

Cancer is a somatic cell pregnancy

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Keywords: tumor antigens, CT antigens, gametogenesis

The provocative title of this commentary stems from continuing reflection on an idea I referred to as "gametogenic program induction in cancer" published in these pages a number of years ago (1). The paper by Silva and colleagues (2) in this issue describes another tantalizing link between gametogenesis and cancer, strengthening the possibility that cancer commandeers aspects of the gametogenic program for its own purposes.

Ever since John Beard, a Scottish embryologist, focused attention on the shared features of cancer and trophoblasts, there has been much speculation that cancers acquire characteristic traits by reactivating genes normally expressed in embryonic and fetal life. The description of oncofetal and cancer-embryonic antigens, such as α -feto protein and CEA, the anomalous production of human chorionic gonadotrophin by a range of histologically distinct cancers, and the finding that developmental genes are involved in the process of invasion and metastases in experimental systems, are a few examples demonstrating how persistent, and at times revealing, this line of inquiry has been. What initially prompted me to pick up my pen in this regard was the discovery of a new class of human tumor antigens, now referred to as CT (cancer/testis) antigens, that were originally identified because of their immunogenicity in cancer patients and their recognition by CD8+ T cells (3, 4) and antibodies (5, 6). Incorporating other approaches such as representational difference analysis and *in silico* methodologies to identify genes with CT characteristics, the list of CT genes has expanded rapidly since their original discovery (7, 8). At present, 90 genes or gene families have been found having the following two distinguishing features: (i) mRNA expression in testis and cancer and (ii) no or highly restricted mRNA expression in normal adult somatic cells. Around 50% of the currently known CT genes reside on chromosome X (CT-X), where they constitute over 10% of the coding sequence and appear to be under strong positive selection (9). The other CT genes (non-X CTs) are randomly distributed on autosomal chromosomes. Monoclonal antibody reagents are now available to a number of CT antigens, thus permitting their examination at the protein level. In testis, spermatogonia are the principle CT-expressing cell type, with little or no expression in subsequent stages of spermatogenesis. Exceptions are CT genes such as SCP-1, which codes for a meiotic protein, and OY-TES-1, coding for the acrosomal binding protein of spermatocytes. In adult ovary, oocytes are rarely CT+, whereas ooblasts in fetal ovary express CT antigens. An extensive analysis of CT antigen expression throughout placental life has recently been published in *Cancer Immunity* (10). Both syncytiotrophoblasts and cytotrophoblasts are CT+, and there is a characteristic temporal expression pattern for each CT antigen. In the case of cancer, both mRNA and immunohistochemical analysis show CT

expression in a wide variety of different human cancers. The frequency of CT expression in many cancer types ranges from 5-40%, with exceptionally high expression of individual CT antigens in certain cancers, e.g. MAGEC1/CT7 in 70% of myeloma (11) and NY-ESO-1 in 80% of synovial sarcoma (12). In contrast to conventional differentiation antigens, the expression of CT antigens in individual cancers is generally highly heterogeneous. Although some tumors show expression in a high proportion of cells, this is the exception; the rule is small subsets of cancer cells expressing CT antigens, sharply delineated from non-CT expressing cells and regions.

The paper by Silva *et al.* (2) describes PLAC1 as the first member of a new class of antigens that specifically relates placentation to cancer. W. F. Chen and his colleagues have made similar observations in a paper published in the Chinese literature (13), as have Koslowski *et al.* in a recent publication (14). PLAC1 is a placenta-specific antigen that is not found in any adult normal somatic tissue. Like CT antigens, PLAC1 is expressed in a range of different cancers and cancer cell lines. However, unlike CT antigens, PLAC1 is expressed at low levels in the testis and not at all in spermatogonia. For this reason, it seems appropriate to distinguish this class of antigens from classical CT-X antigens by designating them cancer/placenta or CP antigens, with PLAC1 as CP1. Although CP1 can be expressed with other CT antigens, CP1 expression appears to have a distinct and independent profile in cancer. XAGE-2 and XAGE-3, two previously recognized CT antigens, also appear to have a CP expression pattern.

Obviously, gene products with the remarkable specificity for cancer shown by CT and CP antigens offer enormous promise as vaccine targets or as targets for small molecules or siRNA, and if cell surface CT antigens are defined, as targets for monoclonal antibodies. Vaccines against two CT antigens, MAGE-3 (15) and NY-ESO-1 (16), are far advanced in their clinical testing, and polyvalent vaccines containing multiple CT/CP antigens clearly represent the next step.

