Glioblastoma (GB) is an aggressive type of brain cancer with a high mortality rate. It is a highly angiogenic tumor exhibiting an extremely invasive nature. As such, its brain microenvironment plays a crucial role in its progression. Microglia are the brain resident immune cells that have been shown to facilitate GB cell invasion and immune suppression. The mechanism by which GB cells alter microglia behavior is yet to be fully understood. One proposed mechanism involves adhesion molecules such as the Selectins family of proteins which are expressed on the surface of endothelial and immune cells and are involved in immune modulation and cancer immunity. We have previously shown that one member of the Selectin family, P-Selectin (SELP), is expressed by GB cells [1]. Here, we investigated the functional role of SELP in GB-microglia interactions. First, we found that microglia cells facilitate the expression and secretion of SELP by GB cells, and that GB cells facilitate the expression of P-Selectin ligand-1 (PSGL-1) by Glioma-associated microglia/macrophages (GAMs) [2]. We then showed that SELP mediates GAMs-enhanced GB invasion and proliferation in our unique 3D-bioprinted ex vivo models [3,4] and has a role in GAMs activation state. These findings were validated in vivo, showing that inhibition or downregulation of SELP leads to reduced tumor growth, increased overall survival, and improved immune response. Single-cell RNA-seq analysis of the tumors revealed an increase in pro-inflammatory GAMs signature, reduction in cancer cell tumorigenesis potential, and improved T cell activation. Thus, combining SELP inhibition with other immune checkpoint inhibitors, such as anti-PD-1, may have a synergistic effect by harnessing both the innate and the adaptive immune systems against the tumor. Furthermore, we found SELP/PSGL-1 axis to be involved in the progression of brain metastasis originating from melanoma, and breast, and lung cancer. Thus, we have begun an investigator-initiated clinical trial, testing the efficacy of the anti-SELP antibody, Crizanlizumab, alone or in combination with anti-PD-1 antibody, Nivolumab, for GB and melanoma brain metastasis patients (NCT05909618). Crizanlizumab, approved by the FDA and EMA for sickle cell pain crisis (VOC, Vasculo-Occlusive Crisis) of sickle-cell anemia patients, was proven to be safe for human use, and efficient in inhibiting SELP function. As such, it has the potential to reduce tumor burden and improve patient outcomes. Furthermore, SELP can be utilized as a target for nanomedicines such as Sulfonated-poly(lactic-co-glycolic acid) (PLGA)-polyethylene glycol (PEG) nanoparticles (NP) encapsulating a combination of drugs (e.g. BRAF and MEK inhibitors). One such example is our SELP-targeted PLGA-PEG-Glycerol-(SO3)2 NP which showed enhanced accumulation in SELP-expressing 3D cancer models and melanoma tissues, resulting in significantly superior in vivo efficacy and safety profiles. This work can improve our understanding of GAMs function, which may pave the way for new and effective treatments for primary and secondary brain tumors using our SELP-targeted nanoparticle co-delivering a plethora of anti-cancer drug combinations to multiple types of SELP-expressing tumors.

References


Figures

Figure 1. Illustration showing the different roles of SELP in cancer progression. Created with Biorender.com.