Synthetic Lethality Between PRMT5 and MTAP as a Cancer Therapeutic

Emma Xu

Abstract

Synthetic lethality arises when the combined inhibition of two genes results in cell death. Scientists have begun using this phenomenon in cancer treatments to target certain cancers. This review focuses specifically on the synthetic lethal relationship between MTAP and PRMT5, and how this relationship is used in cancer treatments. MTAP breaks down MTA, a natural inhibitor of PRMT5. In certain cancers, MTAP is often deleted as a result of cell mutation. When MTAP is deleted in these cancers, the buildup of MTA partially inhibits PRMT5, causing the cell to become highly dependent on the remaining PRMT5. This vulnerability in cancer cells has led to therapies that specifically target the remaining PRMT5 in MTAP-deleted cancer cells, allowing the treatment to destroy MTAP-deleted cancer cells while limiting damage to healthy cells. Currently, MTA-cooperative PRMT5 inhibitors are going through phase I/II clinical trials. Although several MTA-cooperative PRMT5 inhibitors have exhibited dose-limiting toxicities like nausea and fatigue, early studies still show promising signs for a treatment with the potential to selectively target MTAP-deleted cancer cells while doing minimal damage to surrounding tissue.

Background

Synthetic lethality is a phenomenon that occurs when the simultaneous absence of two genes results in the death of a cell or organism, often occurring when one gene's function is able to make up for another gene's absence. [1]

Recently, synthetic lethality has gained traction among scientists due to its potential applications in cancer treatments. Because cancer cells carry mutations that healthy cells do not, synthetic lethality makes it possible to target tumor cells while sparing normal tissue. This makes synthetic lethality an attractive strategy for developing precise cancer treatments that can reduce side effects present in traditional treatments.

Synthetic lethality happens when one gene is able to compensate for the loss of another gene, allowing the cell to survive. For example, if gene 1 and gene 2 had a synthetically lethal relationship, and gene 1 was inhibited, then the cell would rely entirely on gene 2 to keep the cell alive.

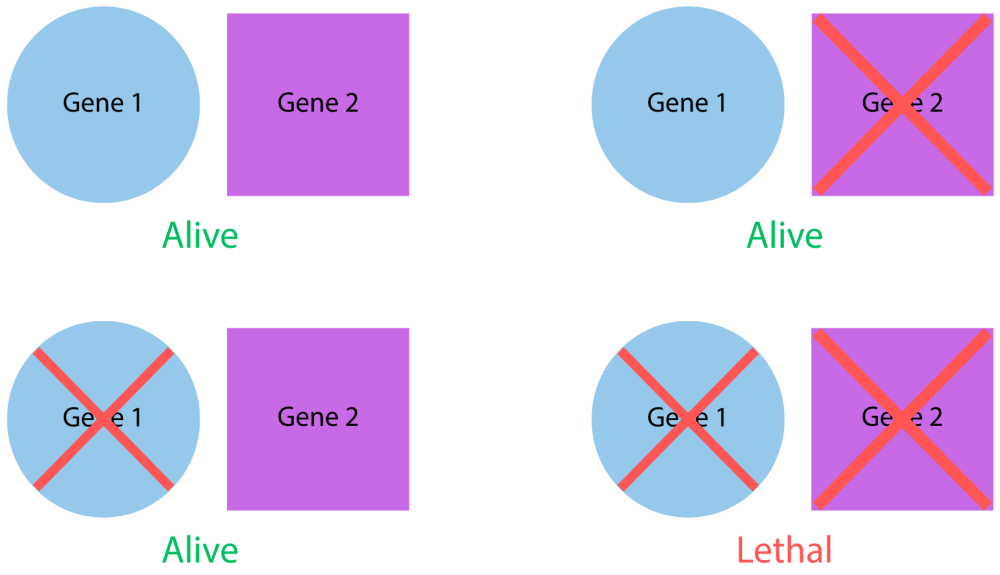

Figure 1. This diagram represents the phenomenon of synthetic lethality. It shows how, among two synthetically lethal genes, when zero or one gene is inhibited or deleted, the cell can survive; however, the deletion of both genes is lethal. Author's own diagram.

Researchers have observed synthetic lethality between the genes protein arginine methyltransferase 5 (PRMT5) and Methylthioadenosine phosphorylase (MTAP). MTAP is deficient in various tumors in diseases such as mesothelioma, bladder urothelial cancer, pancreatic cancer, and lung cancer, creating a selective vulnerability to PRMT5 inhibition. [2]

What is MTAP?

The MTAP gene codes for the MTAP enzyme, which metabolizes methylthioadenosine (MTA), a substrate of MTAP. [3,4]

MTAP is also often co-deleted with the tumor suppressor *CDKN2A* in many cancers, thus making its deficiency a common vulnerability in cancer cells. When MTAP is deleted in cancer cells, MTA begins to build up within the cell, distinguishing it from other healthy cells. [5]

What is PRMT5?

