

## New Doctorial Cancer Research

# Normal and Malignant Germ Cell Development

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Defining normal and malignant germ cell development is crucial for understanding the biology and behavior of germ cell tumors. Germ cell tumors show significant similarities with immature germ cells. Furthermore, treatment sensitivity of germ cell tumors reflects the intrinsic characteristics of the cell of origin, and their derivatives. The aim of this thesis was to identify factors involved in the development of normal and malignant human germ cells. The marker profile of male and female germ cells during normal foetal development was established and compared to the profile found in dysgenetic gonads. Furthermore, the role of extracellular factors such as the microenvironment was addressed, and links between pluripotency, cellular differentiation, and treatment response were investigated.

A number of markers for early germ cells could be confirmed and further characterized.<sup>1,2</sup> In particular, the timing of the regulation of the most relevant markers during normal germ cell maturation was established, distinguishing an immature and a more mature phenotype of human germ cells. The investigated markers were, among others, E-cadherin,  $\beta$ -catenin, TSPY (testis-specific protein, Y-encoded), VASA, and OCT3/4. From our results, we conclude that external factors such as cell-cell signaling create a niche that is essential to ensure normal germ cell development.

The analyses were then extended to tissue samples showing delayed or disturbed maturation. This confirmed markers for the diagnosis of preinvasive malignant germ cells in postpubertal gonads, and resulted in the model that immature germ cells in preinvasive lesions express OCT3/4 and TSPY before progressing to invasive growth.<sup>3</sup>

An amazing finding was the detection of germ cell-lineage differentiation in nonseminomatous germ cell tumors.<sup>4</sup> Human germ cell tumors must therefore be regarded as truly totipotent tumors with unrestricted developmental potential. From a technical point of view, this finding should encourage efforts to cultivate cells with germ cell properties from pluripotent embryonal carcinoma cell lines. If successful, this could result in a readily accessible cell system without the ethical issues and legal restrictions associated with the use of normal primordial germ cells derived from healthy human sources.

Finally, our investigations present findings of different factors supposedly involved in chemotherapy resistance. Neither E-cadherin and  $\beta$ -catenin, nor XPA were found to be associated with treatment resistance in germ cell tumors in general.<sup>5,6</sup> However, these proteins are examples of factors that are differentially regulated during development, and could therefore be involved in mechanisms of the intrinsic resistance seen in teratomas. This illustrates that in germ cell tumors, it is particularly important to interpret results in view of aspects of developmental biology, which are underlying the diverse histologic subtypes.

## REFERENCES

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**Comment by Ewa Rajpert-De Meyts**  
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This thesis is an example of a fruitful collaboration between two European research groups prominent in testis cancer research. The author, Friedemann Honecker, a young physician trained in internal medicine and oncology at the Department of Oncology & Hematology, University of Tübingen, Germany, decided to do more basic research at the Laboratory for Experimental Patho-

Oncology, Department of Pathology, Josephine Nefkens Institute, Erasmus University in Rotterdam, the Netherlands. His venture resulted in an excellent doctoral thesis and in six papers published in prestigious international journals, including three articles in a top pathology journal, the *Journal of Pathology*.

The thesis aimed to shed more light on the pathogenesis of germ cell tumours by better characterization of the expression pattern of selected genes, such as OCT-3/4, TSPY, VASA, E-cadherin, and  $\beta$ -catenin during gonadal development and early stages of germ cell neoplasia. The research resulted in a detailed description of the developmental expression profile of these genes in both normal and dysgenetic male and female gonads and confirmed that the developmental delay of early germ cell maturation is the key event that leads to neoplastic transformation of germ cells. This work provided a very good definition of an early neoplastic germ cell.

The interesting observation of primitive OCT-3/4-positive germ cells within a nonseminomatous tumor, indicative of possible differentiation of germ cells from stem cells of this tumor (presumably embryonal carcinoma) may have important clinical implications, if confirmed independently in more cases or by other groups. Finally, the thesis investigated and excluded a possible association of some genes with treatment resistance in germ cell tumors. All in all, this is a very impressive doctoral thesis and a valuable contribution to world literature in the germ cell cancer field.