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Letter to the editor:

A RECENT OVERVIEW ON SULFORAPHANE AS A DIETARY EPIGENETIC MODULATOR

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Dear Editor,

Gene expression is mediated by chromatin epigenetic changes, including DNA methylation, histone modifications, promoter-enhancer interactions, and non-coding RNA (microRNA and long non-coding RNA)-mediated regulation (Chen et al., 2017). Approximately 50 % of all tumor suppressor genes are inactivated through epigenetic modifications, rather than by genetic mechanisms, in sporadic cancers (Meeran et al., 2010; Su et al., 2018). Accumulating evidence suggests that epigenetic modulators are important tools to improve the efficacy of disease prevention strategies (Ratovitski, 2017; Carlos-Reyes et al., 2019; Hassan et al., 2019).

Sulforaphane ([1-isothioyanato-4-(methyl-sulfinyl)butane], SFN) is a naturally occurring, sulfur-containing isothiocyanate derivative that is found in the seeds and sprouts of cruciferous vegetables such as broccoli, cabbage, cauliflower, and kale (Vanduchova et al., 2019). Because SFN induces the nuclear factor erythroid 2-related factor 2 (Nrf2)-antioxidant response element pathway that induces the cellular defense against oxidative stress (Trio et al., 2016), SFN has received increased attention because it acts as an antioxidant, antimicrobial, anti-inflammatory, and anticancer agent (Vanduchova et al., 2019). Various mechanisms, including apoptosis activation, nuclear factor-κB pathway inhibition, and cell cycle arrest induction, have been proposed to explain the beneficial effects of SFN in preventing multiple types of cancer (Tortorella et al., 2015). Indeed, the increasing attention of SFN as an epigenetic modulator continues to contribute to new developments in clinical trials.

This letter presents a summary of key recent studies investigating the function of SFN as an epigenetic modulator in several human diseases (Table 1). I believe that this letter will stimulate future research on the development of SFN as an epigenetic modulator for successful chemoprevention and alternative therapeutic approaches.

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Table 1: Recent updates on sulforaphane (SFN) as a dietary epigenetic modulator

Effects	Epigenetic regulation	Reference
Anticancer	SFN promotes demethylation at the promoter region of *Nrf2* to increase activation of Nrf2, which induces chemoprevention of human colon cancer.	Zhou et al., 2019
	SFN induced the expression of tumor suppressor *p21* via epigenetic mechanisms (decreasing in histone deacetylase 2 and 3 at the protein level and histone methyltransferase enzymatic activity) in breast cancer cells.	Royston et al., 2018
	SFN downregulated histone deacetylase 5 (HDAC5) transcription by blocking USF1 (upstream transcription factor 1) activity in breast cancer cells, resulting in inhibition of the HDAC5-lysine-specific demethylase 1 axis to suppress breast cancer growth.	Cao et al., 2018
	SFN analogs altered histone acetyltransferase/histone deacetylase activities and histone acetylation status, linked to deregulated homologous recombination/non-homologous end joining repair activities in colon cancer cells.	Okonkwo et al., 2018
	SFN demethylated CpG sites of the promoter of miR-9-3, known as a tumor suppressor miRNA, and reactivated miR-9-3 expression via attenuating enzymatic DNA methyltransferase (DNMT) activity and protein expression of DNMT3a and histone deacetylase 1, 3 and 6 in human lung cancer A549 cells.	Gao et al., 2018
	SFN-induced cell cycle arrest, nitro-oxidative stress and genotoxicity were accompanied by global DNA hypomethylation, decreased levels of DNA methyltransferase 1 and 3B, diminished pools of N^6-methyladenosine RNA methylation and changes in microRNA profile (upregulation of sixty microRNAs and downregulation of thirty-two microRNAs) in breast cancer cells.	Lewinska et al., 2017
	SFN reduced the tumor formation and growth of melanoma stem cells by reducing histone methyltransferase EZH2 levels and histone H3 lysine 27 trimethylation.	Fisher et al., 2016
	SFN inhibited the expression and activity of human telomerase reverse transcriptase, the catalytic subunit of telomerase, through modulation of acetylation of histone H3 lysine 18 and di-methylation of histone H3 lysine 4, resulting in induction of cell death and growth arrest in prostate cancer cells.	Abbas et al., 2016
	SFN led to hypomethylation of tumor suppressor gene promoters, phosphatase and tensin homologue (PTEN) and retinoic acid receptor beta 2 (RARbeta2), resulting in up-regulation of expression of these genes in human breast cancer cells.	Lubecka-Pietruszewska et al., 2015
	SFN reversed the expression of silenced tumor suppressor genes, including *RARβ* (retinoic acid receptor beta), *CDH1* (cadherin 1) and *DAPK1* (death-associated protein kinase 1) through the reversal in the 5′-CpG island methylation and by inhibiting the activity of DNA methyltransferases and histone deacetylases in human cervical cancer cells.	Ali Khan et al., 2015

Effects	Epigenetic regulation	Reference
Treatment of Alzheimer's disease	SFN increased the expression of *Nrf2* and promoted the nuclear translocation of Nrf2 by reducing DNA demethylation levels of the *Nrf2* promoter, thus leading to antioxidative (reducing reactive oxygen species and malondialdehyde, and increasing superoxide dismutase) and anti-inflammatory effects (decreasing the levels of pro-inflammatory cytokines) in a cellular model of Alzheimer's disease.	Zhao et al., 2018
Cell protection	SFN protects against ethanol-induced apoptosis by decreasing ethanol-induced reduction of H3K4me3 at the promoter regions of the *Snail1* transcriptional factor, restoring the expression of *Snail1* and epithelial-mesenchymal transition in ethanol-exposed neural crest cells.	Li et al., 2019
	SFN restored the expression of B-cell leukemia/lymphoma-2 (Bcl-2) and attenuated ethanol-induced apoptosis through restoring acetyl-histone H3 binding to *Bcl-2* promoter in ethanol-exposed neural crest cells.	Yuan et al., 2018
Anti-inflammatory effects	SFN inhibited expression of LPS (bacterial lipopolysaccharide)-induced cluster of differentiation 14 (CD14) that enhances the inflammatory response, through the suppression of *CD14* gene body (coding sequence) methylation that might be caused by the downregulation of DNA methyltransferase 3a expression in pulmonary alveolar macrophages.	Yang et al., 2015

Conflict of interest

The author declares no conflict of interest.

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