Dr.Shilpee Dutt

Sustained inhibition of PARP-1 activity delays glioblastoma recurrence by enhancing radiation-induced senescence

Recently Dr. Shilpee Dutt's lab at ACTREC published important manuscripts in 'Cancer Letter' that address the fundamental issue of radiation resistance and recurrence in glioblastoma multiforme (GBM). GBM is the most aggressive and malignant primary brain tumor with median overall survival of barely 18 months. Despite multimodal therapy recurrence in GBM is inevitable making GBM the most difficult brain tumor to treat. GBM recurrence is due to the residual disease cells that are left after surgery and radio-therapy. Therefore, it is imperative to eliminate residual cells to prevent recurrence and improve patient outcome. However, because brain tumor biopsies are not available after therapy there is little understanding of the survival mechanisms of these residual cells. The only possibility to access and study these cells is by an innovative approach that models the clinical scenario of therapy resistance — an approach that is crucial for the development of effective therapies. With this aim, Shilpee Lab at ACTREC have developed a cellular model system from clinically relevant naïve primary GBM patient samples and cell lines that mimic clinical scenario of GBM resistance and recurrence. Using this system, they are able to capture the rare population of cells (residual resistant cells) that survive radiotherapy and are responsible for relapse.

In the study by Ghorai et al. published in 'Cancer Letters', Dr. Dutt's group sheds light on the understanding of an emerging area of cancer 'Therapy Induced Senescence' (TIS) and recovery from it that influence therapy resistance and recurrence. Earlier Dr. Dutt's group have shown that radio-therapy induces the formation of multinucleated giant cells (MNGCs) and senescence in residual resistant cells of Glioblastoma (GBM). Importantly, these cells were able to escape senescence to give rise to aggressive recurrent tumour. Using clinically relevant GBM patient sample derived primary cultures, in this

manuscript they describe a novel role of PARP-1, a DNA repair protein, in radiation induced senescence and recovery from senescence. Despite the reported PARP-1 over expression and activation in glioblastoma, applying *in vitro* cell-based assays and biochemical experiments, Ghorai et al. for the first time show that the reduced PARP-1 activity is important for manifestation of radiation resistant GBM by increasing multinucleated giant cell formation and TIS. In contrast, regaining PARP-1 activity as well as hyper-activation is absolutely required for the emergence of relapse GBM population. These data provide novel insights into the dynamic activity of PARP-1 during resistance and recurrence of GBM. Currently PARP-1 inhibitor is in clinical trial for newly diagnosed GBM, these findings will have important implication in understanding the clinical outcome of PARP1 based GBM therapeutics.

Sustained Inhibition of PARP-1 Activity Delays Glioblastoma Recurrence by Enhancing Radiation-Induced Senescence. Atanu Ghorai, Tejashree Mahaddalkar, Rahul Thorat, Shilpee Dutt*. Cancer Letters. 2020 Oct 10;490:44-53. doi: 10.1016/j.canlet.2020.06.023