, widely opened arteries, thus enabling abundant blood supply to the maternal-fetal exchange area within the placenta. It is known that extravillous cytotrophoblasts deriving from fetal cytotrophoblastic shell migrate into segments of the spiral artery wall, through retrograde endovascular (invrasvation) and interstitial migratory pathways (extravasation) into the decidua basalis to trigger the disappearance of endothelial and VSMC. In this process, trophoblasts become buried intramurally within a fibrinoid layer, which replaces the original muscular medial layer. Such trophoblast invasion converts the ends of spiral arteries into a wide caliber vessel that can better deliver maternal blood to the expanding intervillous space of the placenta (Figure 1A). Defective or incomplete trophoblast invasion can result in pathological pregnancies, including preeclampsia and intrauterine growth restriction. Therefore, understanding the cellular mechanisms governing the interaction between intramural trophoblast and vascular wall cells is yet to be determined.

In this issue of *Circulation Research*, Keogh et al provide important initial insight into what these trophoblastic cells are doing to induce disorganization of the muscular layer of the spiral arteries over the first trimester of pregnancy. They based themselves on the idea that the loss of spiral muscular layer is because of apoptosis of the VSMC, apoptosis most likely triggered by a paracrine signal arising from trophoblasts. Besides the mitochondrial intrinsic pathway, the membrane-bound death receptors of the tumor necrosis receptor family represent the major autocrine/paracrine or extrinsic pathways that induce apoptosis in cells. The archetypal tumor necrosis receptor family death receptor is known as the Fas receptor. This receptor binds its cognate ligand FasL present in neighboring extracellular space, inducing receptor trimerization and binding of the adapter protein FADD (Fas Associated Death Domain) to the intracellular part of Fas receptor. The Fas/FADD complex converts procaspase 8 into active caspase 8, which in turn activates other downstream caspases, ultimately leading to DNA fragmentation and cleavage of cellular proteins. In previous studies, the same authors already made the interesting point that apoptosis triggered by the release of soluble FasL from invading trophoblasts may contribute to the loss of both endothelial and VSMC from the walls of spiral arteries during pregnancy. More recently, other trophoblast-associated mechanisms have been evoked for the induction of endothelial cell apoptosis in the utero-placental environment. Thus, a major histocompatibility complex, the so-called HLA-G1 complex has recently been proven to inhibit angiogenesis through an apoptotic pathway by direct binding to CD160 receptor expressed by activated endothelial cells.

Tumor necrosis factor apoptosis inducing ligand (TRAIL) is the more recently discovered second member of TNF family ligand that is highly homologous to FasL and which, like FasL, displays widespread expression throughout the body, including endothelial and VSMC. As quoted by Koegh et al, initial interest in TRAIL came from hope that TRAIL could selectively induce apoptosis in cancer cells but not in normal cells. The antitumorogenic properties of TRAIL prompted the rapid identification of TRAIL receptors designated as TRAIL-R or DR (for death receptor). Unlike TRAIL-R1 (DR4) and TRAIL-R2 (DR5), TRAIL-R3 and TRAIL-R4 have no functional death domain which confines minimal signaling capacity to these receptors. Because they keep the ability to bind TRAIL they have been designated as decoy receptors DcR1 and DcR2. TRAIL receptors DR4 and DR5 and Fas have overlapping intrinsic signaling pathways, in particular the ability to recruit FADD and to activate pro-caspase 8. The interesting point here is that all these receptors are widely expressed not only in malignant, but also in normal cells. Moreover, unlike DR4 and DR5, DcR1 and...
The aforementioned concept of decoy receptors for TRAIL, DcR2, are unable to induce apoptosis but instead seem to block it by trapping TRAIL. Koegh et al, are the first to establish a relationship between fetal trophoblast-derived TRAIL and cell death in VSMC. Although VSMC have been proven to express Fas, the specific question of whether they also express the TRAIL-Rs has never been specifically addressed. Using flow cytometry and immunohistochemistry, Koegh et al detected the expression of both DR4 and DR5 in VSMC of human aortic and spiral artery VSMC. Exogenous TRAIL, either added to aortic VSMC or perfused into denuded spiral artery segments induced smooth muscle apoptosis, an effect proven to be mediated by DR4 and DR5. Conversely, they found that extravillous trophoblasts isolated from first trimester placenta express TRAIL. Impressively, in a video they also show direct contact between trophoblast and aortic SMC, with typical blebbing of the VSMC several hours after interaction between the cells. Also, a recombinant human DR4-Fc construct inhibits VSMC death induced by trophoblast-derived FasL binding to Fas on the EC (not shown).

