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Could trophoblasts be the immune cells of pregnancy?

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Trophoblasts, cells that form an outer layer around a fertilized egg and develop into the major part of the placenta, have now been shown to respond to inflammatory danger signals, researchers from Norwegian University of Science and Technology (NTNU) found in a recent study published in *Journal of Reproductive Immunology*, December 2014.

The researchers said their findings were an important step in understanding how inflammatory responses in the placenta can contribute to the development of pregnancy disorders such as preeclampsia.

The trophoblast inflammatory response varies from one pregnancy to another.

"This is also the first time researchers have shown the many different inflammatory mechanisms that trophoblasts have," said Guro Stødle and Line Tangerås, the two first authors of the study.

Infections caused by bacteria or viruses and tissue injury may set off an inflammatory response in the human body, in which immune cells, blood vessels, proteins and other mediators work together to eliminate the threat and repair the damage.

"Pregnancy is a delicate setting where the mother and fetus must adapt properly to each other to coexist, and an inflammatory response can disturb this delicate balance and cause complications. This is seen in

preeclampsia, a potentially severe inflammatory pregnancy disorder threatening both the mother and fetus," Stødle says.

In preeclampsia, inflammation in the placenta contributes to poor placental development, later leading to systemic inflammation in the mother, manifesting as high blood pressure and protein in the mother's urine.

Inflammatory responses to injury or infection are directed by Toll-like receptors (TLRs). They are central to the body's danger response machinery and initiate inflammation by recruiting all cells needed to repair the injury. The TLR expression of a cell defines its potential to respond to danger and take part in inflammation.

Fetal-derived trophoblasts are the main cell type of the placenta and initial reports indicate that these cells may express TLRs.

"To investigate a role for trophoblasts in placental inflammation, we performed a study in which we aimed to determine whether trophoblasts of early pregnancy expressed the ten TLRs and whether these receptors were responsive to danger signals," Tangerås said.

The researchers collected first trimester placenta tissue samples at the Department of Gynecology and Obstetrics at St. Olavs Hospital. The laboratory experiments were performed at the Centre of Molecular Inflammation Research (CEMIR) at Norwegian University of Science and Technology.

"We discovered that trophoblasts isolated from first trimester placentas showed a broad TLR expression," Stødle said.

Functional responses to danger signals were detected for six of the TLRs, and the activation led to production of pro-inflammatory

cytokines.

"This clearly indicates a role for fetal trophoblasts in danger response and inflammation in the placenta, and that trophoblast TLRs may play an important role in inflammatory diseases during pregnancy, such as preeclampsia," the researchers said.

The research group at CEMIR will continue to study how the trophoblast-mediated immune activation in the placenta can help us understand the underlying harmful inflammation that is associated with a pre-eclamptic pregnancy.

To understand how inflammatory responses can contribute to the development of preeclampsia, the researchers will continue this work by comparing specific danger responses in blood samples and samples from placentas from healthy pregnancies with samples from women who developed preeclampsia.

More information: Line H. Tangerås, Guro S. Stødle, Guro D. Olsen, Ann-Helen Leknes, Astrid S. Gundersen, Bente Skei, Anne Jorunn Vikdal, Liv Ryan, Bjørg Steinkjer, Merete F. Myklebost, Mette Langaas, Rigmor Austgulen, Ann-Charlotte Iversen, "Functional Toll-like receptors in primary first-trimester trophoblasts", *Journal of Reproductive Immunology*, Volume 106, December 2014, Pages 89-99, ISSN 0165-0378, dx.doi.org/10.1016/j.jri.2014.04.004

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