Why the body’s response to pregnancy may help us better understand cancer

Svetomir Markovic knew something was different. Sometime around 2010, a fellow scientist at the Mayo Clinic had agreed to donate her healthy blood for use in the research laboratory where Markovic studies the interface between cancer and the immune system. In previous testing of the woman’s blood, her immune cells functioned normally. But then something changed, and nobody knew why.

“We thought our assays weren’t working,” recalls Markovic, a hematologist and oncologist whose research focuses on developing immunotherapies for melanoma and non-Hodgkin’s lymphoma. Or perhaps the reagents had expired, or the laboratory’s machines needed fine-tuning. For nearly a month, the team puzzled over the woman’s changing lab values. “At this point, she was quite visibly pregnant,” Markovic laughs, noting how obvious the answer seems in hindsight. “It finally dawned on me — what if it’s the pregnancy?”

Sensing that the question’s answer could have implications for his cancer research, Markovic decided to study cells of the placenta, the disk-shaped organ that develops during pregnancy and connects the mother’s blood supply with that of her fetus. In the eight years since then, Markovic and other researchers have discovered some remarkable similarities in how cancer cells and placental cells regulate the immune system. This knowledge may one day lead to better cancer detection and treatment. For now, though, researchers are focused on deciphering the underlying process — and answering a sobering question: Are the cells of death exploiting the mechanisms intended to promote the cells of life?

Typically, when the body senses a foreign substance such as a virus or a bacterium, it sends immune cells to attack the invader while also bolstering the immune system as a whole. Cancer cells are vulnerable to this kind of attack because they produce mutated proteins that the immune system may identify as foreign. But cancer cells can escape immune surveillance using a variety of techniques to disguise themselves.

Until recently, Markovic says, most scientists believed that outside of localized changes near the cancer cells, the immune system of cancer patients essentially functioned normally. But as a young researcher in the early 2000s, he wasn’t convinced this told the whole story. He tested that idea by comparing immune-cell activity in the blood of healthy people and cancer patients.

What he found was that cancer doesn't merely disrupt the immune response around the tumor — it affects the entire system. One of his team's early findings, published in 2011, was that tumors have high levels of a particular protein known to suppress the immune system and induce a state of system-wide chronic inflammation. He says in his experiments, the immune system "was totally unable to fight." What's more, it became increasingly protective of cancer cells. He wondered: "How could a tiny cancer cell cause such dysfunction across the whole body's immune system?"

Markovic theorized that tumors train the immune system to tolerate their foreign protein, though he wasn't sure how until the pregnant researcher's blood got him thinking. Researchers already knew that a woman's immune system changes during pregnancy. Perhaps these changes could help explain what happens during cancer.

Like tumor cells, fetal cells are foreign to the body. Half of their genes come from another source (and in the case of donor eggs or embryos, all of the genes are foreign). If an organ this incompatible were transplanted into the body, it would likely be rejected. But during pregnancy, the fetus is protected from the mother's immune system by the placenta, which has specialized cells — called trophoblasts — that can burrow into the mother's body without exciting an attack by the immune system.

During pregnancy, a mother's immune system isn't switched off, but it is strategically suppressed, especially during the first trimester to allow for successful implantation. A subset of immune cells that manage immune system suppression, known as regulatory T cells, begins learning to tolerate the fetal cells as non-foreign. Stanford researchers recently discovered that the changes in an expectant mother's immune system follow a specific timeline in full-term pregnancies, which they dubbed an "immunological clock of pregnancy." Interestingly, as the clock progresses, regulatory T cells become increasingly able to tolerate fetal cells.

Markovic and his team at the Mayo Clinic wondered if tumors might be employing some of the same tactics as the placenta to outsmart the immune system: "Tumor cells may mimic trophoblastic cells of the placenta in that they downregulate danger signals while increasing expression of immunosuppressive mediators," Markovic and his co-authors wrote in a 2015 review paper published in the journal Frontiers in Immunology. So he and his team compared the top 20 to 30 known immune system regulators in pregnancy with cancer's immune system regulators.

"I nearly fell off my chair when I saw the data," Markovic says. "There was such a profound similarity in regulation of the immune system by the placenta and by cancer. They were the exact same players doing the exact same thing."

