Title: PAX3-FOXO1: Zooming in on an “undruggable” target

Authors: Marco Wachtel, Beat W. Schäfer

PII: S1044-579X(17)30158-X
DOI: https://doi.org/10.1016/j.semcancer.2017.11.006
Reference: YSCBI 1405

To appear in: *Seminars in Cancer Biology*

Received date: 14-6-2017
Revised date: 31-10-2017
Accepted date: 13-11-2017

Please cite this article as: Wachtel Marco, Schäfer Beat W.PAX3-FOXO1: Zooming in on an “undruggable” target.*Seminars in Cancer Biology* https://doi.org/10.1016/j.semcancer.2017.11.006

PAX3-FOXO1: Zooming in on an “undruggable” target

Marco Wachtel and Beat W. Schäfer*

University Children´s Hospital, Children’s Research Center and Department of Oncology, Steinwiesstrasse 75, CH-8032 Zürich, Switzerland

*To whom correspondence should be addressed: Department of Oncology, University Children´s Hospital, Steinwiesstrasse 75, CH-8032 Zürich, Tel +41442667553 or +41446348852, email: beat.schaefer@kispi.uzh.ch

Abstract

Driver oncogenes are prime targets for therapy in tumors many of which, including leukemias and sarcomas, express recurrent fusion transcription factors. One specific example for such a cancer type is alveolar rhabdomyosarcoma, which is associated in the majority of cases with the fusion protein PAX3-FOXO1. Since fusion transcription factors are challenging targets for development of small molecule inhibitors, indirect inhibitory strategies for this type of oncogenes represent a more promising approach. One can envision strategies at different molecular levels including upstream modifiers and activators, epigenetic and transcriptional co-regulators, and downstream effector targets.

In this review, we will discuss the current knowledge regarding potential therapeutic targets that might contribute to indirect interference with PAX3-FOXO1 activity in alveolar rhabdomyosarcoma at the different molecular levels and extrapolate these findings to fusion transcription factors in general.

Key words

Targeted therapies, fusion transcription factors, PAX3-FOXO1, alveolar rhabdomyosarcoma, post-translational modifications, protein turnover

1. Introduction

Targeted therapies are generally believed to have the potential to revolutionize cancer therapy. Optimally, targeted drugs should affect cancer and spare normal cells in the body, thereby greatly enlarging the therapeutic window over currently used chemotherapy-based approaches. Prime targets for such drugs are altered (mutated or overexpressed) driver oncogenes present in a given tumor. Some of them are frequently expressed, such as EGFR mutations in non-small-cell-lung cancer (NSCLC) or mutant BRAF in melanoma, while other potentially actionable targets are expressed only in a minority of patients or even in single individuals only. Analysis of the mutational landscape by next generation sequencing (NGS), as already implemented in the clinics for some entities, allows identification of such targets and helps to tailor patient specific therapies with targeted drugs [1]. However, in other tumor types, actionable targets are not (or only in rare cases) available and therefore this strategy is less helpful. Examples are several pediatric malignancies such as leukemia and sarcoma, which are associated with specific chromosomal translocations, generating fusion oncogenes. Typically, these are,