Editorial

The use of malaria glycosaminoglycan to block cancers—lessons from the human placenta

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The placenta is a specialized organ that is required for the establishment of human pregnancy. During placentation, trophoblast cell proliferation, migration and invasion occur in a highly regulated manner (1). Dysregulated trophoblast cell proliferation and invasion lead to pregnancies with adverse outcomes (2-4). By comparison, malignant tumours arise when cell proliferation, migration and invasion occur in an uncontrolled manner (5,6). As such, trophoblast and cancer cell invasion may share similar mechanisms, and a recent study by Salanti *et al.* (7) has compared the role of a cell surface protein in human trophoblast and cancer cells.

The malaria parasite Plasmodium falciparum, which replicates within infected erythrocytes, expresses the cell surface membrane glucosaminoglycan, VAR2CSA which enables the parasite to attach to host vascular cells via binding to specific receptors on the cells (8). Salanti *et al.* had demonstrated a number of years ago that VAR2CSA mediates binding of Plasmodium falciparum infected erythrocytes to the placental syncytiotrophoblast which lines the placenta, and is in direct contact with maternal blood (9,10). In placental cells, VAR2CSA binds a distinct chondroitin sulphate (CS) glycosaminoglycan (GAG) chain A (CSA) (11). Importantly, VAR2CSA expressing malaria parasites bind only to a distinct placental specific CS subtype. The placental CS subtype is thought to play roles in trophoblast cell proliferation and invasion, features also shared by cancer cells. This led Salanti *et al.* (7) to investigate whether human cancer cells also express the placental CS subtype.

Similarly, P. falciparum-infected RBC cannot bind anywhere in vascularised tissue except the placenta.

Salanti *et al.* (7) investigated the form of CS present in cancer cells. The authors produced recombinant VAR2CSA (rVAR2) protein and showed that it detected a distinct form of placental-CS produced exclusively in the human placenta and not in other normal tissues or cells. VAR2CSA in Plasmodium falciparum infected erythrocytes bound to human cancer cell lines *in vitro* but not to normal non-malignant primary cells. rVAR2 bound to 95% of patient derived human cancer cell lines of haematologic and mesenchymal origin in a highly specific manner. Human cancer and placental trophoblast cells were demonstrated to express a common and distinct form of CS which can be specifically recognised by recombinant malarial VAR2CSA. Human epithelial derived tumours bound strongly to rVAR2 compared to very minimal binding in adjacent normal tissue from the same patient. The authors analysed 676 malignant tissues from patients with localised stages I–III invasive ductal breast cancer (n=124), stage IIb (n=20) and stage I–III soft tissue sarcomas (n=532). The majority of the cancer tissues demonstrated binding for placental specific CS (placental-CS). Of the sarcoma sub-types investigated, only Ewing sarcomas showed weak or absent binding of rVAR2 in the majority of cases. The authors analysed tissue microarrays containing 47 Ewing sarcoma specimens from adult and pediatric patients and noted weak binding of rVAR2 was due to a general lack of CS chains or a specific lack of placental-CS. Most malignant tumours were strongly positive for placental-CS.

The authors then analysed whether there was an

association with the progression and outcome of melanoma and placental-CS (detected by rVAR) in melanoma. There was increased staining for placental-CS (indicating potential binding) in metastatic and recurrent disease, suggesting placental-CS is a marker for disease progression of melanoma. Similarly, with non-small cell lung cancer, high expression correlated with poor relapse free survival. Overall, diverse human malignant tumour types originating from distinct germ layers displayed distinct placental-CS signatures that the authors suggested may predict disease progression and outcome.

Placental, melanoma, some breast cancer and melanoma cells express CSA-modified proteoglycan, CSPG4 (12,13). CSPG4 is associated with placental trophoblast cell proliferation and invasion (12,14). The authors therefore investigated whether rVAR2 binds tumour cells that do or do not express CSPG4, and their data demonstrated that rVAR2 binds cells that do not express CSPG4 suggesting that placental-CS can be displayed by other proteoglycan protein cores. The authors identified at least 17 other proteins, including CD44, that can bind rVAR2. However, they did not investigate whether all of the proteoglycans can be modified with CS *in vivo*.

The authors investigated inter-tumour diversity in expression of proteoglycans able to display placental-CS, and concluded that rVAR2 may be utilized to broadly target placental-CS chains in human cancers that have different proteoglycan expression profiles. This led the investigators to examine whether VAR2CSA expression in human tumours can be used to deliver cytotoxic therapeutics directly to tumours.

