Mechanisms of ETS1/KDM3A Interaction with PAX3-FOXO1 in Fusion-Positive Rhabdomyosarcoma

Joseph (Joe) Hsieh, Lays Sobral, and Paul Jedlicka

Introduction

Rhabdomyosarcoma (RMS), a malignancy of mesenchymal origin with impaired myogenic differentiation, is the most common pediatric soft tissue cancer. Molecularly, RMS is classified into fusion-negative and fusion-positive RMS (FP-RMS). Clinically, the fusion status has strong prognostic value with FP-RMS representing a highly aggressive disease with dismal outcomes. Thus, there is a dire need for increased knowledge of FP-RMS oncogenesis and therapeutic opportunities.

The fusion forms a novel oncogenic pioneer factor involving PAX3 and FOXO1 that drives aberrant gene expression, promotes metastasis, and impairs differentiation. The oncopfusion PAX3-FOXO1 (P3F) employs epigenetic mechanisms, such as activation of enhancers and recruitment of chromatin factors, to drive FP-RMS disease gene expression. Given the difficulties in targeting P3F, understanding of P3F cofactors may reveal alternative therapeutic strategies for FP-RMS.

Preliminary Data

A P3F/KDM3A/ETS1 regulatory axis driving FP-RMS disease.

Critical Method

How do P3F, KDM3A, ETS1, and cofactors together regulate expression of FP-RMS disease-promoting genes?

Results

ETS1 and BRG1 regulate each other’s, and KDM3A and P3F chromatin recruitment.

Gene expression changes only subtly influenced by H3K27ac changes.

Conclusions

- ETS1, KDM3A, P3F, and BRG1 colocalize at disease-promoting gene enhancers.
- ETS1 and BRG1 regulate each other’s localization to disease gene loci, and regulate KDM3A and P3F chromatin binding.
- Gene expression changes only minimally influenced by H3K27ac levels.

Future Directions

- Verify chromatin recruitment findings in Rh41 cells and examine P3F role in chromatin localization of cofactors.
- Role of ETS1 in modulating P3F chromatin remodeling pioneer activity.
- Role of pETS1-T38 in modulating chromatin recruitment and disease phenotypes.
- Protein-protein interactions between factors.