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The role of trophoblastic epigenetic reprogrammation in benign tumor cells on malignant progression: A molecular hypothesis

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ABSTRACT

Cancer tissues and placental ones share many properties such as invasiveness, metastasis and local immunosuppressive effects. The goal of the present article is to hypothesize a theory about cancer origin that links placental and cancerous tissues at molecular level. This hypothesis explain that cancer origin could be due to low hypoxic conditions in the peripheral zones of benign tumors which might up-regulate the expression of IGF2, and, consequently, trophoblastic genes. In fact, many phenotypic characteristics and molecular markers are shared between these two cell types (cancerous and trophoblastics ones), providing evidences to support this hypothesis. As a consequence, it could be interesting to demonstrate whether cancer start with a cellular reprogrammation towards a trophoblastic fate in order to design new antitumoral strategies focused on this fact.

Introduction

Cancer is characterized by being a mortal disease due to the proliferation of anaplastic cells with invasive, metastatic and angiogenic potential [1]. In 1902, a Scottish embryologist named John Beard explained that cancer could be a transformation of mature cells towards a trophoblastic phenotype. He argued that placental tissues have some of the same characteristics of cancer cells like invasiveness, angiogenesis and metastasis. Moreover, Dr. Beard explained that placental tissues stop growing with pancreatic maduration, at 10th week of pregnancy; cancer cells would do the same with the addition of pancreatic enzymes, and hypothesized that pancreatic insufficiency could be a risk for cancer development [2–4]. However, this theory has been forgotten in academic institutions, especially, due to its lack of scientific evidences. The goal of the present article is to configure a new trophoblastic theory of cancer based on cellular and molecular characteristics that link cancer with trophoblastic cells and tissues.

Hypothesis

Benign tumors start with mutations in oncogenes (for example, K-Ras) and tumor suppressor genes (for example, p53). These mutations provoke a high proliferation ratio of cells with a phenotype that is very similar to normal ones. Nevertheless, these cells have not the ability of invading and metastasizing. Afterwards, in a little known process called tumoral progression, benign tumors transformate into malignant ones, acquiring invasive, neo-angiogenic and metastatic potential [1].

We hypothesize that this process of malign transformation form benign tumors to malignant ones (cancer) is a cell reprogrammation that leads benign tumor cells to the acquisition of trophoblastic characteristics, therefore, these cells are transformed into malignant or cancer ones.

This process could happen as follows. High cell proliferation ratio in benign tumors produce cell masses with hypoxia in their central zones. Hypoxia provokes necrosis of central cells. However, peripheral cells in relation to the necrotic ones, which are submitted to less hypoxia, suffer from an adaptation to hypoxic conditions. One of this consequences is an over expression of HIF-1, which consequently up-regulates the expression of methyl-transferases such as DNMT1 [5,6].

Trophoblastic phenotype requires the expression of IGF2, which in an autocrine way, provoke the expression of placental transcription factors and markers (Cdx2, Trop2, cytokeratin 7, PLAP, Plag1, Peg1/Mest, Peg3). These factors lead cells to a trophoblastic phenotype [7,8]. Our hypothesis is that methyl-transferases over expression mediated by hypoxia could methylate CpG islands in the promotor of H19 gene (which leads cells to a non placental fate) inhibiting the binding of transcription factor CTFC and stimulating the expression of IFG2 (Fig. 1).

This phenomenon could be the explanation to the transformation of benign tumor cells into malignant ones (cancer). So that, cancer cell phenotype might be the consequence of the acquisition of placental (trophoblastic) properties in benign tumor cells. Benign tumor cells would acquire cancerous-trophoblastic properties but would continue maintaining the characteristics of the original tissue. Therefore, cancers are many different depending on the original tissue they come from. But they share these malignant properties (invasiveness, metastatic

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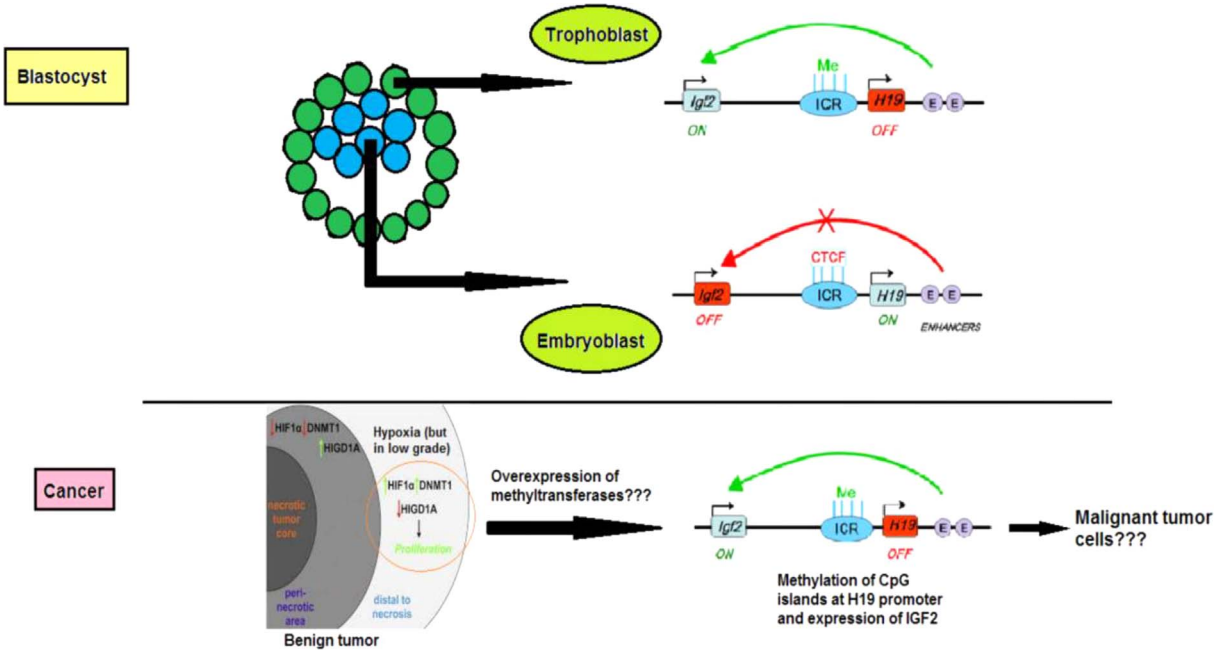

