Why the immune systems of prematurely born babies are susceptible to deadly infections

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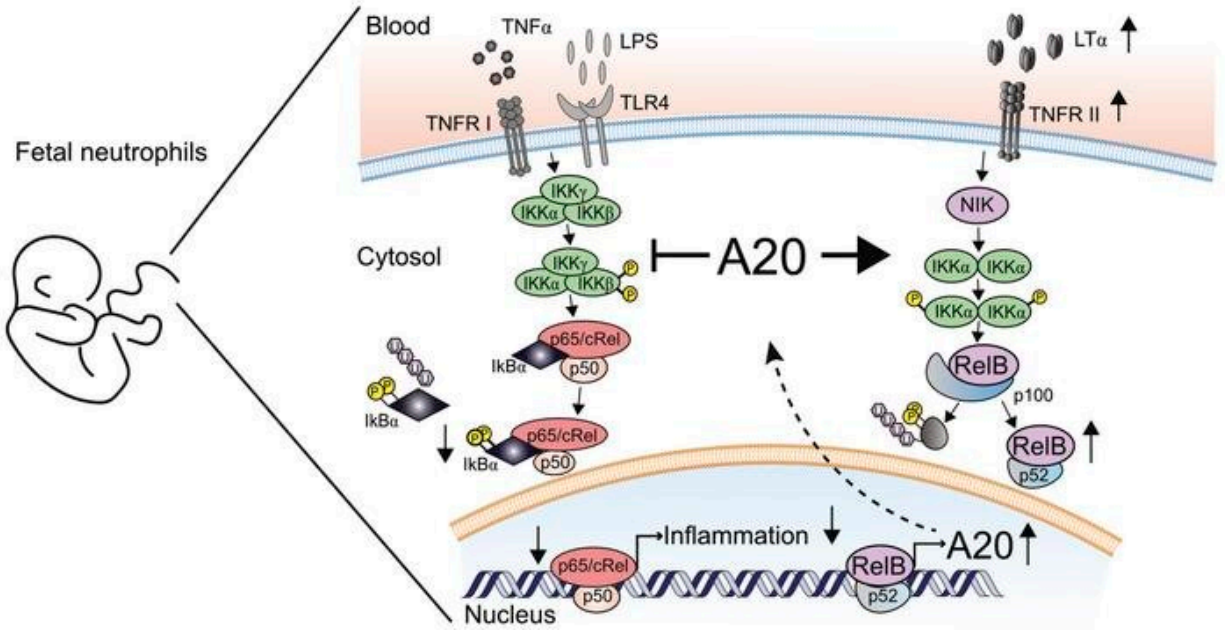

Graphical abstract. Credit: *JCI Insight* (2023). DOI: 10.1172/jci.insight.155968

Every year, thousands of babies in Germany are born many weeks too early and often have to struggle for months. The earlier the babies are born, the higher the risk of life-threatening complications. Infections can lead to sepsis and are among the most frequent causes of death.

"In the case of very prematurely born infants, a bacterial infection can lead to death within hours," says LMU physician Prof. Markus Sperandio. The physiologist and former pediatrician and neonatologist researches the causes of this high susceptibility to infection together with his team at LMU's Biomedical Center Munich. Now the researchers have demonstrated that an immunostimulatory signaling pathway is suppressed in the developing immune system.

The findings are published in the journal *JCI Insight*.

Important immune cells in prematurely born infants do not work properly after birth

Sperandio had already shown in earlier studies that in the fetus and in newborns important cells of the innate immune system—so-called neutrophils—do not work as in adults. In contrast to the situation in adults, fetal and neonatal neutrophils do not manage to sufficiently attach to the walls of blood vessels and extravasate into inflamed tissue. This is necessary, however, to trigger an inflammatory response and thus initiate immune defense.

Now the LMU researchers, working in collaboration with the Children and Women's Clinic at University of Munich Hospital, have investigated which mechanisms are behind this immaturity. By means of a so-called transcriptomic analysis, they compared the gene activity of neutrophils in umbilical cord blood of premature and full-term babies with adult neutrophils. Compared to adults, there is a lot of gene activity in premature and full-term infants that counteracts immune defense. "In this case, these neutrophils act as if they were switched off," says Sperandio.

Balance shift of immunoregulatory signaling

pathways

This particularly affects signals transmitted via the NF-κB signaling pathway, which plays a decisive role in immune and inflammatory responses. It consists of two possible pathways for signals: one that promotes inflammation and one that can suppress it. Therefore, the activity of these two pathways must be finely balanced for proper regulation of the immune response.

"Our experiments have shown that this balance is shifted towards the anti-inflammatory pathway in fetal and neonatal neutrophils," says Sperandio. "Whereas this regulation of neutrophil function is clearly a requirement for normal fetal growth in utero, it leads to immune defense problems in prematurely born infants who have to adapt 'too soon' to the world outside the uterus."

To what extent these findings will be a springboard for new therapeutic approaches in the future remains to be seen. "Due to the complex processes in the growing fetal and neonatal organism, maturation-adapted therapies are conceivable but remain a long way off at this stage," says Sperandio.

More information: Ina Rohwedder et al, A20 and the noncanonical NF-κB pathway are key regulators of neutrophil recruitment during fetal ontogeny, *JCI Insight* (2023). DOI: 10.1172/jci.insight.155968

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