J. Cell. Mol. Med. Vol 17, No 9, 2013 pp. 1096-1098

Foetal defence against cancer: a hypothesis

Hui-Tai Yang [a], Kuo-Ching Chao [b, c, *]

[a] *Department of Internal Medicine, Taipei City Hospital, Taipei, Taiwan*
[b] *Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan*
[c] *Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan*

Received: February 20, 2013; Accepted: May 24, 2013

It was once believed that the placenta blocks direct cell transfer between the mother and the foetus, that is, until the discovery of the maternal and foetal microchimerism which proved the existence of cell trafficking during pregnancy [1, 2]. It has been reported that 100% of the pregnant women at 36th week carry foetal cells in their circulation, the prevalence of which decreases, by 22–75%, after child delivery. The foetal cells found in maternal tissues include cells of mesenchymal and hematopoietic origins, T cell, B-cells and NK-cells, *etc*. Similarly, some maternal cells, such as the lymphoid and myeloid cells, T cells, B-cells, monocyte/macrophages and NK-cells, have been detected in some umbilical cord blood and in a number of young adults.

As cell transfer is possible between mother and foetus, it is highly conceivable that the mother's cancer cells could pass through the placenta to reach the foetus as well. Interestingly enough, statistical data [3–6] showed that in 98 cases of pregnant women with cancer, placental metastasis were noted in 90 cases (91.84%), but foetal metastasis only in 17 cases (17.35%). Among the 90 cases, in those diagnosed with breast cancer (14 cases), ovarian cancer (two cases), and malignant sarcoma (eight cases), although metastatic spread to the placenta was confirmed, no metastasis in the foetuses was found. In addition, in the cases of malignant melanoma, lung cancer, leukaemia and lymphoma, the percentages of placental metastasis were high, but the percentages were relatively low for foetal metastasis. Therefore, based on the above findings, it has been concluded that during pregnancy there must be a defence mechanism blocking the metastasis of these harmful cancer cells to the foetuses. The question is, which cell, or cells, plays this role?

Histologically, maternal and foetal circulations are separated by three components: the trophoblast, the villous connective tissue and the capillary wall. Some reports indicated that probably the trophoblast plays the role of a physical barrier in recognizing and rejecting foreign maternal antigens. Phagocytosis and destruction of tumour cells by the villous syncytiotrophoblast and the villous trophoblast have also been reported [7, 8]. Moreover, it was observed that once the invasion of cancer cells into the chorionic villous takes place, there is almost no avoidance of the foetal metastasis [3, 9]. Hence, the question worth digging into: What happens when the cancer is of the trophoblast origin?

Gestational choriocarcinoma is a highly malignant trophoblastic neoplasm developed during pregnancy, and intraplacental choriocarcinoma is a such type of gestational cancer grown in the placenta that is usually not identified until maternal metastasis has taken place. Review of the literature [10] showed that of 11 cases of intraplacental choriocarcinoma with maternal metastasis, on top of two that were lost to stillbirth, only two were noted to have foetal metastasis. This meant that seven of the 11(63.64%) foetuses were spared of the metastasis of the disease, which also could mean, in cancer of the trophoblast origin, metastasis to the immunogically naïve foetus is still a rarely occurrence despite the maternal metastasis. Therefore, this could suggest that, in addition to the trophoblast, there should be another defence mechanism in the area of placenta or umbilical cord that blocks the trafficking of the cancer cells from the placenta to the foetus.

Wharton's Jelly is the primitive connective tissue of the umbilical cord lying between the amniotic epithelium and the umbilical vessels. The main role of the Wharton's Jelly is to protect the umbilical vessels from compression, torsion and bending. Wharton's Jelly cells (WJCs), also known as the human umbilical cord mesenchymal stem cells (HUMSCs), are cells isolated from the Wharton's Jelly. Wharton's Jelly cells are characterized by their self-renewal and multipotency [11–13]. They showed a great *in vitro* and *in vivo* plasticity, towards lineages such as the hepatocytes [14], pancreatic beta cells [13, 15] and cardiomyocytes [16]. They are also able to support the stem cell niche [17] and synthesize various cytokines [17], and they possess the properties of immunomodulation [18] and homing [19]. Researchers postulated that these mesenchymal stromal cells are likely the cells trapped in the connective tissue matrix during their migration to and from the placenta through the developing umbilical cord during early embryogenesis and remain there for the duration of gestation [20]. It was noted that WJCs not only possess MSC properties but they exhibit properties similar to those attributed to embryonic stem cell (ESC) as well [21]. However, it is still less obvious whether WJC plays a role during embryonic and foetal development.

