In germ cell cancers, the unique reversibility of malignancy and the balance between somatic differentiation and dedifferentiation may be critical to late relapse that is dominated by non-germ cell elements. Targeting regulators of differentiation may provide a solution, and this may be elucidated via serial liquid biopsies (via circulating tumor cells). *Clin Cancer Res; 20(14); 3630–1. ©2014 AACR.

In this issue of *Clinical Cancer Research*, one of the leaders in the development of circulating tumor cell assay systems, Klaus Pantel, and his team have provided a vehicle that may improve prognostication in advanced testis cancer—the measurement of circulating tumor cells (CTC; ref. 1). In itself, it is pleasing to see a prominent group focusing anew on germ cell tumors, given the general tendency of the biomedical community to view germ cell malignancy as a "solved problem." Sadly, this exemplar of the success of careful clinical and translational experimentation recently seems to have become something of a forgotten "poster child" of solid tumor malignancy. It is important to note that patients still die of testicular cancer. Although some deaths are avoidable, and represent the product of inexperienced clinicians tackling a complex and demanding problem, or occasionally patients refusing to cooperate in optimal treatment programs, it is clear that poor-risk metastatic disease and the phenomenon of late relapse constitute problems that simply have not yet been solved.

Studying CTCs in the present context is logical, as others have shown clinical relevance of CTC measurements in other cancers (2, 3), at least as prognostic tools. Although this work may provide additional prognostic refinement, it does not really address the remaining critical issues in the biology and management of germ cell malignancy—viz., the ability to prognosticate in advanced, poor-risk germ cell tumors to stratify patients for optimal initial treatment, to understand the phenomenon of primary chemotherapy resistance, and to understand what controls late relapse (which is usually dominated by non-germ cell elements).

It may be that the factors that control the balance between the development of germ cell malignancy (oncogenesis) versus the development of normal tissues (ontogenesis) are seminal to the phenomenon of late relapse. More than 40 years ago, developmental biologists and pathologists, such as Leroy Stevens (4) and Barry Pierce (5), predominantly working in the mouse teratocarcinoma model, showed the potential reversibility of malignant change and induction of differentiation in association with the function of the STEEL gene (which codes for c-KIT ligand) and with the implantation of fragments of murine teratoma or teratocarcinoma into different sites (4, 5).

In parallel, the existence of a potentially pluripotential human solid tumor stem cell that can give rise to variable somatic differentiation was identified more than 20 years ago (6, 7), resembling aspects of the continuum of differentiation of murine teratocarcinoma (4, 5). This has explained, to some extent, the variable morphology of germ cell malignancy, at gonadal and extragonadal sites, but has not yet led to reliable, targeted therapeutic tools.

The attempt to leverage expression of the c-KIT gene in germ cell malignancy (8) has led to the demonstration of modest antitumor activity of imatinib against resistant seminoma that elaborates c-KIT mutations, in particular, but has not yet been a major step forward, perhaps because of our limited understanding of how this gene really functions in testis cancer, as compared with sarcoma and chronic myelogenous leukemia. Several other sets of genes seem to play regulatory roles within the Venn diagram that represents potentially overlapping control mechanisms in oncogenesis and ontogenesis, as well as in the biology of cryptorchidism and testicular dysgenesis (Fig. 1). These include cyclins A1, D2, and E, TGF-BR3, HOXD, and MAGE (7, 9, 10), although we do not yet understand the exact relationships between these genes and their respective functions in the above context.

Perhaps the so-called “liquid biopsy,” extracting and studying CTCs by identifying evolving molecular changes, may prove useful in characterizing the changing populations of residual cells after completion of primary treatment in poor-risk disease or in identifying those involved in the evolution of late relapse. Nastały and colleagues (1) have already shown
that higher levels of CTC seem to be present in patients with more advanced or resistant germ cell tumors. This result generally correlates with the RT-PCR studies of RNA for germ cell tumors. This result that higher levels of CTC seem to be present in patients with more advanced or resistant germ cell tumors. This result generally correlates with the RT-PCR studies of RNA for advanced disease or with extensive teratomatous differentiation, both of which are often associated with late relapse with nongerm cell elements. The nature of these changes, whether representing patterns of mutation or enhanced expression, may present potential targets for unconventional or targeted therapeutics, reflecting some of the key gene variations in the interplay between oncogenesis and ontogenesis as summarized in Fig. 1.

Returning to the issue of prognostication, the measurement of CTCs or the use of RT-PCR to identify RNA from AFP or HCG may have added a small quantum of additional, useful information, and may have provided an option to refine further the international germ cell tumor prognostic model created by the International Consensus Group (12), predicated on the impact of levels of tumor markers and other measures of tumor burden and sites of growth. Eventually, the interrogation of large data sets will define whether these approaches truly provide useful additional prognostic information, and perhaps may allow us to tailor more precisely our regimens for poor-risk advanced disease or may even allow refinement of our approach to active surveillance of stage I cases.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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2. Pantel K, Brakenhoff RH, Brandt B. Detection, clinical relevance and nongerm cell elements. The nature of these changes, whether representing patterns of mutation or enhanced expression, may present potential targets for unconventional or targeted therapeutics, reflecting some of the key gene variations in the interplay between oncogenesis and ontogenesis as summarized in Fig. 1.

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Testis Cancer: The Forgotten Poster Child

Derek Raghavan


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