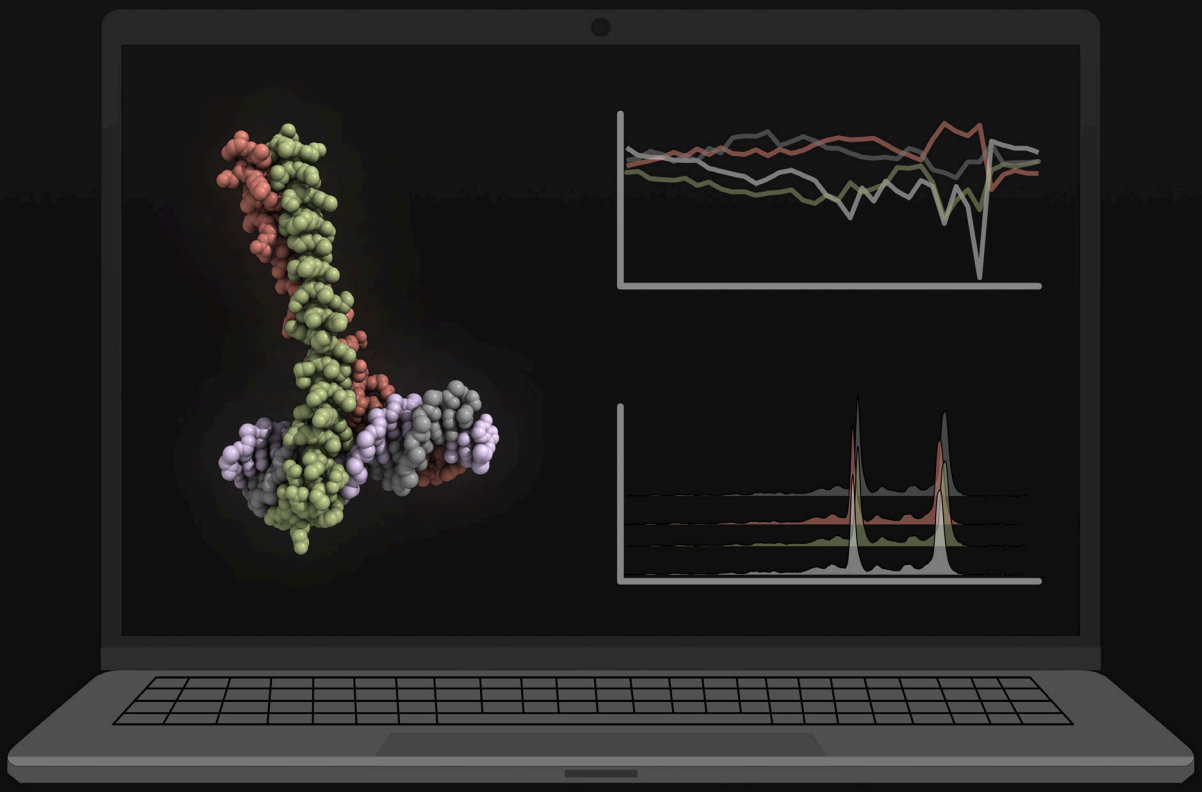
TECHNISCHE HOCHSCHULE DEGGENDORF



BIOINF

ELUCIDATING THE REGULATORY AND FUNCTIONAL ROLE OF AP-1 TRANSCRIPTION FACTORS IN MALIGNANT MELANOMA USING NEXT-GENERATION SEQUENCING.

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Abstract

Projekttitel/ Project title:

Molecular mechanisms of differential transcriptional activity of AP-1 factors c-Jun, Fra-1 and ATF-2, and their functional significance in malignant melanoma

Kurztitel/ Short title:

Transcriptional regulation in malignant melanoma

Einleitung/ Introduction:

The development and progression of malignant melanoma, a highly aggressive type of skin cancer, are characterized by dedifferentiation and molecular changes in melanocytes induced by various gene defects, deregulated signaling pathways, and the deregulation of tumor-relevant transcription factors. Transcription factors, which are proteins that bind specific DNA sequences, belonging to the AP-1 family play an important role in malignant melanoma and were shown to cause changes in the expression of specific, oncogenic target genes, which can result in critical functional alterations and thus in the development of a malignant cell type.

Ziel/ Aim:

This project seeks to further elucidate the role of the AP-1 family in the development and progression of malignant melanoma. More precisely, we want to decipher the molecular mechanism of AP-1-DNA binding modalities, its regulation, and the resulting effects on gene expression as well as the involvement of potential co-transcription factors.

Methode/ Method:

We use Chromatin Immunoprecipitation combined with massively parallel sequencing (ChIP-sequencing) to study the interaction between proteins and the DNA, which simultaneously allows the identification of specific DNA-binding sites. Additionally, RNA-sequencing followed by a Differential Gene Expression (DGE) analysis is performed to gain insights into cancer-related changes in expression patterns induced by aberrant AP-1 regulation.

Ergebnis/ Result:

Our data led to new essential insights into the regulatory mechanisms of AP-1 factors in melanoma. Based on c-Jun and Fra-1 ChIP-Seq experiments, we were able to identify common as well as specific c-Jun and Fra-1 DNA binding sites in different melanoma cell lines. A *de novo* motif analysis revealed the presence of classical AP-1 binding motifs in the majority of all common c-Jun/Fra-1 peaks and that they are located in transcriptionally active regions of the genome. Further, we used additional bioinformatical analyses to focus on other binding motifs near the AP-1 consensus sequence and thereby observed an enrichment of TEAD binding motifs nearby, suggesting a potential role as a co-regulatory factor.

Moreover, we detected a combined AP-1 and TEAD motif in around 100 genes that were significantly deregulated in malignant melanoma, whereby the expression levels of individual genes appeared to be dependent on the melanoma stage. Functional analysis of these genes points to an involvement in biological processes like cell proliferation and cell transformation.

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