Abstract

Cancer, one of the leading causes of death world wide, frequently exhibits a marked sex preference with respect of incidence, course of disease and survival time. The development of malignant tumors is determined by exogenic factors as well as risk modifying gene variants. The specific causes of cancers and of their sex preference are mostly unknown. The identification of tumor risk modifying gene variants is an essential prerequisite for the development of efficient prevention measures and curative therapies on the long run. Importantly, in contrast to tumor suppressor genes cancer risk modifying gene variants are not necessarily expressed in the tissue the tumor arises from, but also can act systemically.

Inbred rodent models are particularly suitable for the analysis of the genetic basis of tumor susceptibility and resistance, respectively, since these animals are genetically identical and can be maintained under standardized living conditions.

After application of ethylnitrosourea (ENU) on postnatal day 1, BDIX rats develop malignant tumors of the peripheral nervous system with an incidence of > 85 %, arising from *Neu/Erbb2* mutated premalignant Schwann cells in the trigeminal nerves. In MPNST resistant BDIV rats, the premalignant cells are eliminated under the participation of the immune system, thereby preventing tumor development. Genome wide association analyses using ENU-treated segregating crosses of BDIX and BDIV rats identified seven autosomal loci controlling tumor risk in an allele- and sex-specific manner. Homozygous BDIV alleles at the locus *Mss4* on chromosome 6 mediated tumor resistance in female (BDIV x BDIX) F_2 rats. The effect of the locus was confirmed by ENU application to congenic BDIX.BDIV-*Mss4a* rats. This strain carries BDIV alleles exclusively in the telomeric 60 % of the tumor resistance haplotype, which was previously identified in the F_2 generation.

This dissertation included fine mapping of the *Mss4* locus originally spanning 20 Mb to approximately 1.1 Mb by exposing three additional congenic and subcongenic rat strains, carrying BDIV alleles in different segments of the tumor resistance haplotype, to ENU and subsequently analyzing their tumor incidences and survival times. The fine mapped *Mss4* interval comprised 15 positional candidate genes. Comparative sequencing of protein coding and regulatory portions of the candidate genes in BDIX and BDIV rats, transcriptional analyses in the trigeminal nerves and functional information were used to prioritize candidate genes with respect to their potential relevance for the sex-specific tumor risk.

Gpx2, encoding glutathione peroxidase 2, has been associated with resistance towards tumor initiation repeatedly, and therefore represented a particularly interesting candidate gene. However the trigeminal nerves of the parental as well as of the (sub)congenic rat strains did not unequivocally express Gpx2 protein. However, an invasion of Gpx2 expressing mast cells in the trigeminal nerves of ENU-exposed BDIX and BDIV rats could be

noticed. Notably peritoneal BDIV mast cells expressed Gpx2 to a higher extent than BDIX mast cells.

The *Esr2* gene encodes the estrogen receptor beta. While in congenic strains each BDIV insert mediated tumor resistance to a similar degree, only the *Mss4a* fragment mediated a sex-specific effect. In contrast to the *Mss4c* and *Mss4d* fragments, it covers the telomeric third of the tumor resistance haplotype which might contain the BDIV variant of a cofactor of *Esr2.* The *Med6* gene constitutes an interesting functional and positional candidate, the BDIV allele of which might interact with *Esr2* to mediate the sex preference of MPNST development by inducing a sex biased regulation of gene expression in trigeminal nerves.