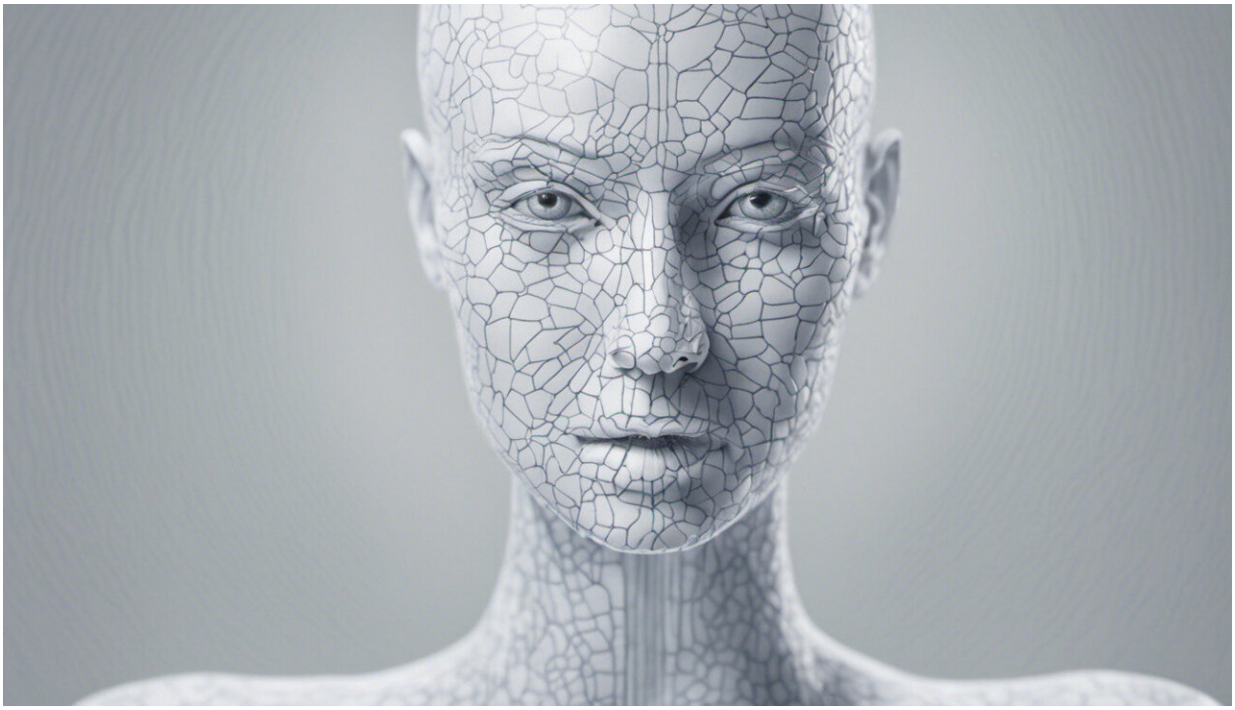
Better understanding of glucosamine action may help to avoid birth defects in diabetic pregnancies

July 27 2016, by Eric Bender



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Most pregnant women with well-controlled diabetes give birth to healthy children. But their babies run much higher risks of birth defects than babies born to women without diabetes, because very early in embryonic development, the babies are exposed to higher levels of glucose in

maternal blood.

In research done in mice, Harvard Medical School researchers at Joslin Diabetes Center have uncovered new clues about the role that glucosamine, another sugar that circulates in blood, can play in early embryonic development.

If glucosamine performs similarly in humans, understanding its role eventually may aid in avoiding birth defects, said Mary Loeken, HMS associate professor of medicine (physiology) and an investigator in the Section on Islet and Regenerative Cell Biology at Joslin. Moreover, her work suggests an approach to developing stem cells that might help to strengthen future regenerative therapies for many diseases.

"The implications of this research go beyond the diabetic population," said Loeken, senior author on a paper published in *Scientific Reports*.