PRMT5 is a gene that encodes the PRMT5 enzyme in the methyltransferase subgroup. This enzyme controls the transcription of other proteins and is crucial to cell survival. [6] PRMT5 controls transcription by binding to S-adenosyl methionine (SAM), a methyl donor, to make symmetric dimethylarginine (SDMA), which is crucial to cell proliferation and growth.

While PRMT5 is crucial in cellular functions, studies have also shown heightened concentrations of PRMT5 in cancerous cells, suggesting that PRMT5 is a common catalyst for tumor formation.

Because PRMT5 is heavily relied on by cancer cells, inhibiting PRMT5 can slow the process of cell growth. [7]

Relationship Between PRMT5 and MTAP

In the process of deleting tumor suppressors, mutated cells also often delete MTAP, resulting in a buildup of MTA. MTA then binds to the PRMT5 proteins, competing with SAM–which is crucial to many of PRMT5's functions–thereby hindering PRMT5 activity. Because PRMT5 is already partially compromised by MTA in specific cancer cells, synthetically inhibiting the remaining PRMT5 in MTAP-deleted cancer cells can further weaken the cell to the point of cellular death. [11]

Potential Treatments Using Synthetic Lethality

With this discovery, scientists have developed MTA-cooperative PRMT5 inhibitors such as MRTX1719, TNG908, and AMG193 as a treatment for MTAP-deleted cancers. [8]
However, because PRMT5 functions are crucial for a cell's survival, these treatments must be carefully dose-limited, as completely inhibiting PRMT5 could also be fatal to surrounding healthy cells.

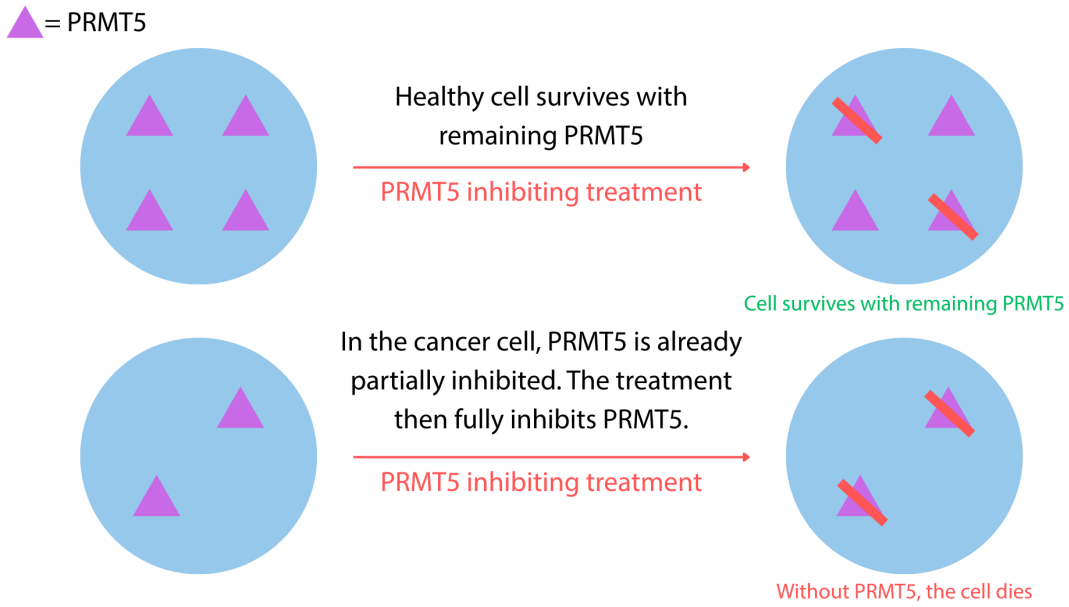

Figure 2. This visual shows how MTA-cooperative PRMT5 inhibitors kill MTAP-deleted cancer cells while keeping healthy cells alive by using dose-limiting treatments. *Note: Graphical components are schematic and do not represent actual cellular morphology.* Author's own diagram.

How do MTA-cooperative PRMT5 inhibitors work?

MRTX1719, TNG908, and AMG193 all work similarly by inhibiting PRMT5 in the presence of MTA (thus called MTA-cooperative PRMT5 inhibitors). They do this by binding to PRMT5's

catalytic site, further blocking space for SAM, which keeps PRMT5 from properly creating SDMA.

By inhibiting PRMT5 through MTA concentrations and not simply targeting PRMT5, these treatments are able to target only cells with high MTA concentration, typically cancer cells, while minimizing damage to surrounding healthy cells. In addition to the partial inhibition of PRMT5 by MTA, this preferential binding mechanism further increases the selectivity of these treatments.