In the literature, MSCs can either suppress or promote tumours. Recently, it was found that culturing human bone marrow mesenchy-

*Correspondence to: Kuo-Ching CHAO,
Department of Internal Medicine, School of Medicine,
College of medicine, Taipei Medical University, Taipei 110, Taiwan.
Tel.: +886-2-27372181
Fax: +886-2-27363051
E-mail: chin3064@tmu.edu.tw

doi: 10.1111/jcmm.12095

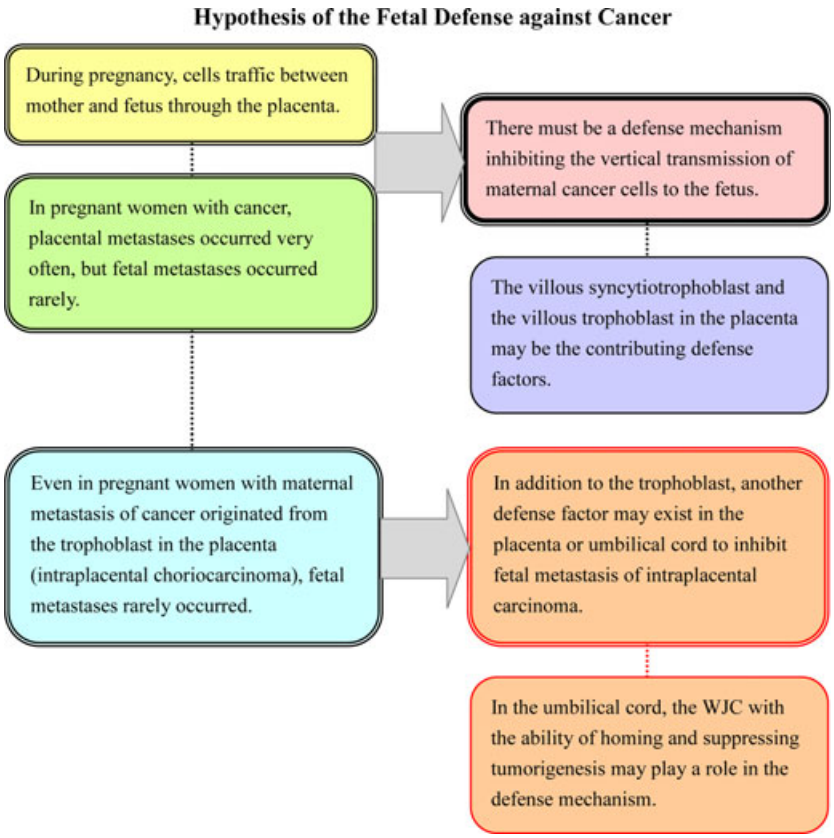

Fig. 1 Hypothesis of the fetal defense against cancer.

mal stem cells (HBMSCs) with tumour necrosis factor-α (TNF-α) enhanced their tumour-suppressive properties through the upregulation of multiple genes with cancer apoptotic activity. The HBMSCs preactivated with TNF-α induced apoptosis in MDA-MB231 breast cancer cells, suppressed MDA-MB231 cell cycling, and inhibited the progression of tumours formed from MDA-MB231 [22]. As for WJCs, they are described as potent immunomodulatory cells and new molecules are discovered *in vitro* almost weekly. One of the more promising molecules is represented by B7-H3, a member of the B7 co-stimulator family. This molecule has been linked to both pro-tumorigenic and antitumor activities [23]. Recent data showed that this molecule, which is not expressed in BM-MSCs, is expressed in WJCs both when kept undifferentiated and in their differentiated progeny [16, 24]. Another set of molecules with importance in the immunomodulatory function of WJC are non-classical HLAs (*e.g.* HLA-E and HLA-G). Both were related to cancer progression or immune evasion by a number of studies [25], and their expression was demonstrated in WJCs by different groups [26, 27].

