Sandra Blöthner
Dr.sc.hum.

Somatic alterations in critical genes in malignant melanoma: Effect on global gene expression

Geboren am 04.06.1973 in Weimar
Diplom der Fachrichtung Biotechnologie am 01.03.2002 an der Fachhochschule Jena

Promotionsfach: DKFZ (Deutsches Krebsforschungszentrum)
Doktorvater: Priv.-Doz. Dr. Rajiv Kumar

The overall aim of this study was to understand molecular genetic events and their consequences in cutaneous malignant melanoma. This thesis has focused on the characterisation of somatic alterations in the *B-RAF* and *N-RAS* proto-oncogenes and the tumour suppressor gene *CDKN2A.* We evaluated the consequences of the most prominent mutation in *B-RAF*, V600E; a common mutation in *N-RAS*, Q61R; and homozygous deletion of the *CDKN2A* locus genes on global gene expression in melanoma cell lines. Additionally, we examined the effect of the V600E *B-RAF* mutation on global gene expression in benign melanocytic nevi. The studies were performed on a large series of metastatic melanoma cell lines and benign melanocytic nevi.

Our main findings suggest (a) high frequency of mutually exclusive mutations in *B-RAF* and *N-RAS* genes in melanoma, (b) overlap between mutations in *B-RAF/N-RAS* genes and *CDKN2A* alterations and (c) relationship between expression and alterations of these genes. The data from global gene expression suggest that alterations in *B-RAF*, *N-RAS* and *CDKN2A* in melanoma result in up- and downregulation of several genes involved in critical cellular functions. Similarly, we also detected up- and downregulation of critical genes in melanocytic nevi when compared with non-nevus skin tissue as well as in nevi with *B-RAF* mutation compared to nevi without mutation. Surprisingly, a number of genes upregulated and downregulated were common to both melanoma cell lines and melanocytic nevi with V600E *B-RAF* mutation.

Thus, our results suggest, mutations in the *B-RAF* gene and to a certain extent in *N-RAS* are early but insufficient events that occur in nevi. The loss of *CDKN2A* most likely constitutes a second genetic ´hit´ required for melanoma progression. Our data in this study are in accordance with recent findings where escape from initial senescence response due to oncogenic mutation has been shown to require loss of additional check points like p16 and ARF. Further, these alterations cause differential regulation of genes involved in critical cell regulation pathways. Upon further validation these results can be used for identification of molecular targets for prognostic and therapeutic purposes.