World Academy of Science, Engineering and Technology
International Journal of Aerospace and Mechanical Engineering
Vol:14, No:12, 2020

Lymphomas as Estrogen-Regulated Cancers

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Abstract : Lymphomas are generally not considered as endocrine-related cancers. However, most lymphoid malignancies show gender differences in incidence and show prognosis with males being more affected. Furthermore, some epidemiological data indicate a protective role of estrogens against Non-Hodgkin lymphomas. Recent studies have demonstrated estrogen receptor β (ERβ) to be the major ER expressed in normal and malignant cells of lymphoid origin. We have analyzed the effects of estradiol and selective ERα and ERβ agonists on lymphoma growth in culture and in vivo. Treating lymphoma cells with estradiol or ERα selective agonist had minor or no effect on cell growth while selective ERβ agonist treatment showed an antiproliferative effect. When grafting mice with murine T lymphoma cells, male mice developed larger tumors compared to female mice, a difference that was abolished following ovariectomy, demonstrating estrogen-dependent growth in vivo. When subcutaneously grafting lymphoma cells to mice, so far growth of all tested human B lymphoma tumors (Raji and Ramos Burkitt lymphoma, SU.DHL4 (GC) and U2932 (ABC) DLBCL, Granta-519, Maver1 and Z138 MCL cells), were reduced following treatment with ERβ selective agonist (ref. 2 and unpublished). Moreover, the number and size of liver foci of disseminating Raji cells was reduced. We have identified target genes and mechanism that could explain the above effects of ERβ agonists. This included effects on angio and lymphangiogenesis. Now we have further analyzed effects of ERβ agonists on Ibrutinib-sensitive and -insensitive MCL cells in xenograft experiments as well as ERβ expression in primary lymphoma material (DLBCL). Preliminary statistical analysis has been done correlating ERβ expression to other biomarkers and clinical data.

Keywords : lymphomas, estrogen receptors, cancer, liver foci
Conference Title : ICGHOST 2020 : International Conference on Ghost Conference
Conference Location : ghost city, Other
Conference Dates : December 12-13, 2020