The authors tested whether fluorescently tagged rVAR2 was internalised in cancer cell lines *in vitro* and *in vivo* in mice. They found that rVAR2 was located in the xenograft tumours *in vivo* and in the cell lines *in vivo* suggesting that rVAR2 can be internalised to deliver cytotoxic compounds to placental-CS expressing cells *in vivo* and proved this *in vivo* in cancer xenografts of castration resistant prostate cancer (CRPC) tumours. Importantly, there was little morphological evidence of adverse effects in normal cells. The authors then produced a drug conjugate consisting of toxin linked to rVAR2 and used this *in vivo*. They found that they could target human tumours *in vivo* with this approach, with no apparent adverse effects in mice without tumours. As non-pregnant mice injected with the 'drug conjugate' had no adverse effects of treatment, it suggests that placental-CS is expressed in low amounts in non-tumour cells and that the binding of the conjugate is specific.

In summary, the data presented in the study by Salanti *et al*. (7) strongly supports the use of placental-CS as a target generally for rVAR2-based cancer therapeutics. It is interesting to speculate whether it may also be useful in therapies that target the placenta, as abnormalities in placentation result in a wealth of severe pregnancy disorders. It remains, however, to be determined whether any potential therapeutic crosses the placenta which may result in embryotoxic effects. While the *in vivo* mouse studies were in xenografts, it will be interesting to determine the effects in non-immune deficient mouse models. It will be fascinating to determine whether there are patient sub-groups who may benefit the most. Overall, the use of rVAR2 to specifically target malignant cancers is an exciting possibility that has the potential to block the development of many tumours.

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References

1. Burton GJ, Jauniaux E, Charnock-Jones DS. The influence of the intrauterine environment on human placental development. Int J Dev Biol 2010;54:303-12.
2. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science 2005;308:1592-4.
3. Winship A, Menkhorst E, Van Sinderen M, et al. Interleukin 11: similar or opposite roles in female reproduction and reproductive cancer? Reprod Fertil Dev 2016;28:395-405.
4. Winship AL, Koga K, Menkhorst E, et al. Interleukin-11 alters placentation and causes preeclampsia features in mice. Proc Natl Acad Sci U S A 2015;112:15928-33.
5. Ferretti C, Bruni L, Dangles-Marie V, et al. Molecular circuits shared by placental and cancer cells, and their implications in the proliferative, invasive and migratory capacities of trophoblasts. Hum Reprod Update 2007;13:121-41.
6. Holtan SG, Creedon DJ, Haluska P, et al. Cancer and pregnancy: parallels in growth, invasion, and immune modulation and implications for cancer therapeutic agents. Mayo Clin Proc 2009;84:985-1000.
7. Salanti A, Clausen TM, Agerbæk MØ, et al. Targeting Human Cancer by a Glycosaminoglycan Binding Malaria Protein. Cancer Cell 2015;28:500-14.
8. Baruch DI, Pasloske BL, Singh HB, et al. Cloning the P. falciparum gene encoding PfEMP1, a malarial variant antigen and adherence receptor on the surface of parasitized human erythrocytes. Cell 1995;82:77-87.
9. Salanti A, Dahlbäck M, Turner L, et al. Evidence for the involvement of VAR2CSA in pregnancy-associated malaria. J Exp Med 2004;200:1197-203.
10. Salanti A, Staalsoe T, Lavstsen T, et al. Selective upregulation of a single distinctly structured var gene in chondroitin sulphate A-adhering Plasmodium falciparum involved in pregnancy-associated malaria. Mol Microbiol 2003;49:179-91.
11. Fried M, Duffy PE. Adherence of Plasmodium falciparum to chondroitin sulfate A in the human placenta. Science 1996;272:1502-4.
12. Van Sinderen M, Cuman C, Winship A, et al. The chrondroitin sulfate proteoglycan (CSPG4) regulates human trophoblast function. Placenta 2013;34:907-12.
13. Wang X, Wang Y, Yu L, et al. CSPG4 in cancer: multiple roles. Curr Mol Med 2010;10:419-29.
14. Baston-Büst DM, Götte M, Janni W, et al. Syndecan-1 knock-down in decidualized human endometrial stromal cells leads to significant changes in cytokine and angiogenic factor expression patterns. Reprod Biol Endocrinol 2010;8:133.

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