PROGETTO

Supervisore:	Rossella Galli
Titolo	Defining tumor-intrinsic and immune-dependent IL-7R regulation in mesenchymal glioblastoma
Curriculum:	Neurosciences and Experimental Neurology
Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento:	https://research.hsr.it/en/divisions/neuroscience/neural-stem-cell-biology.html

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/Lacune di conoscenza

Glioblastoma (GBM) remains a lethal disease despite multimodal therapy (Weller et al., 2024). Transcriptomic profiling has identified proneural (PN), classical (CL), and mesenchymal (MES) subtypes, with MES GBM associated with increased immune infiltration, therapy resistance, and poor prognosis (Wang et al., 2022). While myeloid-driven immune programs in MES GBM cells are well characterized (Gangoso et al., 2021) (Hara et al., 2021), to date no bona fide lymphoid-associated signaling pathway has been shown to be active within human GBM stem cells (GSCs).

Razionale e ipotesi

Using subtype-specific human GSC models, we unexpectedly identified the interleukin-7 (IL-7)/IL-7R axis, classically restricted to lymphoid cells (Barata et al., 2019), as being selectively expressed in MES GSCs. IL-7R is expressed at RNA and protein levels in MES GSCs, enriched in human MES GBM specimens, associated with tumorigenicity and poor patient survival, and maintained in vivo only in immunocompetent hosts, suggesting regulation by the tumor immune microenvironment (TIME).

This project aims to investigate whether IL-7R acts as a tumor-intrinsic signaling node in MES GSCs or represents an immune-induced adaptive program. By integrating genetic perturbation and signaling analyses in vitro with the exploitation of distinct in vivo models with defined immune competence, we will dissect how IL-7R expression is induced, maintained, and functionally exploited by MES GBM cells. Our central hypothesis is that IL-7R expression is initiated by immune-derived cues in vivo and subsequently stabilized by tumor-intrinsic, potentially non-canonical signaling in MES GBM cells.

Obiettivi e finalità specifiche

Aim 1: To define the functional role and downstream signaling of IL-7/IL-7R in MES GSCs.

We will determine whether IL-7R signaling promotes oncogenic, tumor-suppressive, or context-dependent effects by dissecting its function in GSCs through gene silencing. We will also identify the engaged signaling pathways and will determine the contribution of autocrine vs. ligand-independent signaling.

Aim 2: To determine how immune-derived cues regulate IL-7R expression in MES GBM.

By exploiting immunocompetent, immunodeficient, and T cell-deficient mouse models, along with immune co-culture systems, we will define which TIME components are required for IL-7R induction and maintenance.

Risultati attesi

The results of this project will establish IL-7R as a previously unrecognized, immune-responsive signaling module in MES GSCs. By clarifying its tumor-intrinsic functions and immune-dependent regulation, this project will provide mechanistic insight into MES GBM plasticity and identify new opportunities for prognostic stratification and immunotherapy-oriented intervention.

Competenze che dovrà acquisire la/il Dottoranda/o(in inglese, max 600 caratteri spazi inclusi)

The student will have the opportunity to become acquainted with basic molecular and cellular biology techniques (e.g., qPCR, WB, IHC), in vitro cell culturing (GBM cancer stem cells), in vivo methodologies (e.g., orthotopic transplantation, MRI) and some basic bioinformatic tools (e.g., R2 platform, GSEA, single cell transcriptomics analysis).

Bibliografia (massimo 15 voci)

Barata, J. T., Durum, S. K., and Seddon, B. (2019). Flip the coin: IL-7 and IL-7R in health and disease. Nat Immunol 20, 1584-1593.

Berens, E. B., Khou, S., Huang, E. T., Hoffman, A., Johnson, B., Kirchberger, N., Sivagnanam, S., Calistri, N. L., Derrick, D. S., Liby, T. A., et al. (2026). Neoplastic Immune Mimicry Potentiates Breast Tumor Progression. Cancer Res 86, 587-603.

Gangoso, E., Southgate, B., Bradley, L., Rus, S., Galvez-Cancino, F., McGivern, N., Guc, E., Kapourani, C. A., Byron, A., Ferguson, K. M., et al. (2021). Glioblastomas acquire myeloid-affiliated transcriptional programs via epigenetic immunoediting to elicit immune evasion. Cell 184, 2454-2470 e2426.

Hara, T., Chanoch-Myers, R., Mathewson, N. D., Myskiw, C., Atta, L., Bussema, L., Eichhorn, S. W., Greenwald, A. C., Kinker, G. S., Rodman, C., et al. (2021). Interactions between cancer cells and immune cells drive transitions to mesenchymal-like states in glioblastoma. Cancer Cell 39, 779-792 e711.

Wang, L., Jung, J., Babikir, H., Shamardani, K., Jain, S., Feng, X., Gupta, N., Rosi, S., Chang, S., Raleigh, D., et al. (2022). A single-cell atlas of glioblastoma evolution under therapy reveals cell-intrinsic and cell-extrinsic therapeutic targets. Nat Cancer 3, 1534-1552.

Weller, M., Wen, P. Y., Chang, S. M., Dirven, L., Lim, M., Monje, M., and Reifenberger, G. (2024). Glioma. Nat Rev Dis Primers 10, 33.