Ataxia telangiectasia mutated

Ataxia telangiectasia mutated (ATM) is a serine/threonine protein kinase that is recruited and activated by DNA double-strand breaks. It phosphorylates several key proteins that initiate activation of the DNA damage checkpoint, leading to cell cycle arrest, DNA repair or apoptosis. Several of these targets, including p53, CHK2, BRCA1, NBS1 and H2AX are tumor suppressors.

The protein is named for the disorder ataxia telangiectasia caused by mutations of Ataxia telangiectasia mutated (ATM).

DNA repair proteins of ataxia-telangiectasia mutated (ATM), ATM and Rad3-related, and decoy receptor 3 also decreased with NSC745887 treatment. In addition, NSC745887 caused apoptosis by the caspase-8/9-caspase-3-poly(ADP-ribose) polymerase cascade. An in vivo study indicated that NSC745887 suppressed the [18F]-FDG-specific uptake value in brain tumors. Histological staining also indicated a decrease in Ki-67 and increases in γH2AX and cleaved caspase-3 in the brain tumor area. These data provide preclinical evidence for NSC745887 as a potential new small molecule drug for managing glioblastomas [1)].

Kaur et al., found that low ATM (Ataxia-telangiectasia mutated) expression levels in radiation resistant (RR) cells showed a significant ($p = 0.002$) negative correlation with SF2 values. A low ATM expression level in RR cells along with a high tumor volume was also found to negatively correlate with patient survival ($p = 0.011$). Finally, we found that the ATM expression levels in RR cells independently correlated with a poor patient survival ($p = 0.014$).

This data indicate that molecular features of innately radiation resistant GBM cells independently correlate with clinical outcome. The study also highlights the relevance of using patient-derived primary GBM cultures for the characterization of RR cells that are otherwise inaccessible for analysis [2)].

Molecular mechanism underlying ischemic stroke remains poorly understood. We previously reported glucose 6-phosphate dehydrogenase (G6PD) activity in pentose phosphate pathway (PPP) is activated via heat shock protein 27 (HSP27) phosphorylation at serine 85 (S85) by ataxia telangiectasia mutated (ATM) kinase during cerebral ischemia. This mechanism seems to be endogenous antioxidative system. To determine whether this system also works during reperfusion, we performed comparative metabolic analysis of reperfusion effect on metabolism in rat cortex using middle cerebral artery occlusion (MCAO). Metabolic profiling using gas-chromatography/mass-spectrometry analysis showed changes in metabolic state that depended on reperfusion time. Enrichment analysis showed PPP was significantly upregulated during ischemia-reperfusion. Significant increases in fructose 6-phosphate and ribulose 5-phosphate after reperfusion also suggested enhancement of PPP. In relation to PPP, ischemia-reperfusion induced an increase of up to 69-fold in HSP27 transcripts after 24-h reperfusion. Immunoblotting showed gradual increase in HSP27 protein and marked increase in HSP27 phosphorylation (S85) that were time-dependent (4.5-fold after 24-h reperfusion). G6PD activity was significantly elevated after 1-h MCAO (20%), reduced after 1-h reperfusion, increased

gradually thereafter and significantly elevated after 24-h reperfusion. The NADPH/NAD+ ratio displayed similar increasing pattern. Intracerebroventricular injection of ATM kinase inhibitor (KU-55933) significantly reduced HSP27 phosphorylation and G6PD activity, significantly increased protein carbonyl, and resulted in increase in infarct size (100%) 24-h after reperfusion following 90-min MCAO. Consequently, G6PD activation via HSP27 phosphorylation by ATM kinase may be part of endogenous antioxidant defense neuroprotection mechanism that is activated during ischemia-reperfusion. These findings have important implications for treatment of stroke [3].

1)

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2)

Kaur E, Goda JS, Ghorai A, Salunkhe S, Shetty P, Moiyadi AV, Sridhar E, Mahajan A, Jalali R, Dutt S. Molecular features unique to glioblastoma radiation resistant residual cells may affect patient outcome - a short report. Cell Oncol (Dordr). 2018 Oct 26. doi: 10.1007/s13402-018-0411-7. [Epub ahead of print] PubMed PMID: 30361826.

3)

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