Glioblastoma (GBM) carries a dismal prognosis with a median survival of only a little over a year (1). Current standard of care for patients includes maximal surgical resection followed by radiation and treatment with the chemotherapeutic agent temozolomide. However, data over the past decade has revealed that a subpopulation of cells within these tumors, commonly referred to as cancer stem cells (CSCs), are refractory to these therapeutic interventions and can contribute to recurrence (2,3). As a result, numerous research groups have focused their efforts on identifying unique biological features of CSCs in the hope of identifying treatment strategies that will inclusively target the CSCs and potentially reduce recurrence.

To this end, Lee et al. screened the expression levels of a targetable class of proteins called ubiquitin-specific proteases (USPs) that had previously been underexplored in GBM and within CSCs (4). USPs are a subclass of the set of nearly 100 proteins in the human genome known as deubiquitinating enzymes (DUBs). USPs, and DUBs in general, act to remove covalently attached ubiquitin molecules from target proteins, thus reversing the ubiquitin-directed fate of the protein. The balance of substrate ubiquitination by E3 ubiquitin ligases and reversal by DUBs is therefore critical for maintaining the homoeostatic function of a given pathway and alterations in either side of this equation are implicated in cancer among multiple human diseases. From this screen, Lee et al. identified USP1 as upregulated in GBM and specifically within the CSC subpopulation. When forced to differentiate, CSCs no longer expressed USP1, underscoring a unique role within this subpopulation.

USP1 has been studied in detail and is upregulated in a number of cancers. Although, only a handful of substrates for USP1 have been identified thus far, it is clear that USP1 function is permissive for the transformed state. The most well characterized role for USP1 is in the regulation of DNA repair processes where USP1 plays a regulatory role in homologous recombination-mediated repair, translesion synthesis, and interstrand crosslink repair (5-7). In addition, it has been demonstrated that USP1 promotes the stem cell state by stabilizing the Inhibitors of DNA binding (ID) proteins and increased USP1 expression is expected to promote bypass of oncogene-induced senescence (8,9). Given these abilities, and the inherent resistance of CSCs to DNA damage-inducing therapy, the logic for focusing on USP1 as a potential anti-CSC strategy is clear.

In a previous study that employed a screen designed to classify small molecule inhibitors to USP1, a FDA-approved drug used to treat Tourette syndrome and schizophrenia, pimozide, was identified to selectively target USP1 and to reverse the chemo-resistance of non-small cell lung cancer cells to the chemotherapeutic agent, cisplatin (10). This work built on earlier observations that patients taking medication for schizophrenia have lower cancer rates than others, an observation that prompted studies identifying the cytotoxic properties of pimozide toward cancer cell lines (11). Lee et al. used pimozide as well as RNA interference to evaluate the impact of loss of USP1 to the CSC population in GBM. Targeting USP1 reduced CSC self-renewal, viability, and radio-resistance. Prolonged survival in a preclinical orthotopic model when pimozide was combined with radiotherapy underscored the potential clinical relevance of targeting USP1 in GBM as well as other cancers where radiation is standard of care.

The authors attribute the promotion of stem cell maintenance and radioresistance of GBM via USP1...
dependent stabilization of the transcription factor ID1 and the DNA damage response mediator CHK1, both previously identified to be regulated by USP1. Loss of USP1 will have an impact on targets beyond these factors that may serve to enhance clinical efficacy in the background of intra- and inter-tumoral heterogeneity. Additionally, pimozide treatment was shown to compromise hepatocellular carcinoma CSCs by compromising function of the transcription factor, STAT3, identified as a critical regulator of the cancer stem cell fate in multiple tumor types (12). Although attenuation of STAT3 function has not been linked to inhibition of USP1, these data and that by Lee et al. underscore that inhibition of USP1 does compromise the CSCs component within tumors and warrants further investigation as a therapeutic approach.

This work by Lee et al. further emphasizes the potential for clinical exploitation of the ubiquitin proteasome system, DUBs in particular. DUBs are involved in a multitude of cancer-associated processes, including transcriptional regulation, cell cycle progression, oncoprotein stabilization, to name a few. Many, like USP1, are involved in more than one of these processes. Thus, inhibition of a USP offers the ability to target multiple targets/pathways simultaneously and may offer alternatives to achieve inhibition of these pathways. For example, CHK1 inhibitors have long been hypothesized to have significant clinical potential, particularly in combination with DNA-stress inducing agents, yet toxicity has been an issue. Inhibition of USP1 itself causes DNA-stress while at the same time leading to impaired CHK1 function. Perhaps such strategies will offer greater therapeutic windows. The recent identification of small molecule inhibitors for USPs will now allow critical evaluation of this potential. Small molecule inhibitors for USP14 are now entering the first clinical trials for DUB inhibition. Additional small molecules targeting USP7, which is also found to be upregulated in GBM as well as other cancers, and potentially other DUBs, such as USP1, are expected to follow USP14-targeted therapies from bench to bedside in the near future (13,14).

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Footnote

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