Letter to the Editor

Cancer Prevention Research

Mutations of the PDE5A Gene Confer a Survival Advantage in Patients with Colon Cancer

Steven Lehrer, Peter H. Rheinstein, and Kenneth E. Rosenzweig

Islam and colleagues report that sildenafil suppresses inflammation-driven colorectal cancer in mice (1). Intestinal cyclic guanosine monophosphate (cGMP) signaling regulates epithelial homeostasis and has been implicated in the suppression of colitis and colon cancer. In their study, Islam and colleagues demonstrated that the cGMP-elevating ability of the phosphodiesterase-5 (PDE5) inhibitor sildenafil can prevent cancer in the azoxymethane/dextran sulfate sodium inflammation-driven colorectal cancer mouse model.

Here, we use data from The Cancer Genome Atlas (TCGA) to assess survival of colon cancer patients with and without mutations of the *PDE5A* gene.

We assessed the association between PDE5A and colon cancer overall survival using the GDC TCGA Colon Cancer (COAD) cohort in TCGA database. To access and analyze the data, we used the UCSC Xena browser (https://xenabrowser.net). Survival data of the mutant and unmutated PDE5A subgroups were extracted for analysis and generation of Kaplan–Meier curves for overall survival.

Data from 371 patients were analyzed. The tumors were all primary, and each patient had only one tumor. The mean age at diagnosis was 67.1 ± 13.1 (mean ± SD). A total of 51.9% were male, 48.1% were female. 52.4% were white, 14.2% were African American, 2.5% were Asian, and 30.6% were unreported.

A total of 359 patients had an unmutated *PDE5A* gene. Twelve patients had a mutant *PDE5A* gene. The *PDE5A* gene had one or more of these mutations:

- Frameshift variant
- Stop gained
- Splice acceptor variant
- Missense variant
- Synonymous variant
- Splice region variant

Ten of the 12 mutant *PDE5A* genes had a single mutation. One of the mutant genes had two mutations (stop gained + missense); the other had three mutations (stop gained + 2 missense).

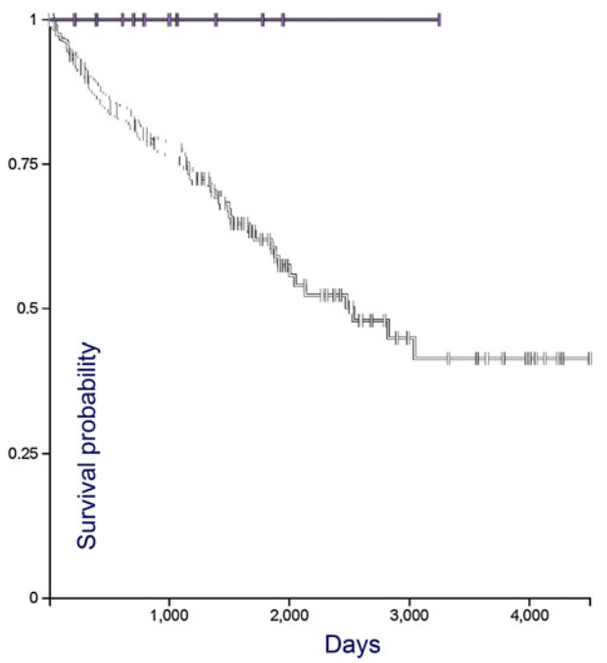

Figure 1.
Survival of colon cancer patients, 359 with no mutation of PDE5A (lower curve), 12 with mutation of PDE5A (upper line). The effect of the mutation is significant (log-rank 3.814, $P = 0.05$).

Survival of colon cancer patients is shown in Fig. 1. A total of 359 patients with no mutation of PDE5A had significantly poorer survival than 12 patients with mutation of PDE5A. The effect of the mutation is significant (log-rank 3.814, $P = 0.05$).

Chronic inflammation is involved in many forms of cancer. Aspirin and other NSAIDs reduce the risk of multiple cancer types due to their anti-inflammatory properties. Another NSAID, sulindac, inhibits the development of cancer through PDE5 suppression.

Sildenafil is a small molecule that inhibits PDE5. The study of Islam and colleagues validates PDE5 as a colon cancer chemoprevention target in mice (2), as did a second mouse study (3). Our analysis of TCGA data corroborates this finding in humans. Further studies are needed to determine whether sildenafil or other PDE5 inhibitors might be colon cancer preventives or treatments.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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