Aside from the challenge of using CT/CP antigens as targets for therapy and as markers for diagnosis and monitoring disease progression, there are several other issues that need resolution:

1. What is the basis for CT/CP expression in cancer? Hypomethylation/demethylation is known to accompany and characterize gametogenesis and carcinogenesis and is clearly involved in the anomalous expression of several CT antigens. However, the question is what initiates this process of hypomethylation/demethylation in cancer. We can also ask what other genes or gene programs relevant to cancer are brought to life in this way? A similar mechanism may account for the anomalous appearance of TL (thymus/leukemia) antigens in mouse leukemia and the activation of murine leukemia viruses in mouse tumors (17), two well-studied parallels to CT activation in human cancer.
2. What functions do CT/CP gene products have in cancer? Because many of the cardinal features of cancer are also characteristic of gametogenesis/placentation, e.g. migration,

invasion, immune subversion, apoptosis resistance, induction of angiogenesis, etc., it takes little imagination to think that CT/CP gene products controlling these processes during gametogenesis confer these same capacities on the cancer cell. Even karyotypic abnormalities of cancer could have their origin in the anomalous expression of CT antigens, namely those such as SCP-1 which are involved in meiosis. In this case, imposing a meiotic program on a mitotic cell could result in the chromosomal anarchy of cancer cells. Although there are a number of studies linking CT antigen expression to cellular function, e.g. resistance to apoptosis, chemotherapy sensitivity/resistance, migration, proliferation, etc., the search for the role of these gene products in cancer is only beginning (8, 18, 19, 20, 21). Because of the large number of CT antigens, many possibly with overlapping functions, and indications that some may be components of transcriptional networks, a strict gene to function relationship may be difficult to define.

3. The heterogeneous CT expression in tumors is striking and not understood. One of the most intriguing possibilities is that CT antigen expression marks cancer stem cells, and that CT expression disappears as the cancer cells differentiate and lose clonogenic capacity. The parallel here would be the disappearance of CT antigen expression as spermatogonia undergo differentiation into sperm. Before coming to a conclusion about CT antigens as markers for cancer stem cells, we need to assess their expression during development, and particularly in normal somatic stem cells. One study suggests that mesenchymal stem cells express certain CT antigens (22). However, before accepting this conclusion, the reliability of the serological detection systems needs to be firmly established.
4. What is the relation between oncogene/suppressor gene mutations and activation of CT antigens in cancer? The accepted view is that cancer results from the accumulation of mutational events, releasing cells from normal restraints that control their behavior. A continuing process of random mutation leads to the emergence of individual traits that together provide the cancer cell with growth and survival advantage, and with invasive and metastatic properties. An alternative view sees the cancer cell acquiring this composite phenotype in a more efficient fashion by co-opting normally silent programs that control and coordinate the complex multi-gene processes involved in gametogenesis/development. Cancer-related activation, via mutation or epigenetic activation of master switches orchestrating gametogenesis, could provide the cancer cell with a panoply of traits that, expressed in the wrong place (somatic cells) and at the wrong time (adult life), would be called malignant. According to this script, the classical mutations associated with cancer (e.g. ras, p53) represent keys to the door of cancer, but the furnishings (phenotype) that characterize the room (cancer) are derived from genes programming life's origin and acting early in development. Furthermore, as we define more precisely the genetic profile distinguishing spermatogenesis, oogenesis, and placentation, we may find that different cancers have a predilection for activating only one or the other of these gametogenic programs. Finally, the silencing of suppressor genes in cancer by hypermethylation/methylation may also be a reflection of the dynamic and normal state of these genes during gametogenesis, just as selective hypomethylation of CT genes in germ cells and cancer cells reveals this link between normal and abnormal (malignant) differentiation.

Although cancer is usually thought of as a disease of growth, perhaps a closer parallel would be to consider it a disease of reproduction. Thus, the motivation to think of cancer in terms of gametic recapitulation or as a somatic cell pregnancy. These are intriguing ideas that I justify putting forth in the spirit of an observation made by Alfred North Whitehead, the distinguished mathematician and philosopher. For him, it was more important that an idea be interesting than true. Truth simply added to interest.

Abbreviations

CP, cancer/placenta; CT, cancer/testis

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