New Doctorial Cancer Research

Germline Genetic Alterations Affecting CDKN2A, MDM2, and CDKN1A in Melanoma and Breast Cancer Patients

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The main goal in this work was to characterize selected genetic alterations that were potentially cancer risk modulating in melanoma and breast cancer patients. During a study initiated to analyze factors possibly causing chemoresistance in malignant melanoma, one of the study participants was found to be of a family likely to harbor an inherited cancer syndrome. This family revealed abnormally high incidence of melanomas, including two individuals diagnosed with two or more primary melanomas. We aimed at identifying, and performing a full characterization of, the underlying genetic mechanism.

We identified the genetic mechanism to be large genomic deletion of 10,150 bps within the CDKN2A gene (the gene encoding the tumor suppressors p16\textsuperscript{INK4a} and p14\textsuperscript{ARF}). One of the deletion breakpoints was located to position 6093 upstream of exon 1\textalpha{}, and the other to position 161 of exon 2, thus removing exon 1\textalpha{} and half of exon 2.\textsuperscript{1} Initially, the melanoma-prone family displayed linkage to 9p21 (location of CDKN2A), but no mutations in the CDKN2A gene were identifiable through use of routine screening methods. The observation leading us to the identification of the deletion came from cDNA-based analyses, with subsequent sequencing of BAC-clones carrying large genomic fragments. Based on this observation, we have postulated that at least some of the cases where inherited malignant melanoma display linkage to 9p21, but no mutations are identified, may be caused by deletions that are not easily identified through routine screening methods.

In a previous breast cancer study performed by our group, focusing on the CDKN1A locus, the first observation of \textit{p21G251A} is described.\textsuperscript{2} This polymorphism was found not to correlate to resistance to chemotherapy. Subsequently, we explored the possible association between this novel polymorphism and breast cancer risk.

Through screening of the prevalence of \textit{p21G251A} in different breast cancer cohorts and healthy controls, we found this polymorphism to be significantly correlated to the subgroup of locally advanced breast cancers (\(p = 0.0049\)).\textsuperscript{3} This is the first identified genetic change specific for locally advanced breast cancers.
The finding that this subclass of breast cancers correlates to a polymorphism in a gene involved in cell cycle regulation, such as $p21^{WAF1/CIP1}$, is highly interesting and makes sense in a biological perspective, because locally advanced cancers may be expected to be fast growing.

Since the first report on the alternative mRNA (encoding p21B) from the CDKN1A locus, this transcript has been studied by our group. Because very little is known about this second CDKN1A product, we aimed at performing a large screening, addressing the potential role of p21B mutations as breast cancer risk factors.

The screening of p21B revealed that mutations affecting this transcript are rare. In 521 breast tumor samples analyzed, only one point mutation affecting the p21B protein was observed. No mutations were found when screening a panel of 20 established cell lines. However, a novel polymorphism, $p21B_{G128T}$, was identified, and a screening for this polymorphism was performed in an extended breast cancer cohort and a large cohort of healthy controls. The distribution of $p21B_{G128T}$ was found to be similar among breast cancer patients and healthy controls ($p = 0.273$). These data have provided the first indications that mutations of p21B, although the protein is thought to be involved in apoptosis, do not play a key role in carcinogenesis. Furthermore, the polymorphism $p21B_{G128T}$ was found not to be associated with breast cancer risk.

REFERENCES


Comment by Dr. Randi Syljuåsen
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The dissertation focuses on genetic germline alterations that modulate breast cancer and malignant melanoma risks. A major result of this work was the identification of a novel deletion in the CDKN2A gene in a melanoma-prone family. This is an important finding since most conventional mutation screening techniques will fail to detect this deletion, and such deletions could therefore potentially be a common mechanism in melanoma and other hereditary cancers. Another major finding was the association between the p21 polymorphism p21G251A with locally advanced breast cancer. The p21G251A polymorphism may therefore play an unknown specific functional role to promote the development of locally advanced cancers. The dissertation is thoroughly and well done, and represents a highly valuable contribution to the field of germline alterations and cancer risk.