In a previous study [28], we reported the interactions between selected WJC (HUMSC) and MDA-MB231 which caused MDA-MB231 breast cancer cell death, include (1) binding mechanism: breast cancer cell apoptosis from direct cell-cell contact with WJC and infusion of some substance into cancer cell by WJC; (2) cell-in-cell mechanism (a novel phenomenon we named 'cic-apoptosis'): breast cancer cell apoptosis following forming of a cell-in-cell structure of WJC internalized within cancer cell; (3) indirect (cytokine) mechanism: attenuation of breast cancer cell growth from one or more cytokines secreted, predominantly, by co-cultured WJC and MDA-MB231 or by WJC alone, without direct contact with cancer cells. The WJC was proved to have the ability of homing and suppressing tumorigenesis [28–30] both *in vitro* and *in vivo*. Therefore, we can make a bold assumption that, in addition to the trophoblast in the placenta, WJC in the umbilical cord also plays a role in the foetal defence against the invasion of maternal or placental cancer cells. In the event of cancer cells occurrence in the placenta, WJCs may home to the site and induce apoptosis of the cancer cells. We invite further investigations that are much needed to help substantiate our hypothesis which states that WJCs may not just be the cells accidentally embedded in the Wharton's Jelly during embryogenesis but are cells purposely placed there as an essential guard in the umbilical cord during foetal development. Moreover, the WJC induced apoptosis of cancer cells, different from cell necrosis, does not cause severe inflammation, and that may shed light on cell therapy for cancer in the future.

Conflicts of interest

The authors confirm that there are no conflicts of interest.

Journal of Cellular and Molecular Medicine published by John Wiley & Sons Ltd and Foundation for Cellular and Molecular Medicine.