Loeken, who studies how diabetes drives changes in the early embryo that lead to birth defects, began looking at a gene called GLUT2 after other researchers showed that it is activated in mouse embryos. GLUT2 can transport glucose from blood into cells, but it doesn't perform this efficiently unless the levels of glucose are very high. So what was its role in embryonic development?

Studying mouse models of diabetes, Loeken and her team first showed that modifying the mice genetically to lack GLUT2 protected the mice from producing embryos suffering from malformations when the mothers were diabetic. However, the Joslin scientists also found evidence suggesting that fewer of these embryos were surviving even when the mothers were not diabetic. This indicated that GLUT2 performs some function that is important for early embryonic survival.

Other researchers had shown that GLUT2 also can transport

glucosamine, but whether GLUT2 functions as a glucosamine transporter under normal conditions has not been demonstrated. Loeken thought that embryo cells may need to obtain glucosamine from the mother's circulation. To examine the role of glucosamine, which can't be effectively adjusted in live animals, the Loeken lab created a line of mouse embryonic stem cells with activated GLUT2 that was grown in a culture with levels of glucose that are normal in mouse blood—unlike most stem cells, which are grown in very high levels of glucose.

In their latest paper, the investigators showed that GLUT2 can move glucosamine into these stem cells, and giving the cells this sugar greatly increased their rates of proliferation, while not having much effect on the ways they differentiated into other forms of more specialized cells.

Boosting proliferation could help embryos develop normally. Early embryos are "rapidly proliferating sets of cells," Loeken said. "They need to make more of themselves and they need to grow in size."

Among its functions in the cell, glucosamine is needed to assist in protein processing and the creation of signaling proteins. Cells can make glucosamine from glucose, but that takes away critical resources from energy production and building blocks for cell growth. "If a cell can't take up glucosamine, it will sort of starve," she said, so GLUT2 is critical. Additionally, she said, her research suggests that glucosamine, under some conditions, may be considered an essential nutrient for embryonic cells.

However, the GLUT2 protein also can play a destructive role if the maternal blood has high levels of glucose. "GLUT2 is not a very good glucose transporter under normal conditions, but when glucose levels are high it transports glucose very efficiently," Loeken points out. "So if the mother has diabetes, it could allow the embryo to act like a glucose sponge."

Her earlier research in mice embryos revealed that exposure to high blood glucose levels for a little as one day can produce a high rate of defects in the neural tube, the predecessor to the brain and spinal cord.

"Additionally, at high glucose concentrations, transport of glucosamine is significantly inhibited," Loeken adds. "This suggests that the adverse effects of high glucose on embryos are not just that more glucose is getting into cells, but also that less glucosamine is being taken up. Therefore, the beneficial effects of glucosamine on growth may be compromised."

Loeken cautions that no one has yet shown whether GLUT2 is expressed in human embryos, although research by other investigators has shown a correlation between mutations of GLUT2 in humans and risk of neural tube defects.

Her work also suggests that the high proliferation ability of mouse embryonic stem cells created in normal levels of glucose with activated GLUT2 may help to point the way for generating stem cells for future regenerative medicine treatments.

Most researchers now engineering embryonic stem cells or embryonic-like "induced pluripotent stem cells", with either mouse or human cells, grow them in glucose levels that are much higher than is normal in the body. That means that the metabolism of these new cells doesn't match the conditions the cells may find at the organ they are meant to repair

Today, glucosamine tablets are sold for joint pain, but they are not recommended for pregnant women, a point that Loeken stresses. Glucosamine mechanisms in humans are not fully understood, and there are unfavorable effects when glucosamine levels get too high. Even if adding small amounts of glucosamine eventually might be proven to be helpful, achieving the right levels in a pregnant woman's blood "would

be a delicate balance," she said.

More information: Jin Hyuk Jung et al. Embryonic Stem Cell Proliferation Stimulated By Altered Anabolic Metabolism From Glucose Transporter 2-Transported Glucosamine, *Scientific Reports* (2016). DOI: 10.1038/srep28452