Regulation of the human umbilical circulation in pregnancies with harmonious or restricted fetal growth

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Main research interests

Our research team is conducting biomedical research projects in the field of developmental origins of adult health and disease (**DOHaD**), with a particular interest to intrauterine growth restriction (IUGR) and perinatal hypoxia.

Adverse events occurring *in utero* or soon after birth could induce long-term adverse effects, thus increasing the risk to develop chronic diseases in adulthood. Notably, individuals born after IUGR have an increased risk to develop cardiovascular and metabolic diseases later in life.

Our research projects aim to better understand cellular and molecular mechanisms implicated in the developmental programming of pathological responses, in order to identify early biomarkers and to design novel therapeutic strategies and/or preventive interventions.

Our projects include *ex vivo* assessment of **vascular reactivity**, using isolated vascular rings in organ chambers, with a particular attention to the nitric oxide (NO)/cyclic GMP relaxing pathway. Biochemical and molecular investigations are then performed to identify the mechanisms contributing to the observed vascular dysfunction.

Finally, we pay a specific attention to the **sexual dimorphism** in the observed alterations. Indeed, sex is an important biological factor, which has been often neglected. However, there is increasing evidence that males and females display important differences in physiological responses and susceptibility to diseases, particularly in the field of cardiovascular diseases. Our research team observed several differences in vascular physiology and pathology depending on the sex of the individual.

Proposed project

We previously demonstrated that intrauterine growth restriction (IUGR) was associated with structural and functional alterations in the human umbilical cord (1). Notably, NO-induced relaxation was impaired in the umbilical vein of growth-restricted females as compared to neonates with harmonious fetal growth (AGA, appropriate for gestational age) (1-2). This sex-specific alteration of NO-induced relaxation was linked to several alterations in the NO/cGMP signaling pathway (2).

Now we plan to investigate the relative contribution of the different vascular cell types (endothelial progenitor cells, endothelial cells and smooth muscle cells) to the umbilical circulation in physiological and pathological conditions. We have developed a method to isolate primary cells from human umbilical arteries and vein and from cord blood. Biological samples will be collected in term newborns, with or without IUGR. After isolation and culture of vascular cells, the functional properties of these cells will be studied to identify potential alterations; molecular investigations will then help to determine the implicated mechanisms. Finally, interactions between the different cell types will be investigated by performing co-cultures or using conditioned media transfer.

This study will lead to a better understanding of the sex-specific regulation of the human umbilical circulation in pregnancies with harmonious fetal growth or IUGR, and thus contribute to devise potential therapeutic interventions to prevent or limit the development of IUGR and its short- and long-term adverse consequences.

1. Intrauterine growth restriction is associated with structural alterations in human umbilical cord and decreased nitric oxide-induced relaxation of umbilical vein. Peyter AC, Delhaes F, Baud D, Vial Y, Diaceri G, Menétrey S, Hohlfeld P, Tolsa JF. Placenta. 2014; 35(11):891-9.

2. Intrauterine growth restriction is associated with sex-specific alterations in the nitric oxide/cyclic GMP relaxing pathway in the human umbilical vein. Beaumann M, Delhaes F, Menétrey S, Joye S, Vial Y, Baud D, Jacquier Goetschmann M, Tolsa JF, Peyter AC. Placenta 2020; 93:83–93.