

New Doctorial Cancer Research

Diagnostic and Prognostic Value of Molecular Cytogenetic Analyses of Sextant Biopsies from Prostate Cancer Suspects



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Prostate cancer is one of the most prevalent human malignancies and a common cause of cancer-related morbidity and mortality. The great variation in clinical behavior of these tumors creates a major dilemma in the treatment-decision process, since not all men with microscopic carcinoma require aggressive radical therapy. Given the present-day absence of a reliable way to predict which cancers will remain indolent and which are going to kill the host if left untouched, identification of molecular markers that could stratify these patients according to risk of disease progression would have a strong health and socioeconomic impact. Through six original reports, this thesis describes the application of molecular cytogenetic techniques, namely, chromosomal comparative genomic hybridization (cCGH), array-based CGH (aCGH), and fluorescence in situ hybridization (FISH), to diagnostic needle-biopsy samples from prostate cancer suspects, with the goal of identifying genetic markers with diagnostic or prognostic significance in this neoplasia. The same analyses were additionally performed on normal, benign, premalignant, and malignant lesions of the prostate collected from patients diagnosed with cancer (prostatectomy specimens), in order to better characterize the spectrum of aberrations underlying prostate cancer development and progression.

We show that most prostate carcinomas display genomic copy number changes, as opposed to benign hyperplasias and premalignant lesions, and that several genetic aberrations confer a more aggressive phenotype to these tumors. Specifically, increased genomic complexity, gain at chromosome arms 7q and 8q, and loss at 6q, 10q, and 13q were associated with progression into locally invasive and/or metastatic disease. More importantly, we demonstrate that it is possible to reliably detect these alterations in ultrasound-guided prostate biopsies from prostate cancer suspects, enabling us to obtain relevant information at a stage in which it may aid the therapeutic decision process for these patients. In particular, gain at 8q detected in sextant biopsies was independently associated with poor disease-specific survival, identifying patients at a higher risk of dying from the disease even after a short follow-up time.

We conclude that molecular cytogenetic analysis of diagnostic sextant biop-

sies is feasible and informative for the clinical management and follow-up of patients diagnosed with prostate cancer, and show that a standard protocol can easily be established in the clinical practice to identify patients to whom potentially curative surgery should be offered, while sparing the remaining to the significant side effects associated with this intervention. Our work additionally provides a comprehensive characterization of the profile of DNA copy number changes detectable in this malignancy, allowing the proposal of a genetic pathway involved in prostate carcinogenesis.

Comment by Anne Kallioniemi
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The thesis work by Francilm Ricardo da Silva Ribeiro focuses on a very important aspect of prostate cancer research, namely, the identification of molecular markers that could be used in predicting the clinical course of the disease. The thesis includes six original publications that have been published in high-quality international journals. In three of the articles, cytogenetic and molecular cytogenetic techniques have been applied to search for genetic changes in diagnostic needle-biopsy specimens in prostate cancer suspects, with a special emphasis on identification of aberrations that are associated with disease progression. The results obtained nicely illustrate that increased copy number at the 8q region, especially at the *MYC* oncogene locus, is an independent indicator of poor prognosis in prostate cancer. This is an important discovery, but further large-scale studies are still needed in order to fully establish the actual clinical utility of this finding.

The second main theme in the thesis work has been the elucidation of the genetic progression pathway of prostate cancer. In this part of the work, samples representing various stages of prostate cancer development, ranging from benign and premalignant lesions to advanced cancer specimens, were evaluated using comparative genomic hybridization (CGH). In addition, a comprehensive meta-analysis of previously published CGH studies on prostate cancer was performed. A combination of data from these sources allowed the candidate and coauthors to suggest a genetic progression model in which two different pathways lead to prostate cancer development. Such a model provides new interesting information on the genetic background of this disease and seems to imply that all prostate cancers are not genetically equal. Finally, the recently discovered *TMPRSS2-ERG* fusion gene was also examined and was shown to occur already in a subset of premalignant lesions, i.e., in high-grade prostatic intraepithelial neoplasias. This is a novel finding that illustrates that the *TMPRSS2-ERG* fusion is an early event in prostate cancer pathogenesis. Taken together, this thesis has provided a wealth of new information on the genetic changes associated with prostate cancer development and progression.