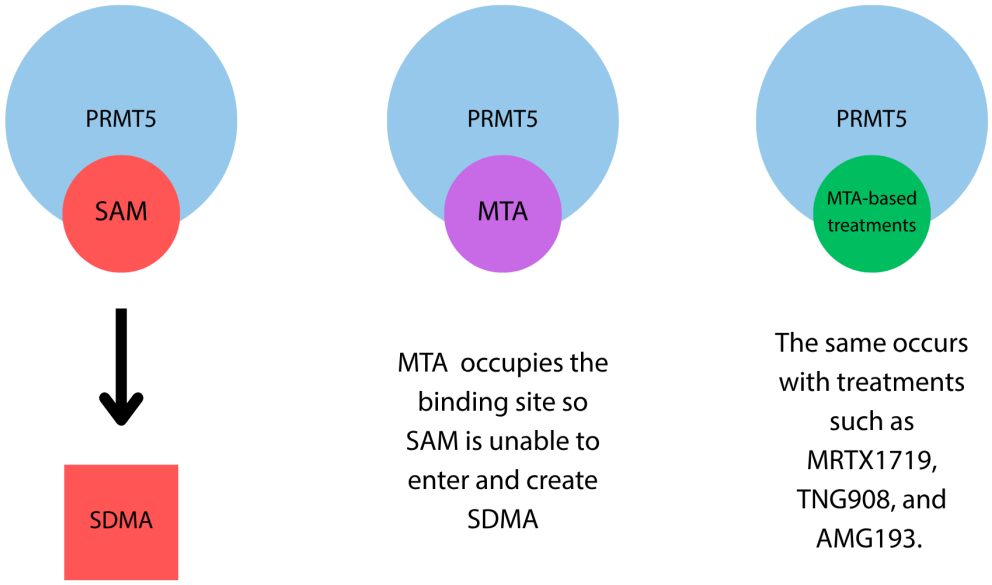

Figure 3. This visual demonstrates how MTA and MTA-cooperative drugs work to inhibit PRMT5 functions. Author's own diagram.

How can these treatments be useful?

Compared to other cancer treatments, therapeutics using synthetic lethality are beneficial because their MTA-targeting behavior allows it to minimize damage to healthy cells with normal levels of MTA. Furthermore, these treatments can be combined with other treatments to show enhanced effects on tumor inhibition. [9]

Discussion

Currently, many MTA-cooperative PRMT5 inhibitors such as MRTX1719, TNG908, AMG193, and AZD3470 are in phase I/II clinical trials and are being tested for side effects, suggested dosage, and efficacy.

Although MTA-cooperative PRMT5 inhibitors can be useful in closely targeting cancer cells, there have been downsides and inconsistencies in academic literature. These treatments have a very narrow therapeutic window and are specific only to MTAP-deleted cells. Although the inhibitors can be effective in inhibiting PRMT5 itself, they show inconsistencies in attacking and

effectively removing all cancer cells. Tests are still in progress to determine what could be causing this discrepancy. [10]

Additionally, many MTA-cooperative PRMT5 inhibitors have shown dose-limiting toxicities that cannot effectively treat cancers without harmful side effects such as fatigue, nausea, and dyspepsia. For instance, PF-06939999, a MTA-cooperative PRMT5 inhibitor, showed hematologic side effects such as thrombocytopenia, anaemia, and neutropenia, causing its clinical trials to be terminated early on in phase I.

However, while there are currently still drawbacks, continuing these clinical trials may be worthwhile in the long run because it can serve as a potential treatment that minimizes side effects. Additionally, although MTA-cooperative PRMT5 inhibitors cannot serve as a general treatment for most patients, patients with MTAP-deleted cancers still make up about 15% of all cancer patients, making these inhibitors relevant to a substantial subset of oncology cases. MTA-cooperative PRMT5 inhibitors also show promising results with cancers that have high rates of CDKN2A deletion such as non-small cell lung cancer, pancreatic cancer, and glioblastoma. [5,10]

Conclusion

As cancer treatments surrounding PRMT5 inhibition continue to progress, MTA-cooperative PRMT5 inhibitors show strong potential as a targeted therapy for MTAP-deleted cancers. By using the synthetically lethal relationship between MTAP and PRMT5, these treatments are able to selectively kill cancer cells while reducing damage to healthy tissue. Although current clinical trials have revealed challenges such as dose-limiting toxicities, narrow therapeutic windows, and inconsistent tumor elimination, ongoing research continues to improve the safety and effectiveness of these therapies. With further development, MTA-cooperative PRMT5 inhibitors may become an important advancement in precision oncology and provide new treatment options for patients with difficult-to-treat cancers.

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