Fig. 1. Molecular mechanisms of trophoblastic tissues and malignant tumors origin. This figure resumes the hypothesis exposed. As it can be seen in the origin of trophoblast cells (green) in blastocyst, there is a methylation that impedes transcription factor CTCF to bind to the promoter of H19. Therefore, H19 is not expressed and there is an expression of IGF2 that is responsible for trophoblastic cell fate. The hypothesis expose that in cancer would occur the same. Benign tumor cells (grey) in their zones of medium-low hypoxia would upregulate HIF-1 and methyltranferases, which would provoke the expression of IGF2 and the acquisition in benign tumor cells of trophoblastic properties such as invasiveness, metastasis, immunosuppressive potential, turning into malign tumor cells or cancer.

potential, etc) that would be due to the reprogrammation of benign tumors towards a trophoblastic phenotype.

Supporting arguments

Last years many studies have provided more information at different levels about cancer and placental tissues that support the hypothesis about the linking between cancer and trophoblastic tissues.

In terms of physiology, cancer and trophoblastic tissues have similarities. Cancer cells have a very big increase in their endocytic ability, phenomenon that is profited by nanotechnology to target chemotherapy in a specific way to tumors (the EPR or *enhanced retention and permeability phenomenon*). Placental cells also have a very big endocytic ability, allowing the transport of substances like immunoglobulins by transcytosis [9,10].

Moreover, placental tissues have a very big expression of membrane proteins that function as transporters, many of them with detoxifying function. Cancer cells also have membrane transporters like p-glycoprotein or MRP, which take out chemotherapeutic drugs from the cell [1,10].

In addition, trophoblastic cells have the ability to invade endometrial corium at the implantation. Cancer cells can also invade near tissues (locoregional invasion) [1]. Trophoblastic cells can even get rid of placenta and travel by blood to other places in maternal organism [10]. This phenomenon is very similar to the beginnings of cancer metastasis. In fact, TGF-beta factor, a very important protein implicated in cancer invasiveness and metastasis [1], also regulates invasiveness of placental cells in endometrium [11]. Metalloproteinases, which are also responsible for invasiveness of cancer cells, are over expressed in trophoblastic tissues [1,12].

In the same way that placenta is a immuno-privileged organ, cancer cells and tissues have the ability of escaping immune system. It has been discovered that the mechanisms used by trophoblastic tissues and cancer are similar. Cancer and placental tissues have a very low expression of MHC class I [13,14]. Moreover, they have a high expression of molecules that induce tolerance like PDL-1 or ligands for CTLA-4 [15–17], that diminish the action of CD8 cytotoxic lymphocytes. In addition, cancer and placental cells have an over expression of HLA-G, which is implicated in immune tolerance, inhibiting the function of NK cells [18–20]. As a matter of fact, HLA-G is over expressed in melanoma, breast or gastric cancer [21–23]. Besides, both placental and cancer tissues contain immunosuppressive macrophages called M2 and over express the immunosuppressive cytokine IL-10 [24–27]. The enzyme IDO (indoleamine-2,3-dioxygenase), which is very important in immunosuppression is expressed in cancer and placental tissues [28].

Moreover, as Dr. Beard hypothesized, recent experiments demonstrate that cancer cells die with the addition of pancreatic pro-enzymes, such as trypsinogen, in culture [29].

Molecular markers such as transcription factors and other proteins are shared between trophoblastic and cancer cells. Transcription factors such as Plag1, Peg1/Mest, Peg3, Trop2 [30–32] are highly expressed in trophoblastic cells and are also over-expressed in cancer respect to normal cells. In addition, these transcriptions factors are the responsible for trophoblastic cell phenotype. Other marker, called placental alkaline phosphatase (PLAP) is highly expressed in placenta and it has been detected at high levels in seminoma, melanoma, ovarian and pancreatic cancer [30,31,33–36]. A very specific placental marker is PAPP-A (Pregnancy-associated plasma protein) [30,31]. This marker is part of the screening at first term of pregnancy. It has recently been discovered that this marker is expressed in many cancers. Besides, some experiments demonstrate that inhibiting PAPP-A stops cancer growing, invasiveness and metastasis. For example, in lung, melanoma and ovarian cancer [37–39]. Syncytin is an endogenous retroviral element. It controls the fusion of cells and makes possible the formation of syncytiotrophoblast [40]. This protein has also been detected in many cancers such as endometrial and breast, having immunosuppressive and antiapoptotic activity [41–43]. CD133 is a marker for cancer stem cells. It is also over expressed in placental cells [7,44]. Chaperone receptor “sigma” has been detected and expressed in cancer in a specific way respect to normal cells. Agonists for this receptor such as siramesin are being investigated as new antitumorals. Sigma has been detected in placenta apart form cancer, and more exactly, it acts as a chaperone for