In particular, two molecules known to play a role in cancer's suppression of the immune system are PD-L1 and galectin-9. They inhibit the abilities of tumor-infiltrating white blood cells and increase the abilities of immunosuppressive regulatory T cells. PD-L1 sits on the surface of cells and acts as a kind of stop sign, telling T cells not to attack. To gauge the dampening of the whole immune system, Markovic and his team tested levels of galectin-9 and PD-L1 in the blood plasma of pregnant women and of cancer patients. To determine local immune control, where the invasive tissue interfaces with normal cells, post-birth

placentas and stage-four melanoma tumors were examined.

When compared with the blood of healthy, non-pregnant control subjects, galectin-9 levels in both pregnant women and cancer patients were significantly elevated. Similarly, PD-L1 levels were raised in both groups. In the local areas — the trophoblastic cells of the placenta and the edges of the tumor — both molecules were found at high concentrations. In a 2016 study published in the journal Placenta, Markovic's team concludes that there are indeed "striking similarities between trophoblasts and tumors."

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Of course the immune cells in the pregnant scientist's blood had stopped behaving "normally": the immune system in pregnancy is anything but normal.

This realization "pushed one entire laboratory project in the direction of understanding the immunology of pregnancy as a model for immunity of cancer," Markovic says. One of his students went on to pursue a Ph.D. on this topic.

Markovic is not alone. Researchers at other institutions are also uncovering parallels between pregnancy and cancer. In both conditions, the immune system does not merely ignore the invasive cells, it actively encourages their growth. Scientists at the Rosalind Franklin University of Medicine and Science in Chicago found a "remarkable similarity" between the cells that support the growth and development in placentas and in tumors. They do this "by activating the portion of the immune response which initiates and helps control tissue repair," the researchers note in the June 2017 issue of Gynecologic Oncology.

Scientists at the University of Otago in New Zealand have also noted that this altered immune function occurs when a certain set of genes is turned on or off. "Essentially, we are using the human placenta as a model to identify genes that play a key role in invasion in both the placenta and cancer," wrote Chi Sutherland, a Ph.D. candidate leading the project, in an email.

"There is an increasing body of evidence in support of functional and molecular similarities between the placenta and cancer; however, no one has looked at the particular class of genes that we are interested in," she added.

Sutherland is looking at a subset of genes known as retrotransposon-derived genes (RDGs). In the

placenta, RDGs have been found working in pathways associated with many of the tools of invasion: immune suppression, blood vessel growth, cell proliferation, and inflammation.

Among mammals, the human placenta mounts one of the most extensive invasions of the uterine wall. This high level of interaction makes nutrient and waste transfer between mother and fetus more efficient, but it also risks provoking a stronger maternal immune response.

During conception and fetal development, the invasion process is amazingly complex and intricately regulated, explains Sutherland. In cancer, that regulation is lost. “We think that these genes, which are normally only expressed in the placenta to facilitate invasion, are becoming reactivated in cancer cells and supporting invasion in this context too,” she says. Her project aims to identify more placental RDGs and determine whether they are also activated in cancer cells, and if so, whether they promote cancer cell invasion.

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“We think some of these genes could be ‘hijacked’ by cancer cells and may contribute to the shared invasive characteristics of the placenta and cancer,” Sutherland says. If this is the case, then cancer cells do, in fact, exploit the very mechanisms that make it possible for a fetus to survive inside a woman’s womb.

Currently, several medications that inhibit PD-L1 are used in cancer immunotherapy. The problem is that when T cells are allowed to attack, they can destroy both cancer cells and healthy cells, leading to a wide array of side effects. Sutherland says the genes she studies are already silenced in healthy adult tissue, so theoretically researchers should be able to design therapies that re-silence them in cancer cells without side effects.

For his part, Markovic plans to research diseases of the placenta, to see whether there is an on/off switch for its control of the immune system. He is hopeful that if better understood, these biological mechanisms could illuminate new ways of treating cancer. As of today, his team has one “candidate molecule” that they hope to bring into clinical studies within the next 18 months, and a second one that is showing great promise.

And of course, it is not lost on Markovic — and certainly not on his wife, he says — that this promising line

of inquiry might never have been explored, had that female colleague not been working as a medical research scientist at the Mayo clinic eight years back; had she not volunteered to donate her blood for Markovic's research; and had she not continued to work — and donate — after becoming pregnant.

When Markovic told his wife, a cardiologist, about his discovery of the striking similarities between how tumors and placentas control the immune system, he describes her as being wholly unsurprised.

"See?" Markovic recalls her replying. "Women had the answer all along."

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