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Cancer germline gene activation
Friend or foe?

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The human male germ line is passed on via the production of haploid sperm, which, upon fusion with the female gamete, the ovum, will form a diploid zygote that will ultimately become a genetically unique individual. Male gametogenesis occurs throughout the lifespan of adult males. Sperm production is restricted to the seminiferous tubules of the testis, and this process is continually fed by the mitotic proliferation of germline stem cells (GSCs). The GSCs are a sub-group of spermatagonial cells, which are found at the basal layer of the seminiferous tubules. Upon receipt of differentiation signals, spermatagonial cells will undergo differentiation, first maturing to primary spermatocytes and then ultimately through to fully differentiated spermatozoa. During this cellular differentiation, meiosis occurs, reducing the chromosomal content from diploid to haploid status and driving genetic variation.

Spermatagonial stem cell maintenance, spermatogenic cellular differentiation, and the reductional chromosome segregation of meiosis requires an array of molecular orchestrators that are unique to the germline, and there are a large number of genes that are specifically activated to regulate distinct processes within the spermatogenic program. These genes are regulated in a highly restricted tissue-specific fashion, and many are tightly silenced in somatic tissues. Male germline genes have been reported to be activated in cancers and can encode antigens known as the cancer/testis antigens (CTAs).[1] CTAs have garnered much interest, as their tight cancer-restricted profile makes them important potential targets for cancer immunotherapies and as diagnostic and prognostic markers;[1] indeed, recent seminal work has also demonstrated that specific assessment of germline gene expression profiles in tumors can be used for highly accurate prognostic stratification in cancer patients.[2] Most of the originally identified CTA genes (also referred to as CT genes if an associated antigen has not yet been demonstrated) are encoded by large paralogous gene families located on the X chromosome. The X chromosome becomes inactivated on entry into meiosis, however, leading Feichtinger and coworkers[3,4] to speculate that there may be a substantial number of additional genes encoding meiosis-specific proteins that could potentially serve as clinically and functionally important factors. Through the meta-analysis of clinical cancer gene expression data sets performed by this group, the CT gene family has now been extended to encompass many more single-copy, autosomally encoded genes.[3,4]

Aside from the unquestionably important potential for clinical application as biomarkers and immunotherapeutic targets, CTA/meiosis-associated genes and their products pose a bigger question that could ultimately reveal a previously unidentified weakness of cancer cells that may provide new therapeutic opportunities. There is increasing evidence supporting the view that CT genes are not simply passively activated as a byproduct of the oncogenic process, and there is a growing consensus that CT genes can actually drive oncogenesis and tumor drug resistance. This is illustrated by 2 additional seminal studies. First Janic and coworkers[5] demonstrated that germline genes were activated in l(3)mbt tumors in *Drosophila melanogaster*, and that some of these were required to promote tumor formation; subsequent meta-analysis of human cancer gene expression data sets by Feichtinger and colleagues[6] indicated that the human orthologs of the these germline genes were also extensively activated in a wide range of human tumors, inferring that an oncogenic soma-to-germline transition could be a feature of many human cancers. Second, in a distinct seminal study by Whitehurst and coworkers[7] that aimed to identify genes that de-sensitized lung cancer cells to the microtubule-stabilizing chemotherapeutic agent paclitaxel, a number of CTA genes were found to be capable of driving chemoresistance, indicating germline genes contribute to therapeutic resistance. Not only do these studies demonstrate that germline genes are important in driving the oncogenic process, it also reveals a new class of therapeutically targetable molecules, the extent and potential of which remains very poorly explored.

The proposal that a soma-to-germline transition is occurring in human cancers to drive oncogenic mitotic proliferation of cells in the soma may infer that activation of a multitude of germline genes is required. However, the evidence to support an extensive co-activation remains weak. It is possible, even likely, that the activation of one or a few key regulatory CT genes can contribute to oncogenesis in the absence of extensive germline program activation. Moreover, it is likely that distinct germline gene functions

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serve to contribute to distinct features of tumor progression and survival. While there are now many detailed questions to be addressed, it is clear that oncogenesis involves the loosening of the constraints on expression of not only X encoded germline genes, but also of the large cohort of meiosis-associated genes identified by Feichtinger and coworkers[3,4] that are autosomally encoded. Activation of meiotic functions, including programmed inter-homolog recombination and reductional chromosome segregation pathways mediated by centromeric monopolarity, in somatic cells clearly has the potential to disturb somatic cellular genetic homeostasis and provide the factors to drive the genetic instability and tumor heterogeneity that is required for oncogenic progression and therapeutic resistance.

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