SEVERELY IMMUNODEFICIENT NOG-EXL MICE ALLOW FOR HUMANIZATION AND DEVELOPMENT OF A HUMAN GlioBlastoma-DERIVED Tumor MICROENVIRONMENT

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Background Cellular immunotherapy has resulted in tremendous therapeutic advances across liquid tumors. However, for solid tumors, including glioblastoma (GBM), significant limitations still exist in successfully translating immune-based adoptive cell therapeutics from the bench to the clinic. The majority of preclinical in vivo GBM models either use human cell lines grown in immunodeficient animals or syngeneic tumors grown in immunocompetent animals. Both approaches lack critical immune components of the tumor microenvironment (TME), thus inherently limiting the ability to adequately model immunotherapies.

Methods Here, we demonstrate the ability of hematopoietic stem cells (HSCs) from a GBM patient to successfully engraft in the severely immunodeficient NOG-EXL mouse strain and generate a patient-derived immune system. Mouse brains, with and without tumors, were evaluated by immunohistochemistry and flow cytometry.

Results Intraosseous injections of a low number (10,000) of CD34+ HSCs, obtained from a bone marrow draw from the patient at the time of tumor resection, resulted in an average of 20% human CD45+ cells in peripheral blood 17 weeks post-transplant. GBM organoids, established from the same patient, were implanted intracranially at Week 18 and allowed to grow for 5 weeks without significant clinical evidence of graft-vs-host disease or macrophage activation syndrome. Immunohistochemical and flow cytometry analyses of mouse brains, with and without tumors, revealed infiltration of human-derived, CD45+/CD33+ cells, in proximity to the tumor engraftment site.

Conclusions These results demonstrate the ability of patient-obtained CD34+ HSCs to engraft and form a TME in severely immunodeficient mice. Subsequent work will focus on the differences between autologous and allogeneic humanized tumor-bearing mice in the context of the originating tumor. Additional future work will focus on testing cellular therapies directed towards the relevant areas of the autologous model.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0005

Abstracts