Recent Advances on Interaction Targets for Anticancer Activity of Caffeine

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Abstract Caffeine (1,3,7-trimethylxanthine) is the most frequently ingested neuroactive drug in the world and has enigmatic effects on tumor cells. Convincing evidence from *in vitro*, animal and human studies suggests that caffeine can inhibit cancer development and progression. Caffeine can easily pass through biological membranes and cross the blood-brain barrier, and it is thereby possible to bind to extracellular or intracellular molecules to exert its functions. This review mainly focuses on recent advances in the direct interaction targets of caffeine in the inhibition of malignancies and will hopefully provide valuable insights into the clinical application of caffeine to the treatment of cancers.

Keywords caffeine, interaction target, adenosine receptor, G6PDH, SIRT3

Introduction

Cancer is a major public health problem that threatens millions of human lives annually, and it is the second leading cause of death after cardiovascular diseases in the world.^[1,2] It has been estimated that 1,806,590 new cancer cases and 606,520 cancer deaths are projected to occur in the United States in 2020.^[1] With aging populations worldwide, the incidence and mortality of malignant tumors are still on the rise. Currently, surgical resection, chemotherapy and radiotherapy have been considered as the standard treatment strategies for different kinds of cancers.^[3] Although many chemotherapy drugs are used for the treatment of malignancies, these drugs have evoked unexpected side effects in patients with cancer, which eventually results in poor chemotherapy effect.^[4] Therefore, more specific drugs with fewer adverse effects are urgently needed. It is encouraging that natural compounds derived from medicinal plants have become valuable resources for the development of antitumor drugs.^[5] Some studies have demonstrated that consumption of caffeinated coffee or tea could reduce the risk of different kinds of cancers.^[6-10]

Caffeine (1,3,7-trimethylxanthine) is an important natural secondary metabolite presenting in beans, leaves, seeds, and fruits of more than 60 plants (Figure 1). The most common sources are coffee beans, tea leaves, and cocoa beans.^[6] This botanically sourced small molecule compound has attracted much attention due to its broad-spectrum biological functions including anticancer activity.^[11-15] Caffeine is recognized as safety by the U.S. Food and Drug Administration. It is absorbed very quickly and peak plasma concentration of 15.9–18.7 µg/mL usually occurs 0.5 h after the ingestion of 500 mg of caffeine.^[16] Approximately 87% of the world's population consumes an average of 193 mg of caffeine every day.^[16] Caffeine can easily pass through biological membranes and cross the blood-brain barrier, and it is thereby possible to bind to extracellular or intracellular molecules to exert its functions.^[17,18] The present review mainly focuses on recent advances on direct interaction targets of caffeine in the inhibition of malignancies

Figure 1 The chemical structure of caffeine.

and will hopefully provide valuable insights into clinical applications of caffeine for treatment of cancers.

Antagonist of Adenosine Receptor

Adenosine is a short-lived autocrine/paracrine mediator that exhibits a generally cytoprotective function in the body.^[19,20] However, the tumor microenvironment shows high concentrations of adenosine due to some abnormal physiological conditions such as inflammation and oxidative stress.^[21] The primary cellular target of caffeine is the G-protein-coupled adenosine receptors, including A1, A2A, A2B, and A3 receptors.^[20] Notably, caffeine shows the highest binding affinity ($K_D \approx 10 \mu\text{M}$) to the A2A receptor.^[22] Studies have shown that caffeine can target A2A receptor to promote antitumor immune response during tumor initiation, suggesting that it may hold therapeutic potential in diminishing the rate of cancer development.^[23] In addition, caffeine could target A2A receptor to protect against reactive oxygen species (ROS) and prevent carcinogenesis in normal skin tissues.^[24]

Inhibitor of G6PDH

Glucose-6-phosphate dehydrogenase (G6PDH) is the NADP⁺-dependent and rate-limiting enzyme in the pentose phosphate pathway (PPP), which plays an essential role in the oxidative stress response by producing NADPH and is considered to play oncogenic roles based on its overexpression and high enzymatic activity in various tumors.^[25,26] Studies have shown that elevated G6PDH activity has become a biomarker for poor prognosis in cancer patients and G6PDH can be a

potential therapeutic target for cancer.^[27] Interestingly, a recent study demonstrated that caffeine could inhibit G6PDH enzymatic activity and suppress renal cell carcinoma (RCC) proliferation.^[15] As for the molecular mechanism, caffeine can directly bind to G6PDH with high affinity ($K_D = 0.1923 \mu\text{M}$) at the structural NADP⁺ binding site, decrease its coenzyme and substrate binding affinities, and inhibit the formation of dimeric G6PDH.^[15] Moreover, inhibition of G6PDH activity by caffeine can disrupt redox homeostasis and suppress RCC tumor growth *in vitro* and *in vivo*,^[15] suggesting that regular consumption of caffeine in the form of tea or coffee may be a convenient and feasible method to treat RCC patients, whose cells show high G6PDH activity. These findings support that G6PDH is a new cellular target for caffeine. Given that caffeine, NADP⁺, and NAD⁺ all show a similar purine structure, and that the NADP⁺- or NAD⁺-dependent reactions catalyzed by metabolic enzymes are ubiquitous in living organisms, it is very possible that caffeine would also affect other NADP⁺- or NAD⁺-dependent metabolic enzymes such as the NAD⁺-dependent and rate-limiting glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH), which plays key roles in cancer development and progression.^[28]

Activator of SIRT3

ROS are derived from the metabolism of molecular oxygen, which can act as an important second messenger in cell signaling and are essential for numerous biological processes in normal cells.^[29] Any aberrance in redox homeostasis is closely associated with human pathogenesis including cancers.^[30] Studies have revealed that most cancer cells exhibit elevated rates of ROS, which contributes to the maintenance of oncogenic phenotype and promotion of tumor progression.^[31] Theoretically, antioxidants could inhibit the production of ROS, thereby killing these tumor cells. Sirtuin 3 (SIRT3), the major NAD⁺-dependent deacetylase in mitochondria, is responsible for deacetylation of two critical lysine residues (lysine 68 and lysine 122) on superoxide dismutase 2 (SOD2) and promotion of its antioxidative activity.^[32] A recent study have demonstrated that caffeine is a small molecule SIRT3 activator, which can directly bind to SIRT3 with high affinity ($K_D = 0.6858 \mu\text{M}$), thereby enhancing SOD2 enzymatic activity and protecting skin cells from UV irradiation-induced oxidative stress.^[17] Given the unique antioxidative properties of caffeine, it might also target SIRT3 to inhibit the development and progression of cancers such as skin cancer, although this needs further verification in the future.

Conclusions

In summary, emerging evidence from *in vitro*, animal, and human studies suggests that caffeine, the most frequently ingested neuroactive drug in the world, can inhibit cancer development and progression. From the chemical point of view, caffeine is a highly stable alkaloid compound that is not easily oxidized, with methyl groups at the 1, 3, and 7 positions of the purine ring structure. It should not easily interact with some protein molecules and exhibit many health effects including antioxidant and anticancer activities. However, adenosine receptor, the NADP⁺-dependent G6PDH, and the NAD⁺-dependent SIRT3 have been proved to be direct cellular interaction targets for the anticancer activity of caffeine. Given the chemical structure of caffeine, it is very likely to affect other NADP⁺- or NAD⁺-dependent metabolic enzymes involved in tumor initiation and growth, which needs further investigation. It is hoped that future studies will provide new insights into the anticancer mechanism of caffeine and further develop caffeine as a potential natural anticancer drug.

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Conflict of Interest

The authors declare no conflict of interest.

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