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cGMP Phosphodiesterases (cGMP PDEs) As Therapeutic Targets in Cancer

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Dear Editor,

Cyclic guanosine 3', 5' monophosphate (cGMP), as a second messenger, plays a key role in cell proliferation, differentiation, and apoptosis. It is formed by guanylyl cyclase (GC) from its precursor, guanosine triphosphate (GTP) (1). GC enzymes can be found in 2 major forms: soluble or cytosol form (sGC) and particulate or transmembrane form (pGC) (1). The level of this second messenger is regulated through catalysis of cGMP degradation into its inactive form (5'-GMP) by 8 phosphodiesterases (PDEs) including: dual-specificity PDEs (PDE1, PDE2, PDE3, PDE10, and PDE11) hydrolyzing both cGMP and cyclic adenosine 3', 5' monophosphate (cAMP); and cGMP-specific PDEs (PDE5, PDE6, and PDE9) only hydrolyzing cGMP (2, 3).

Increased expression of cGMP-specific PDE mRNAs has been reported in several human carcinomas, including breast carcinoma, bladder cancer, squamous cell carcinoma, colon adenocarcinoma, lung cancer, pancreatic cancer, and prostate cancer, compared to the adjacent normal tissues (4). Previous studies have demonstrated that an increase in intracellular cGMP decreases cell population growth and induces apoptosis; also, GMP-specific PDEs have been suggested to be involved in cancers (5). Therefore, selective inhibitors of these PDEs might be potential anticancer agents.

Accordingly, multiple selective inhibitors of cGMP-specific PDEs, particularly PDE5 inhibitors (e.g., sildenafil, vardenafil, sulindacsulfone, and tadalafil) and PDE9 inhibitor, BAY 73-6691, induced apoptosis and exerted antiproliferative effects on the cell lines (in vitro studies) (6-10).

Based on the results, cGMP could be associated with multiple human cancers. Therefore, inhibitors of cGMP PDEs, especially cGMP-specific PDEs, could be potential anticancer agents. Nevertheless, animal studies and clinical trials are needed to confirm the findings.

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