MAIN FIELDS OF RESEARCH; ABSTRACT

Diffuse large B-cell lymphoma (DLBCL) is the most frequently occurring type of malignant lymphoma of adults in the Western hemisphere. Several cancer promoting signaling pathways are overactivated in DLBCL. Among those, the interleukin 10 receptor / signal transducer and activator of transcription 3 (IL-10R/STAT3) axis has been suggested as a critical regulator of lymphomagenesis. Both elevated IL-10 serum levels and amplified IL-10R expression are frequently observed in DLBCL patients. However, little is known about the cancer cell-intrinsic mechanisms underlying IL-10R-mediated tumor progression.

Our hypothesis is that amplified IL-10R expression triggers IL-10 secretion and subsequent ligand binding results in enhanced downstream signaling with STAT3 serving as the main signal transducer for DLBCL cell proliferation. The ultimate goal is to determine how IL-10R signaling precisely assists DLBCL cells in survival, and if other mediators besides STAT3 play a crucial role in this pathway. Therefore, we employ subcutaneous and orthotopic xenotransplantation models alongside MYC-driven spontaneous and serial transplantation models of lymphomagenesis, in which individual components of the IL-10R/STAT3 signaling axis are ablated.

Preliminary data show that several of the 13 DLBCL cell lines express both IL-10R and IL-10, and those exhibit strong steady-state STAT3 phosphorylation, which was almost completely abrogated by IL-10R knockout. Further, IL-10R knockout reduced the tumor burden strikingly in subcutaneous and orthotopic mouse models. Moreover, reduced cell numbers upon IL-10R neutralization in vitro further highlighted IL-10R signaling as an important mediator of DLBCL cell survival. Besides, a critical role of STAT3 in B-cell differentiation was demonstrated by GC B-cell specific STAT3 knockout in vivo. These mice showed significantly decreased frequencies of GC B-cells and lymph node weights.

Our first findings emphasize IL-10R signaling as a promising target in DLBCL that needs to be further mechanistically investigated. Ultimately, a potential link between IL-10R signaling and patterns of genetic alterations and tumor aggressiveness will be assessed.

SPECIAL TECHNIQUES AND EQUIPMENT

Flow cytometry, lentiviral CRISPR-Cas9 gene editing, humanized MISTRG(6) mouse models, in vivo imaging system (IVIS), microscopy, cell culture, Western blotting, qRT-PCR, ELISA, cloning.