Thus, referring to the studies in the field, it is tempting to hypothesize that a putative decrease of the ratio between DcR and DR expression in spiral VSMC during first trimester pregnancy, attenuates the competition level for the binding to TRAIL, which in turn facilitates medial disruption by trophoblast-derived TRAIL. However, DcR regulation in a physiological situation remains to be assessed. Future studies examining the relative expression of DcRs and DRs in extravillous trophoblasts over the first trimester of pregnancy would help in clarifying this question.

Although it is conceivable that trophoblasts indeed induce spiral artery smooth muscle disorganization, it can be discussed the possible endovascular or interstitial origin of the trophoblast invading the vascular wall in vivo and responsible for the VSMC death. The endovascular route would imply that trophoblast-associated endothelial cell apoptosis and endothelium vacuolation would represent an initial crucial step which leads to media disorganization. Such a situation may occur deeper in the myometrial bed where interstitial trophoblast are less dense, compared with the most decidua basalis where intramural trophoblasts have better chance to be derived from interstitial trophoblasts much more concentrated in the decidual interstitium. Overall, these observations prompt the controversial question as to whether endovascular and interstitial become distinct trophoblast subtypes, taking separate mechanistic pathways to contribute to the remodeling of spiral arteries. These questions require further investigations.

In other respects, a link between DR4 and DR5 and the status of the p53 tumor suppressor gene has also been extensively documented. It is now well accepted that this transcription factor controls critical steps in the cell cycle and mediates cell apoptosis, not only through the mitochondrial pathway, but also via a receptor-mediated pathway involving the DRs. Moreover p53-response elements have been shown to be present on the DR5 gene promoter. Finally events which upregulate the DRs, like γ irradiation in spleen and small intestine, have also been shown to be mediated by p53. Future goals may involve the analysis of the p53 status in trophoblasts during early pregnancy.

Another relevant question raised by the studies of Keogh et al, is whether remodeling of spiral arteries depends entirely on the action of trophoblasts or whether other cells might be involved. In this context, the role of uterine natural killer cells (uNK) has been questioned several times in animal studies over the recent years. The hypothesis that uNK may be a physiological actor of spiral artery remodeling has been prompted by a series of observation, including an increased number of uNK in the placental bed and the existence of molecular interactions between uNK and the HLA-antigens on the trophoblasts. As a summary, two major possible roles of uNK in spiral artery remodeling have been proposed. In the first proposition, uNK directly acts on vascular smooth muscle remodeling. This assumption is strongly supported by the absence of smooth muscle layer remodeling in NK-deficient mice, in contrast to normal control animals. Interferon-γ appeared to be the key cytokine produced by murine uNK and participating in the spiral artery modifications. Besides the direct action of uNK cells on spiral artery smooth muscle, it
has also been suggested that uNK cells control spiral artery remodeling by controlling the trophoblast invasion. In support to this, it has recently been demonstrated that human decidual NK cells, but not circulating NK cells, control trophoblast invasion through the release of cytokine IL-8 and chemokine interferon-inducible protein 10 that bind to receptors expressed on invasive extravillous cytotrophoblasts and stromal cells present in the decidua basalis. Over-all an array of previous findings show that uterine NK cells have beneficial effects in early pregnancy instead of being detrimental.

Functional studies of TRAIL system and its potency in triggering spiral artery smooth muscle apoptosis in pre-eclamptic women should be useful in determining whether DRs in these cells can be considered as potential therapeutic targets. Apoptosis in VSMC has essentially been described as being involved in most vascular diseases. But as Keogh et al make clear in this issue of Circulation Research, physiologic VSMC apoptosis also takes part in regulating the reproductive process.

Sources of Funding
The publication costs of this editorial are supported by the Institut National de la Santé et de la Recherche Médicale, France. The authors are financially supported by the Institut National de la Santé et de la Recherche Médicale, France (J.J.H., P.L.B.), the University Louis Pasteur Medical School, Strasbourg, France (J.J.H.), the University Paul Sabatier, Toulouse, France (P.L.B.), and the European Union Network of Excellence EMBIC (Control of Embryo Implantation) (P.L.B.)

Disclosure
None.

References


Key Words: spiral artery, placenta, death receptors, TRAIL.
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Circ Res. 2007;100:754-756
doi: 10.1161/01.RES.0000263394.59727.ca

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