

New Doctorial Cancer Research

Application of Stem Cell Markers in Search for Neoplastic Germ Cells in Dysgenetic Gonads, Extragenadal Tumors, and in Semen of Infertile Men



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Current areas of research on germ cell tumors (GCTs) include pathogenesis and mechanisms of differentiation, while clinical attention focuses on early detection and avoidance of unnecessary overtreatment. Novel findings regarding diagnosis of GCTs located in various anatomical sites are described in the thesis, with special emphasis on testicular GCTs and their common progenitor, carcinoma in situ (CIS). Recognition of CIS enables minimal treatment intervention before tumor development, but testicular GCTs are only sporadically diagnosed at this asymptomatic preinvasive stage. To develop approaches for development of a simple screening method for early detection of CIS, global gene expression studies have been performed^{1,2} with confirmation of established markers (i.e., PLAP, OCT-3/4, KIT) and identification of novel markers (i.e., AP-2gamma, NANOG).^{3,4} Several noninvasive detection methods have been tested, and an AP-2gamma-based immunocytological semen analysis has shown a clinical potential with a specificity of 93.6%, but a sensitivity of 54.5%. The assay was the first where diagnosis of CIS was obtained by noninvasive screening in a supposedly healthy control participant.⁵ The CIS expression profile shared many similarities with embryonic stem cells and provided additional support to the hypothesis of the origin of CIS from primordial germ cells or gonocytes. Comparative studies of gonadal and extragonadal GCTs in males and females have revealed many similarities, pointing toward similar, but not identical, origins.^{6,7} Moreover, infertility and testicular cancer are connected in the Testicular Dysgenesis Syndrome and 25% of contralateral testes from testicular GCT patients harbor dysgenetic features, including impaired spermatogenesis.⁸ Thus, the studies on which this thesis is based provided potential diagnostic tools, including detection of CIS cells in semen, measurement of additional GCT markers in serum, and novel stem cell markers for immunohistochemical diagnosis of GCTs located in the gonads and in extragonadal (reviewed in Ref. 9), thus contributing to a better understanding of initiation and progression of GCTs as well as better clinical management.

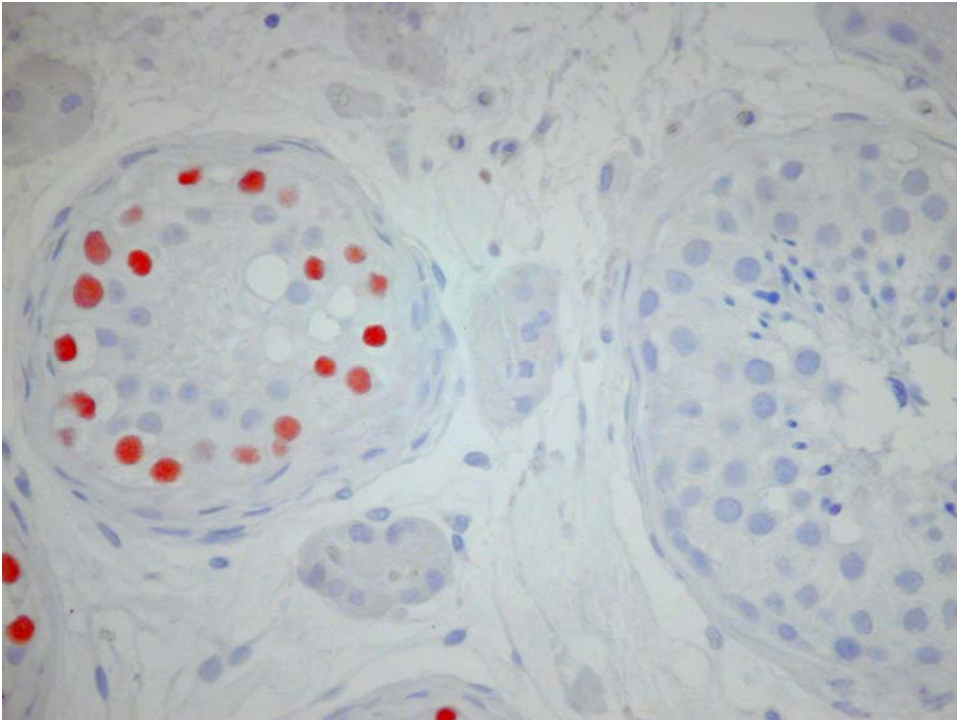


FIGURE 1. Testicular tissue is shown, where the tubule at the left contains the precursor cells of testicular germ cell tumors, the carcinoma in situ (CIS) cells that are stained with AP-2gamma immunohistochemically. At the right is a tubule with full spermatogenesis, where none of the cells express AP-2gamma. AP-2gamma is a solid CIS marker and suitable for noninvasive screening of exfoliated CIS cells.

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Comment by Professor Aleksander Giwercman

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Testicular germ cell cancer (TGCC) is a fascinating disease, from the clinical as well as the biological points of view. There is now a good evidence for the hypothesis of foetal origin of this malignancy. However, we still do not know why the incidence of TGCC has been increasing for decades. Although the cure rate in many countries is close to 95%, the long-term side effects of the treatment of the young men suffering of TGCC are serious and efforts should be made to diagnose the disease at the early, noninvasive, stage when cytotoxic treatment or radiotherapy are not needed. The intriguing issues of the biology of TGCC include the fact that different histological types of TGCC seem to have a joint precursor—carcinoma in situ (CIS). Furthermore, tumors with similar histology to that of TGCC can be found in the ovaries and in extragonadal sites as the retroperitoneum, mediastinum, and brain. The PhD thesis of Christina Engel Hoei-Hansen is a new and impressive product of the line of research initiated in 1972 by Niels Erik Skakkebaek's discovery of CIS. In the list of supervisors, he is

joined by two other internationally well-established scientists within this area of research, his colleagues from the Department of Growth and Reproduction at the Rigshospitalet, Copenhagen, Denmark, Ewa Rajpert De-Meyts and Henrik Leffers. This mixture of clinical, biological and molecular expertise combined with Christina Engel Hoei-Hansen's capability to bridge these areas, give this PhD thesis a true "translational" touch. Using the techniques of differential display and cDNA microarrays, novel markers of CIS and TGCC were discovered. Through applying these markers, a link between CIS and fetal gonocytes as well as between gonadal and extragonadal germ cell tumors have been established. Furthermore, the new markers were used to develop methods for detecting CIS in semen. For the first time ever, testicular malignancy was diagnosed in a man who delivered a semen sample for routine infertility workup. This gives a hope for future possibility of early, noninvasive detecting of TGCC. The thesis is based on 11 papers published in highly ranked international journals. It is very well written and gives an excellent state-of-the-art overview on the biology and early detection on TGCC. I will highly recommend this to those who want a comprehensive introduction or updating in this exciting area of science.