Dominique Scherer
Dr.sc.hum.

Variants in pigmentation and DNA repair genes: Role in basal cell carcinoma of skin and cutaneous melanoma

Geboren am 14.12.1978 in Münster
Diplom der Fachrichtung Biologie am 31.03.2006 an der Ruprecht Karls Universität Heidelberg

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

The purpose of the present thesis was to determine the impact of polymorphisms in the *melanocortin receptor 1* (*MC1R*) gene and in genes that act in DNA repair pathways on skin cancer susceptibility. MC1R activation results in an increase of eumelanin, the type of melanin that protects the skin against damaging UV radiation. We observed that polymorphisms within the gene that potentially reduce MC1R function were associated with an increased risk of basal cell carcinoma of skin and melanoma. The risk was doubled for carriers of variants that are associated with red hair and fair skin (RHC variants). Estimation of the proportion of disease risk that is attributed to *MC1R* variants was more than 25% for both types of skin cancer. Interaction of MC1R variants and host factors in BCC revealed that *MC1R* variants imparted risk of the disease not only due to the effect on pigmentation. Moreover, significant interaction between *MC1R* variants and the T241M polymorphism in the homologous DNA repair gene *XRCC3* was observed in BCC implying the probable involvement of MC1R in DNA repair, while no significant interaction was observed for MC1R variants with other pigmentation related genes *tyrosinase* (*TYR*) or *agouti signalling protein* (*ASIP*) or with pigmentation unrelated polymorphisms on the long arm of chromosome 1.

The investigation of susceptibility to melanoma performed in Spanish and German populations revealed association of the disease with distinct *MC1R* variants. Essentially, in the Spanish population non-RHC variants as well as RHC variants significantly increased the risk of

melanoma, while in the German population only RHC variants imparted risk. In addition, *MC1R* variant carriers were also at elevated risk of second primary melanoma. Furthermore, we observed that *MC1R* variants influence the frequency of somatic mutations in *BRAF* and *NRAS* genes in melanoma tumours. Carriers of *MC1R* variants seemed to be less prone to develop mutations in *BRAF* compared to non-carriers. In contrast, *MC1R* variant carriers revealed higher *NRAS* mutation frequency than non-carriers.

DNA repair mechanisms constitute intrinsic mechanisms to protect cells against endogenous or exogenous damage. Disruption of the mechanisms undoubtedly leads to genomic aberration. In a combined analysis of previously published studies we observed no significant association between polymorphisms in DNA repair genes and risk of melanoma. Nevertheless, four variants in three DNA repair genes significantly modified progression of the disease. The *XRCC1* R399Q variant was significantly associated with increased overall survival and metastasis free survival, while carriers of the *XRCC1* -77 variant showed decreased survival following metastasis. In addition, the two variants *ERCC2* K751Q and *ERCC5* D1104H were significantly associated with reduced overall survival.