1. Introduction

The Sirtuins are a part of the class III histone deacetylase family of enzyme sharing a conserved 275 amino acid catalytic core domain. There are seven members of the Sirtuin family designated as Sirtuin 1 to Sirtuin 7. The Sirtuin family can regulate a vast amount of non-histone protein targets by lysine deacetylation allowing them to be master regulators of many cellular activities. Some of the cellular activities regulated by Sirtuins include gene expression, metabolism, telomere activity, cell cycle differentiation, epithelial-mesenchymal transition (EMT), apoptosis, DNA repair, senescence and oxidative stress response (Callaghan and Vassilopoulos, 2017).

Sirtuin-1 (or referred to as Sirt-1) is also known as Nicotinamide Adenosine Dinucleotide (NAD)-Dependent Deacetylase Sirtuin 1 (Rahman and Islam, 2011). Sirt-1 is described to be mostly located in the nucleus of cells but has been reported to import and export sequences leading to its detection in the cytosol (Duan, 2013). In terms of its activity, Sirt-1 catalyzes enzymatic reaction which cleaves NAD and transfers the acetyl group of the protein substrate into the part of the cleaved NAD forming nicotinamide and a unique metabolite O-acetyl-ADP ribose (Rahman and Islam, 2011).

Sirt-1 is described to be in the crossroads of cancer, aging, and stemness. Sirt-1 is thought to be able to control three important cell signaling pathways, Hedgehog (Shh), Wingless (Wnt), and Notch pathway. Sirt-1 is able to repress Shh signaling effectors Gli1 and Gli2. This epigenetic mechanism is thought to be aberrant in medulloblastoma; thus, activation of BCL6/BCOR/SIRT1 complex may be exploited therapeutically and may be used in Shh-dependent cancers. Sirt-1 is known to mediate the Wnt pathway through deacetylation of β-catenin thus promoting transcription of Wnt/β-catenin target genes. Finally, Sirt-1 is thought to be a negative regulator of Notch signaling by deacetylation of n conserved lysine groups in the Notch Intracellular Domain (Callaghan and Vassilopoulos, 2017). Its' importance in stem cells also leads to its study in cancer stem cells. For instance, Sirt-1 inhibition in CD133+ glioma cancer stem cells could lead to radiosensitivity through radiation-induced apoptosis (Chang et al., 2009).

Gliomas are the most common type of primary intracranial tumors representing 31% of all brain and central nervous system (CNS). Also, it makes up 81% of all malignant brain and CNS tumors. The study of Glioma incidence is difficult due to its rarity. Therefore, as gliomas make up the largest contributor to malignant brain tumors, many databases tend to use it to mirror the incidence of glioma. The brain cancer incidence is highest in Europe with the age-standardized rate (ASR) of 5.5 per 100,000 people, followed by the North Americas with ASR of 5.3 per 100,000 people. The prognosis of gliomas differs greatly in relation to the subtype of glioma with oligodendrogliomas having the best relative survival (~60% survival at 10 years) and Glioblastoma Multiforme (GBM) having the worst possible outcome (~5% survival at 10 years). Finally, there are very diverse and poorly confirmed risk factors in gliomas but generally, heredity, ionizing radiation, and allergies are among the most commonly studied risk factors (Ostrom et al., 2015).

Gliomas are pathologically divided into astrocytoma, oligodendroglioma, and mixed oligoastrocytoma. The majority of gliomas are astrocytic making up 82% of all gliomas, followed by unspecified gliomas (7%), oligodendroglial gliomas (6%) and mixed oligoastrocytomas (3%). Furthermore, in 2007, the World Health Organization recognized four grades of gliomas based on their microscopic appearances. For instance, in astrocytoma, grade I is designated as pilocytic, grade II as low grade diffuse, grade III as anaplastic diffuse, and grade IV as GBM. While there are only two grades (Grade II or low grade, and Grade III or anaplastic) for Oligodendrogliomas (Cohen and Colman 2015).

There are three important pathways which are disrupted in Gliomas which are the phosphatidylinositol-3-kinase (PI3K) pathway, p53 apoptosis regulation pathway, and cell cycle regulation through cyclin-dependent kinases and retinoblastoma. Furthermore, isocitrate dehydrogenases are also found to be mutated in 80% of grade 2-3 gliomas along with secondary GBM (Cohen and Colman 2015).

A study by Qu and colleagues attempted to modulate Sirt-1 by inhibition and activation. They found that Sirt-1 activation could induce tumorigenesis and inhibition could induce glioma inhibition (Qu et al., 2012). Many others also reported reduction in cell proliferation by Sirt-1 inhibition through miRNAs and small molecules acquiring reducing cell proliferation and invasion (Chen et al., 2015; Huo et al., 2017; Li et al., 2015) It is also studied for its importance in the cancer stem cells of glioma helping maintain stemness, and increasing radiosensitivity (Chang et al., 2009; Lee et al., 2014).

SRT1720 has previously been used by Yao and colleagues to increase Sirt-1 activity in gliomas. I intend to investigate the role of Sirt-1 in cell proliferation, clonogenicity, and cell migration. This study could be the start to delve deeper into the role of Sirt-1 as a master regulator of multiple pathways. In the future, elucidating the different targets of Sirt-1 could open up alleys in glioma therapeutics.