Podcast Interview: Yoel Sadovsky and Carolyn B. Coyne

PNAS: I’m Jessica Johnson. Welcome to Science Sessions.

During pregnancy, the placenta provides crucial support to the developing fetus in terms of nutrition, oxygenation of the blood, waste removal, hormone production, immunity, and protection from many microbial infections. I spoke with two researchers who are working to discover the mechanism by which the placenta blocks transmission of infectious microbes from the mother to the fetus. Yoel Sadovsky is a professor of obstetrics and gynecology, and Carolyn Coyne is an associate professor of microbiology and molecular genetics at the University of Pittsburgh. Along with their co-authors, the researchers were recently awarded the 2013 Cozzarelli Prize for excellence and originality in the Biomedical Sciences for their paper titled, “Human placental trophoblasts confer viral resistance to recipient cells.”

PNAS: Carolyn, how did you first become interested in investigating the role of the placenta in protecting the fetus from viral infection?

Coyne: My research had always focused on cellular barriers against viral infection. About 5 ½ years ago I was pregnant with my son, and I was sitting preparing very large scale amounts of infectious virus in our tissue culture hood and it was very early on in my pregnancy but there was this moment of thinking wait a minute, should I really be doing this? That moment is I think what really sparked my interest in this. If you want to talk about an essential barrier to life, that is the placenta. I had a graduate student at the time who is Elizabeth Delorme-Axford who is the first author of our manuscript, and we were very naïve about the placenta, the structure, and trophoblasts, the cells that comprise the placenta are called trophoblasts. Yoel’s lab has perfected the technique of culturing primary placental trophoblasts. He said I’m happy to give you some of those cells for pilot experiments to begin to dissect these events of how these trophoblasts protect against infection. And I think that’s really what launched the project.

Sadovsky: When Carolyn and her team came to us, we had been working for quite some time on mechanisms by which the placenta protects the developing embryo in the mother during pregnancy. We did not really study viruses but we were very much intrigued by the question posed by Carolyn and her team because of the significance of viral infections to the well-being of the fetus and also the mother during pregnancy. We know clinically that many of those infections can affect the fetus and can cause lifelong developmental problems.

PNAS: What was your first step in investigating this question?
Coyne: As any good virologist, I have in my freezer lots of different kinds of viruses. So I said to my student, “let’s try to infect these primary trophoblast cells with viruses that will usually infect many cell types.” And none of the viruses infected to any significant or even insignificant levels. What that told me was that the trophoblasts were really resistant to pan-viral infection.

**PNAS: How did you think the trophoblasts were protecting themselves from viral infection?**

Coyne: At the time I said to my student, “wouldn’t it be really interesting if trophoblasts secrete a factor.” And at the time I was thinking something like a cytokine that would be secreted from these cells that are limiting their ability to be infected by viruses.

**PNAS: So would such a factor secreted from placental trophoblasts during a pregnancy be responsible for protecting the fetus from viral infection as well?**

Sadovsky: One of the common means that the placenta uses to communicate with the mother and the fetus during pregnancy is not only hormones, but also the placenta produces vesicles of different types. And the content of the vesicles seems to be important.

Coyne: Yoel said we should really look at these small vesicles called exosomes that are secreted from trophoblasts and contain microRNAs. So the simple experiment that we did was to grow these naïve primary trophoblast cells and we just collected the conditioned medium from these cells and took that media and exposed normally very permissive cells, so by permissive I mean cell types that can be robustly infected with our panel of viruses, and what we found was that if we treated these normally very permissive cell types with this conditioned medium, now those cell types were refractive to viral infection. So what that told us was that there was a factor present in this conditioned medium that was then transferring this viral resistance to non-placental recipient cells.

Sadovsky: We found that if we remove the vesicles from the medium, we lose the effect. And then interrogating what’s in the vesicles, indeed we found those small microRNAs. And to prove that those microRNAs play a role, we generated cells that now express those microRNAs that are unique to the placenta and those cells had not had those microRNAs expressed in them, but now by virtue of exogenous expression of these microRNAs, we were able to confer resistance at least in part to viruses in those recipient cells.
PNAS: So the trophoblasts were producing vesicles, or exosomes, which contained microRNAs that conferred resistance to viral infection to non-placental cells. How was this happening?

Coyne: There are a number of canonical pathways that function in cells to alter or enhance their resistance to viral infection. The pathway turned out to be something called autophagy which literally means self-eating. And it’s a process that exists in cells normally to clear degraded organelles. In the last 5 years or so it’s emerged as a pathway by which host cells will resist viral infection. These cells will sense the presence of a pathogen, a virus most commonly, and they’ll induce autophagy. It’s a mechanism to clear the foreign, invading virus. It was very obvious that autophagy was very potently induced in these cells.

Sadovsky: We’re now interrogating what potential other mechanisms may be released from trophoblast cells and potentially synergize or interact with those small RNA molecules to induce the affect. We should highlight the fact that even if the microRNAs or whatever mechanism we uncover do not directly affect the fetus, if you protect the mother, you protect the entire pregnancy.

Coyne: It’s important to note that I don’t think these microRNAs or these vesicles exist to prevent viral infections or microbial infections. I think these vesicles and microRNAs have more far-reaching roles in sustaining pregnancy, and I think it just so happens that one of the very nice benefits of them is that they then protect against microbial infection.

PNAS: Thanks for listening. The Cozzarelli Prize is awarded annually by PNAS to acknowledge recently published papers that reflect scientific excellence and originality. You can find Science Sessions podcast interviews with all of the 2013 Cozzarelli Prize winners at PNAS.org.