Critical Reviews™ in Oncogenesis, 13(3):261–263 (2007)

New Doctorial Cancer Research

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

Stian Knappskog

Stian Knappskog

Section of Oncology, Institute of Medicine, University of Bergen

Ph.D. Dissertation date: March 30, 2007
Supervisor: Professor Per Eystein Lønning
and Professor Johan Lillehaug

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 $p16^{INK4a}$ and $p14^{ARF}$). One of the deletion breakpoints was located to position 6093 upstream of exon 1α, and the other to position 161 of exon 2, thus removing exon 1α and half of exon 2.[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 $p21^{G251A}$ is described.[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 $p21^{G251A}$ in different breast cancer cohorts and healthy controls, we found this polymorphism to be significantly correlated to the subgroup of locally advanced breast cancers ($p = 0.0049$).[3] This is the first identified genetic change specific for locally advanced breast cancers.

0278–940X/07/$35.00

The finding that this subclass of breast cancers correlates to a polymorphism in a gene involved 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,[4] 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.[5] 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

1. Knappskog S, Chrisanthar R, Staalesen V, Børresen-Dale AL, Gram IT, Lillehaug JR, Lønning PE. Mutations and polymorphisms of the p21B transcript in breast cancer. Int J Cancer. 2007;121:908–10.
2. Staalesen V, Leirvaag B, Lillehaug JR, Lønning PE. Genetic and epigenetic changes in p21 and p21B do not correlate with resistance to doxorubicin or mitomycin and 5-fluorouracil in locally advanced breast cancer. Clin Cancer Res. 2004;10:3438–43.
3. Staalesen V, Knappskog S, Chrisanthar R, Nordgard SH, Løkkevik E, Anker G, Østenstad B, Lundgren S, Risberg T, Mjaaland I, Gram IT, Kristensen VN, Børresen-Dale AL, Lillehaug JR, Lønning PE. The novel p21 polymorphism p21 G251A is associated with locally advanced breast cancer. Clin Cancer Res. (2006);12(20):6000–4.
4. Nozell S, Chen X. p21B, a variant of p21(Waf1/Cip1), is induced by the p53 family. Oncogene. 2002;21:1285–94.
5. Knappskog S, Geisler J, Arnesen T, Lillehaug JR, Lønning PE. A novel type of deletion in the CDKN2A gene identified in a melanoma-prone family. Genes Chromosomes Cancer. 2006;45:1155–63.

Comment by Dr. Randi Syljuåsen

Institute for Cancer Research, The Norwegian Radium Hospital

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.