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Scientists show NLRP2 protein's role in maintaining fertility later in life

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Led by Prof. Mohamed Lamkanfi (VIB–Ghent University), researchers have demonstrated in animal models that a protein called NLRP2 plays an important role in early embryogenesis, the process of cell division in fertilized eggs that occurs before they implant into the lining of the uterus. In addition, the protein was shown to become more important with increasing maternal age, as blocking NLRP2 in eggs prevented them from developing in blastocysts. As a similar protein exists in humans, these insights may lead to greater understanding of reproductive disorders and novel paths to treatment. The study was recently published in the *Journal of Experimental Medicine*.

About one in six couples experience fertility issues, and maternal age is considered the primary factor driving the demand for in-vitro fertilization and other reproductive technologies. Although scientists have a good understanding of the roles hormones play in embryonic development, little is known about the mechanisms that govern early embryogenesis. The study conducted by Prof. Lamkanfi and his team have helped to shed light on age-linked elements that influence embryonic development.

No role in immunity or inflammation

Before this research, scientists had widely believed that the NLRP2 protein played a role in the immune system, as similar proteins were found to have key roles in controlling infections and regulating

inflammation. Prof. Lamkanfi's team had initially expected similar findings for NLRP2 and focused the study accordingly – but they were surprised not to find any link between the protein and immune functions.

Prof. Mohamed Lamkanfi (VIB-UGent): "Contrary to expectations, we failed to find any role for NLRP2 in immunity and inflammation. As a result, we refocused our studies on reproduction after discovering that NLRP2 is specifically produced by egg cells, or oocytes, showing that the protein is critical to the maintenance of oocyte quality later in life."

Found to affect maternal fertility

The research, which was conducted in mice, suggests that mutations in NLRP2 may give rise to early menopause and other conditions associated with the pathological decline of maternal fertility. Older adult mice deficient in NLRP2 showed strikingly lower rates of reproduction compared with younger NLRP2-deficient mice, suggesting that the protein becomes more important to fertility as the mice aged.

Prof. Lamkanfi: "At the same time as our research was being conducted, small human studies provided anecdotal evidence that mutations in human NLRP2 might be linked with increased susceptibility to reproductive disorders. Our findings further support a role for the protein in the reproductive system."

The future of NLRP2 research

Humans encode a second NLRP2 gene – named NLRP7 – that is found to be mutated 60% of the time in patients that experience familial cases of biparental molar pregnancies, which occur when fertilized eggs implant into the wall of the uterus but fail to develop into normal embryos.

More information: Anna A. Kuchmiy et al. NLRP2 controls age-associated maternal fertility, *The Journal of Experimental Medicine* (2016). DOI: 10.1084/jem.20160900