Phosphodiesterase

A phosphodiesterase (PDE) is any enzyme that breaks a phosphodiester bond. Usually, people speaking of phosphodiesterase are referring to cyclic nucleotide phosphodiesterases, which have great clinical significance.

However, there are many other families of phosphodiesterases, including phospholipases C and D, autotaxin, sphingomyelin phosphodiesterase, DNases, RNases, and restriction endonucleases (which all break the phosphodiester backbone of DNA or RNA), as well as numerous less-well-characterized small-molecule phosphodiesterases.

The cyclic nucleotide phosphodiesterases comprise a group of enzymes that degrade the phosphodiester bond in the second messenger molecules cAMP and cGMP. They regulate the localization, duration, and amplitude of cyclic nucleotide signaling within subcellular domains. PDEs are therefore important regulators of signal transduction mediated by these second messenger molecules.

Studies show that phosphodiesterase-V (PDE-V) inhibition reduces cerebral vasospasm (CVS) and improves outcomes after experimental subarachnoid hemorrhage (SAH).

Expression of type 5 phosphodiesterase (PDE5), a cGMP-specific hydrolytic enzyme, is frequently altered in human cancer, but its specific role in tumorigenesis remains controversial.

Herein Cesarini et al., by analyzing a cohort of 69 patients affected by glioblastoma multiforme (GBM) who underwent chemo- and radiotherapy after surgical resection of the tumor, we found that PDE5 was strongly expressed in cancer cells in about 50% of the patients. Retrospective analysis indicated that high PDE5 expression in GBM cells significantly correlated with longer overall survival of patients. Furthermore, silencing of endogenous PDE5 by short hairpin lentiviral transduction (sh-PDE5) in the T98G GBM cell line induced activation of an invasive phenotype. Similarly, pharmacological inhibition of PDE5 activity strongly enhanced cell motility and invasiveness in T98G cells. This invasive phenotype was accompanied by increased secretion of metallo-proteinase 2 (MMP-2) and activation of protein kinase G (PKG). Moreover, PDE5 silencing markedly enhanced DNA damage repair and cell survival following irradiation. The enhanced radio-resistance of sh-PDE5 GBM cells was mediated by an increase of poly(ADP-ribosyl)ation (PARylation) of cellular proteins and could be counteracted by poly(ADP-ribose) polymerase (PARP) inhibitors. Conversely, PDE5 overexpression in PDE5-negative U87G cells significantly reduced MMP-2 secretion, inhibited their invasive potential and interfered with DNA damage repair and cell survival following irradiation. These studies identify PDE5 as a favorable prognostic marker for GBM, which negatively affects cell invasiveness and survival to ionizing radiation. Moreover, our work highlights the therapeutic potential of targeting PKG and/or PARP activity in this currently incurable subset of brain cancers [1)].

1)
Cesarini V, Martini M, Ricci Vitiani L, Luca Gravina G, Di Agostino S, Graziani G, Giorgio D'Alessandris Q, Pallini R, Larocca LM, Rossi P, Jannini EA, Dolci S. Type 5 phosphodiesterase regulates glioblastoma multiforme aggressiveness and clinical outcome. Oncotarget. 2017 Jan 14. doi: 10.18632/oncotarget.14656. [Epub ahead of print] PubMed PMID: 28099939.