Medical University of Graz

Investigating the function of NR4A nuclear receptor family in Myc-driven lymphomagenesis

Summary

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Supervisor:	PD Dr. Alexander Deutsch
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between August 14, 2020 00:00 and October 10, 2020 23:59 (Europe/Zurich)

Description

Background:

Aggressive lymphomas represent the most common type of lymphoid malignancies with a five-year survival rate of 60%. Despite effective initial treatment, one-third of all patients will experience a relapse, warranting more research to discover novel therapeutic strategies. We have previously published a comprehensive study on *NR4A* nuclear receptor expression analysis in lymphoid neoplasms that revealed a marked reduction of all three members -namely *NR4A1, NR4A2,* and *NR4A3*- in the majority of aggressive lymphoma patients. Interestingly, functional characterization demonstrated that *NR4A1* and *NR4A3* induce apoptosis of aggressive lymphoma cells by regulating a similar pattern of pro-apoptotic genes *in vitro* and suppresses tumor growth in a xenograft model. For *NR4A1*, we additionally observed that loss of this gene leads to a marked acceleration of lymphomagenesis *in vivo*, concomitant with increased expression of immune checkpoints. Immuno-competent, but not immune-deficient, mice transplanted with *Nr4a1*-deficient lymphoma cells also exhibited rapid lymphoma development, reduced survival, and upregulation of immune checkpoints.

Hypothesis and Objectives:

These data indicate that *NR4A1, NR4A2,* and *NR4A3* have a redundant tumor-suppressive function in lymphomagenesis and that all three members are possibly involved in the regulation of the immune checkpoint-mediated immune evasion. Therefore, we will determine: (1) the effects *NR4A3* loss in combination with or without a B cell-specific *NR4A1* and/or *NR4A2* in Myc-driven lymphomagenesis using transgenic mouse models; (2) the target genes of all three nuclear receptors by combing RNA- and ChIP-Seq analyses; (3) the regulatory function of *NR4A1, NR4A2,* and *NR4A3* on the checkpoint mediated immune evasion in co-culture experiments and immune-competent and -deficient mouse models.

Methodology:

- Transgenic mouse models
- Western blot analysis
- FACS analysis – B cell development and tumor microenvironment
- RNA- and ChIP-Seq
- Immune-lymphoma co-culture experiment
- Immune cell-mediated lysis
- Transplantation experiments

References:

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