

INTERVIEW about

Trophoblast invasion
with

Justine S. Fitzgerald, Tobias G. Poehlmann,
and Udo R. Markert Abteilung für Geburtshilfe,
Placenta-Labor, Friedrich-Schiller-Universität Jena,
Bachstr. 18, 07743 Jena, Germany
markert@med.uni-jena.de



What is known about trophoblast invasion?

Justine S. Fitzgerald, Tobias G. Poehlmann, and Udo R. Markert: During the first trimester of pregnancy, the placenta is in the process of building its architecture. In doing so, the placenta undergoes several phases of construction and destruction. The main placental stroma cell, the trophoblast, must form and anchor pillars of fetal tissue (villi), while simultaneously sculpturing a network of lacunae between the villi (intervillous space) and finally pioneer its way through its maternal surroundings, the decidua, to find maternal spiral arteries and establish a vital “life-line” of vasculature into the lacunae. Thus, it is a vital characteristic of the trophoblast to be able to invade its surrounding tissue.

Trophoblast cells are divided into several subgroups, most of which possess invasive capacities, others are rather non-invasive and encompass a more

structural or endocrine function. Generally though, all trophoblast cells originate from an invasive cast and have the capacity to engage the invasive phenotype.

The process of invasion consists of the ability of a cell to degrade its surrounding tissue, the extra-cellular matrix (ECM). Trophoblast cells accomplish this through secretion of especially matrix metalloproteinases (MMPs) and other proteases. This method is similar to those used by tumorous cells. Another similarity between these two cells is their modes of motility. This is where the likeness ends, though. Healthy trophoblast cells remain well differentiated, and its invasion is strictly contained both in area and time. The bright mind recognizes this further vital attribute of trophoblast cells, so it is no surprise why trophoblast research attracts the attention of many young life scientists today.

Are signaling pathways involved?

Justine S. Fitzgerald, Tobias G. Poehlmann, and Udo R. Markert: Yes, virtually all main signaling pathways that are involved in invasion processes found in malignancies are also involved in trophoblast invasion.

Many members of signaling pathways are utilized in response to cytokines and interleukins that are present in the placenta and seem to control or orchestrate the structural remodeling mentioned above. Much research has been dedicated to elucidating the influence of these

mediators on the ability of trophoblast to move, proliferate, differentiate, secrete and invade; in some cases, the signaling pathways have also been unearthed, but there is much more work yet to come, and we are far from understanding everything (1). One difficulty in interpreting these data is that it often concerns non-primary cells, in other words malignancies of trophoblastic origin (choriocarcinoma cells) or trophoblast cell lines. Although these cells are excellent models, they are still an imperfect mirror of the natural setting.

What is the role of STATs?

Justine S. Fitzgerald, Tobias G. Poehlmann, and Udo R. Markert:

STATs, or Signal Transducers and Activators of Transcription, are

intracellular proteins that are capable of mediating an extracellular signal by manipulating the transcription of target proteins. These often happen to be those that are significant for growth, development and longevity.

STAT3 has been found to be important in the development of cancer as it may also act as an oncogene. Furthermore, loss

What could be the clinical relevance?

Justine S. Fitzgerald, Tobias G. Poehlmann, and Udo R. Markert: Preeclampsia, the disease with the highest pregnancy related maternal lethality in western countries and associated with major risks for mother and fetus is caused by impaired trophoblast invasion. Preeclampsia is a disease which presents clinically with hypertension, edema and proteinuria. The pathomechanisms of these symptoms were unknown until trophoblast invasion research was intensified.

Extravillous cytotrophoblast, a trophoblastic phenotype, possess high motile and invasive capacities in order to infiltrate deep into the decidual matrix, reach the maternal spiral arteries, erode their musculoelastic media and parcel them by differentiating into endovascular cytotrophoblast. These now regulate the flow of blood volume into the intervillous space by influencing flow resistance (6). When trophoblast invasion is shallow, the placenta is not only poorly anchored in the matrix tissue, but also suboptimally vascularized. It is no wonder that this results in a higher risk of intrauterine growth retardation and abruptio placentae (6-8). Thus far, nothing is

reported about the role of STAT3 in dysregulation of trophoblast invasion during preeclampsia, but the data presented above suggests its possible involvement. Preeclampsia might be associated with reduced STAT3 activation. On the other hand, trophoblast cells have the potential to degenerate into cancerous cells. The spectrum of dysregulation ranges from abnormal proliferation of placental tissue (molar pregnancy) to highly malign tumours (choriocarcinoma), and are summarized under the term “gestational trophoblastic disease (GTD).” Choriocarcinoma are associated with constitutively activated STAT3 (2).

Acknowledgement: The Placenta-Lab is member of the European Network of Excellence “EMBIC” (Embryo Implantation Control; www.embic.org)

REFERENCES

1. Polheimer J et al. *Placenta* 26, 21, 2005
2. Corvinus FM et al. *Am J Reprod Immunol* 50, 316, 2003
3. Poehlmann TG et al. *Placenta* 26, 37, 2005
4. Fitzgerald JS et al. *Int J Biochem Cell Biol* 37, 2284, 2005
5. Fitzgerald JS et al. *Chem Immunol Allergy* 88, 181, 2005
6. Bischof P et al. *Hum Reprod Update* 2, 262, 1996
7. Zhou Y et al. *J Clin Invest* 99, 2139, 1997
8. Mathiesen L et al. *Chem Immunol Allergy* 89, 49, 2005