Karolinska Institutet

Department of Biosciences and Nutrition

Estrogens and Lymphoma growth

ACADEMIC DISSERTATION
For the degree of Doctor of Medicine at Karolinska Institutet, public defense will be held at seminar room red, floor 6, Novum.

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ABSTRACT

Lymphomas are generally not considered as endocrine-associated cancers. Nevertheless, most lymphoid malignancies show a gender difference in incidence and prognosis, with males being more affected. The molecular mechanism for this gender difference is unknown. Some epidemiological data show a protective function of estrogens against Non-Hodgkin lymphomas (NHL). Recent studies have demonstrated estrogen receptor β (ERβ) to be the major ER expressed in normal and malignant cells of lymphoid lineage.

In **Paper I**, we demonstrated a gender differences in tumor growth by grafting mice with murine T lymphoma cells. We found that male mice developed larger tumors compared to female mice, a difference that was abolished following ovariectomy, suggesting estrogen regulated growth *in vivo*. In addition, we looked into the effects of 17β-estradiol, selective ERα and selective ERβ agonists on lymphoma growth in culture and *in vivo*. Treatment with 17β-estradiol had minor effects on lymphoma growth, whereas the selective ERβ agonists diarylpropionitrile (DPN) and KB9520 showed potent antiproliferative and proapoptic effect. This study for the first time showed *in vivo* that ERβ agonists may be useful in the treatment of lymphomas.

In **Paper II**, we studied ligand-activated ERβ effects on human lymphomas. Treatment with the selective ERβ agonist DPN significantly suppressed lymphoma growth in grafting experiments using Granta-519 Mantle cell lymphoma (MCL) and Raji Burkitt lymphoma (BL) cells in immunocompromised (NOD/SCID gamma) mice in comparison to vehicle treated mice. Importantly, activation of ERβ inhibited vascularization. Furthermore, using a disseminating Raji BL cell line, we showed that ERβ activation reduced dissemination of subcutaneous grafted tumors. We also showed by immunohistochemistry that ERβ is expressed in primary MCL tumors. These results suggest that targeting ERβ with agonists may be valuable in the treatment of some lymphomas, affecting several aspects of the malignant process including proliferation, vascularization and dissemination.

In **Paper III**, we showed that when grafting human DLBCL cells to NOD/SCID gamma mice, tumor growth was faster in males compared to females. We also demonstrated high expression of ERβ1, with small or no ERα expression in DLBCL cells. Furthermore, when treating mice grafted with human DLBCL cells with the selective ERβ agonist diarylpropionitrile (DPN), lymphoma growth was significantly suppressed. Furthermore, ERβ1 expression analysis in primary DLBCL tumors from patients by immunohistochemistry revealed nuclear or cytoplasmic expression of ERβ1 in more than 86% of the cases. No statistical significant correlation of neither nuclear nor cytoplasmic ERβ1 expression to age, gender, the International Prognostic Index and DLBCL subtype was observed. Nevertheless, high cytoplasmic together with low nuclear expression of ERβ1 was found to be a favorable prognostic factor for overall survival (P=0. 03) in DLBCL patients treated with Rituximab and CHOP.

In conclusion, the studies presented in thesis contribute to an explanation of the clinically observed lower incidence and better prognosis of lymphomas in women than men. This highlights a significant role for estrogens, particularly ERβ signaling, in the pathology of NHL. We also suggest that selective ERβ agonists might be a new and useful therapeutic approach for treatment of ERβ expressing lymphomas.

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