

Is anybody out there? Human embryos make contact with mother-to-be

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Scientists at The University of Manchester and Manchester University NHS Foundation Trust have discovered a new way that human embryos are able to communicate with mothers-to-be after just six days.

The team, who publish in the journal *Human Reproduction* today, reveal for the first time that [embryos](#) are able to detect foreign (non-self)

cells—including pathogens—in their environment.

The in vitro (procedures performed outside of the body, usually in a lab) study was funded by the Medical Research Council and NIHR Manchester Clinical Research Facility.

According to the research team, when foreign cells are detected by special proteins called Toll Like Receptors (TLRs) in the embryo, it releases a type of protein called a cytokine.

Elsewhere in the body, the cytokine—called Interleukin-8 (IL8)—usually plays a role in the immune system by recruiting neutrophils to a site of inflammation.

However, its role in the relationship between embryo and mother to be is yet to be discovered.

The scientists observed the behavior on days five and six of the embryos' development, when it is free living in the female body, just before it implants in the lining of uterus and pregnancy begins.

Scientists already know that TLRs are found in the fallopian tube and vagina—known as the maternal tract.

Human sperm have also been shown to express TLRs 2 and 4, however, there has not been similar investigations of [human embryos](#), until now.

Lead author Professor Daniel Brison is an Honorary Professor at The University of Manchester and Scientific Director at the Department of Reproductive Medicine Saint Mary's Hospital

He said: "Early human embryos are highly sensitive to their local environment, however before this study, relatively little was known

about how they detect and respond to specific environmental cues.

"We have discovered a signaling system generated by the embryo which allows communication with mum in a new way.

"We already knew that embryos communicate with mum when they begin to implant, but we don't know why this new signaling happens.

"Perhaps this is an additional way of signaling an [inflammatory response](#) to the maternal tract in response to pathogens, or to modulate the implantation process and the initiation of pregnancy.

"Our data also suggests a balance between suppression and stimulation of the innate immunity response in embryos. That may reflect the need for embryo survival in the presence of benign foreign cells, versus the need for the maternal tract to respond to infection."

The expression of Toll Like Receptors and related genes in human embryos was assessed by a literature search of published data.

Then, 25 five-day-old human embryos were cultured in the presence of Poly (I: C) and flagellin—molecules—or ligands—known to bind to Toll Like Receptors TLR3 and TLR5.

Other TLRs—expressed from the 22 known TLR genes—were not investigated by the team.

Then on day six, they measured gene expression and cytokine production and compared the results to controls.

Professor Brison added: "Though it's very early days, this research gives us a basic understanding of what happens to the embryo in early pregnancy.

"It has implications for both natural and artificial conception, since infections can occur in both the maternal tract and In vitro Fertilization media used for embryo culture and transfer to the uterus.

"It might one day shine a light on infertility: why some embryos do not implant into the uterus, or even help us to identify the quality of IVF embryos developing in culture.

"But much work needs to be done before we can reach that stage. And further investigations are required to determine whether the TLR stimulation response is effective during the embryonic journey in the fallopian tube."

Human embryos surplus to treatment requirements were donated with informed consent from several Human Assisted Reproductive Technology centers.

More information: Wedad S Aboussahoud et al, The expression and activity of Toll-like receptors in the preimplantation human embryo suggest a new role for innate immunity, *Human Reproduction* (2021). [DOI: 10.1093/humrep/deab188](https://doi.org/10.1093/humrep/deab188)

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