TECHNISCHE HOCHSCHULE DEGGENDORF

TRANSCRIPTIONAL REGUALTION IN MALIGNANT MELANOMA

THE AP-1 MEMEBERS C-JUN AND FRA-1 MEDIATE BIDIRECTIONAL TRANSCIPTION REGULATION IN MALIGNANT MELANOMA

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Abstract

Projekttitel/ Project title:

The AP-1 members c-Jun and Fra-1 mediate bidirectional transcription regulation in malignant melanoma

Kurztitel/ Short title:

Transcriptional regulation in malignant melanoma

Einleitung/ Introduction:

Malignant melanoma, a highly aggressive type of skin cancer, evolves from the transformation of melanocytes. Its stepwise progression to a metastatic cell state is characterized by specific mutations and dynamic transcriptional changes, largely driven by deregulated signaling pathways and tumor-relevant transcription factors (TFs). The AP-1 family is a versatile group of TFs known to be relevant in malignant melanoma by controlling the expression of specific target genes which causes functional and molecular alterations. This fosters the acquisition of cancer-related traits including migration and invasion, thereby supporting a malignant phenotype.

Ziel/ Aim:

The project aims to get a more detailed view on the AP-1 family in malignant melanoma by understanding the molecular mechanisms related to AP-1 DNA-binding modalities and the impact on tumor development and progression mediated by AP-1-regulated gene expression.

Methode/ Method:

Chromatin Immunoprecipitation combined with massively parallel sequencing (ChIP-sequencing) was used to study the interaction between AP-1 members c-Jun and Fra-1 with the DNA, concurrently allowing the identification of genome-wide binding sites. RNA-sequencing followed by a Differential Gene Expression (DGE) analysis further allowed us to obtain insights into cancer-related changes of expression patterns in malignant melanoma and combine them with genes potentially regulated by AP-1.

Ergebnis/ Result:

Peak detection and subsequent intersection of the ChIP-seq data sets using the HOMER software toolbox demonstrated a high overlap between c-Jun and Fra-1 binding sites, with the majority of all peaks (~80%) possessing a classical AP-1 binding motif. Genomic peak annotation showed that around 10% of overlapping c-Jun/Fra-1 binding sites are located in promoter regions of genes. Notably, integrating the results from our DGE analysis revealed an upregulation of the expression of around two-thirds of potential c-Jun/Fra-1 target genes in melanoma, while the remaining ones were negatively regulated. In accordance with this, we detected a positive correlation between the expression fold-change and the transcriptional activation marker H3K27ac. Bioinformatical enrichment analyses illustrated that upregulated genes are enriched in cancer-related processes such as migration and cell adhesion, whereas the downregulated ones were linked to pigmentation.
Overall, our data suggest a bidirectional regulation mode of c-Jun and Fra-1 by positively coordinating the transcription of genes associated with a more invasive phenotype, while repressing those accounting for melanocyte differentiation.

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