References

1. **Lo YM, Lo ES, Watson N, *et al.*** Two-way cell traffic between mother and fetus: biologic and clinical implications. *Blood*. 1996; 88: 4390–5.
2. **Herzenberg LA, Bianchi DW, Schroder J, *et al.*** Fetal cells in the blood of pregnant women: detection and enrichment by fluorescence-activated cell sorting. *Proc Natl Acad Sci USA*. 1979; 76: 1453–5.
3. **Potter JF, Schoeneman M.** Metastasis of maternal cancer to the placenta and fetus. *Cancer*. 1970; 25: 380–8.
4. **Dildy GA 3rd, Moise KJ Jr, Carpenter RJ Jr, *et al.*** Maternal malignancy metastatic to the products of conception: a review. *Obstet Gynecol Surv*. 1989; 44: 535–40.
5. **Jackisch C, Louwen F, Schwenkhagen A, *et al.*** Lung cancer during pregnancy involving the products of conception and a review of the literature. *Arch Gynecol Obstet*. 2003; 268: 69–77.
6. **Alexander A, Samlowski WE, Grossman D, *et al.*** Metastatic melanoma in pregnancy: risk of transplacental metastases in the infant. *J Clin Oncol*. 2003; 21: 2179–86.
7. **Wang T, Hamann W, Hartge R.** Structural aspects of a placenta from a case of maternal acute lymphatic leukaemia. *Placenta*. 1983; 4: 185–95.
8. **Harpold TL, Wang MY, McComb JG, *et al.*** Maternal lung adenocarcinoma metastatic to the scalp of a fetus. Case report. *Pediatr Neurosurg*. 2001; 35: 39–42.
9. **Rothman LA, Cohen CJ, Astarloa J.** Placental and fetal involvement by maternal malignancy: a report of rectal carcinoma and review of the literature. *Am J Obstet Gynecol*. 1973; 116: 1023–34.
10. **Liu J, Guo L.** Intraplacental choriocarcinoma in a term placenta with both maternal and infantile metastases: a case report and review of the literature. *Gynecol Oncol*. 2006; 103: 1147–51.
11. **Wang HS, Hung SC, Peng ST, *et al.*** Mesenchymal stem cells in the Wharton's jelly of the human umbilical cord. *Stem Cells*. 2004; 22: 1330–7.
12. **Mitchell KE, Weiss ML, Mitchell BM, *et al.*** Matrix cells from Wharton's jelly form neurons and glia. *Stem Cells*. 2003; 21: 50–60.
13. **Chao KC, Chao KF, Fu YS, *et al.*** Islet-like clusters derived from mesenchymal stem cells in Wharton's Jelly of the human umbilical cord for transplantation to control type 1 diabetes. *PLoS ONE*. 2008; 3: e1451.
14. **Campard D, Lysy PA, Najimi M, *et al.*** Native umbilical cord matrix stem cells express hepatic markers and differentiate into hepatocyte-like cells. *Gastroenterology*. 2008; 134: 833–48.
15. **Anzalone R, Lo Iacono M, Loria T, *et al.*** Wharton's jelly mesenchymal stem cells as candidates for beta cells regeneration: extending the differentiative and immunomodulatory benefits of adult mesenchymal stem cells for the treatment of type 1 diabetes. *Stem Cell Rev*. 2011; 7: 342–63.
16. **La Rocca G, Lo Iacono M, Corsello T, *et al.*** Human Wharton's jelly mesenchymal stem cells maintain the expression of key immunomodulatory molecules when subjected to osteogenic, adipogenic and chondrogenic differentiation in vitro: new perspectives for cellular therapy. *Curr Stem Cell Res Ther*. 2013; 8: 100–13.
17. **Lu LL, Liu YJ, Yang SG, *et al.*** Isolation and characterization of human umbilical cord mesenchymal stem cells with hematopoiesis-supportive function and other potentials. *Haematologica*. 2006; 91: 1017–26.
18. **Cho PS, Messina DJ, Hirsh EL, *et al.*** Immunogenicity of umbilical cord tissue derived cells. *Blood*. 2008; 111: 430–8.
19. **Rachakatla RS, Marini F, Weiss ML, *et al.*** Development of human umbilical cord matrix stem cell-based gene therapy for experimental lung tumors. *Cancer Gene Ther*. 2007; 14: 828–35.
20. **Wang XY, Lan Y, He WY, *et al.*** Identification of mesenchymal stem cells in aorta-gonad-mesonephros and yolk sac of human embryos. *Blood*. 2008; 111: 2436–43.
21. **Fong CY, Chak LL, Biswas A, *et al.*** Human Wharton's jelly stem cells have unique transcriptome profiles compared to human embryonic stem cells and other mesenchymal stem cells. *Stem Cell Rev*. 2011; 7: 1–16.
22. **Lee RH, Yoon N, Reneau JC, *et al.*** Preactivation of human MSCs with TNF-alpha enhances tumor-suppressive activity. *Cell Stem Cell*. 2012; 11: 825–35.
23. **Loos M, Hedderich DM, Friess H, *et al.*** B7-h3 and its role in antitumor immunity. *Clin Dev Immunol*. 2010; 2010: 683875.
24. **Anzalone R, Corrao S, Lo Iacono M, *et al.*** Isolation and characterization of CD276+/HLA-E+ human subendocardial mesenchymal stem cells from chronic heart failure patients: analysis of differentiative potential and immunomodulatory markers expression. *Stem Cells Dev*. 2013; 22: 1–17.
25. **de Kruijf EM, Sajet A, van Nes JG, *et al.*** HLA-E and HLA-G expression in classical HLA class I-negative tumors is of prognostic value for clinical outcome of early breast cancer patients. *J Immunol*. 2010; 185: 7452–9.
26. **Weiss ML, Anderson C, Medicetty S, *et al.*** Immune properties of human umbilical cord Wharton's jelly-derived cells. *Stem Cells*. 2008; 26: 2865–74.
27. **La Rocca G, Anzalone R, Corrao S, *et al.*** Isolation and characterization of Oct-4+/HLA-G+ mesenchymal stem cells from human umbilical cord matrix: differentiation potential and detection of new markers. *Histochem Cell Biol*. 2009; 131: 267–82.
28. **Chao KC, Yang HT, Chen MW.** Human umbilical cord mesenchymal stem cells suppress breast cancer tumourigenesis through direct cell-cell contact and internalization. *J Cell Mol Med*. 2012; 16: 1803–15.
29. **Ma Y, Hao X, Zhang S, *et al.*** The *in vitro* and *in vivo* effects of human umbilical cord mesenchymal stem cells on the growth of breast cancer cells. *Breast Cancer Res Treat*. 2012; 133: 473–85.
30. **Ayuzawa R, Doi C, Rachakatla RS, *et al.*** Naive human umbilical cord matrix derived stem cells significantly attenuate growth of human breast cancer cells *in vitro* and *in vivo*. *Cancer Lett*. 2009; 280: 31–7.