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Dietary agents as histone deacetylase inhibitors:

sulforaphane and structurally related isothiocyanates

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Dietary agents such as sulforaphane (SFN) and related isothiocyanates exert anti-cancer effects via multiple mechanisms. These mechanisms include epigenetic changes resulting from the inhibition of histone deacetylase (HDAC) activity. Initial studies on HDAC inhibition by SFN in human colon and prostate cancer cells in vitro were supported by experiments in vivo, showing similar HDAC changes in preclinical models of gastrointestinal and prostate cancer. Pilot studies also showed HDAC inhibition in circulating peripheral blood mononuclear cells when humans consumed a single dose of SFN-rich broccoli sprouts. The possible implications of dietary HDAC inhibitors are discussed here.

Sulforaphane is an isothiocyanate found in cruciferous vegetables, such as broccoli and broccoli sprouts. This anticarcinogen was first identified as a potent inducer of phase 2 detoxification enzymes, but evidence is mounting that SFN acts through other chemoprotective mechanisms.[1,2] One exciting new avenue of SFN research focuses on the inhibition of HDAC activity.[3,4] HDACs affect histone acetylation status and transcription factor access to DNA, thereby derepressing epigenetically silenced genes in cancer cells, resulting in cell cycle arrest and/or apoptosis.[2,3] The field of HDAC inhibition study has focused historically on potent compounds for cancer therapy, but this focus shifted recently toward dietary chemopreventive agents acting as weak HDAC ligands.[4]

HDAC INHIBITION BY SFN AND STRUCTURALLY RELATED ISOTHIOCYANATES

SFN was first reported to inhibit HDAC activity in human colon cancer cells[5] and then in various human prostate lines,[6] with evidence for an increase in both global and local histone acetylation status, such as on the promoter regions of *P21* and *bax* genes. The findings on HDAC inhibition by SFN were recently extended to human breast cancer lines.[7]

In vivo, SFN retarded the growth of prostate cancer xenografts[8] and suppressed spontaneous intestinal polyps in the *Apc*^{min} mouse,[9] with evidence for altered histone acetylation status and HDAC inhibition. In human subjects, a single ingestion of 68 g (1 cup) of broccoli sprouts inhibited HDAC activity in circulating peripheral blood mononuclear cells 3-6 h after consumption, with a concomitant induction of histone H3 and H4 acetylation.[8] These findings provided the first translational evidence for HDAC inhibition by a natural “whole food”, namely broccoli sprouts, and support for an epigenetic mechanism of SFN action at intake levels readily achievable in humans.

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Because the HDAC mechanism involves competitive inhibition by the metabolites SFN-*N*-acetylcysteine and SFN-cysteine, rather than the parent compound SFN,[5] we speculated that other structurally related isothiocyanates might inhibit HDAC activity if they were metabolized via the mercapturic acid pathway. An in vitro screen of structurally related isothiocyanates in the HDAC activity assay supported this possibility.[4] Additional work with the synthetic isothiocyanate phenylhexyl isothiocyanate provided evidence for HDAC inhibition and chromatin remodeling in human leukemia cells, leading to growth arrest.[10] In the last report, it was noteworthy that the inhibition of HDAC activity was associated with changes in multiple histone "marks". Specifically, there was a dose-dependent increase in acetylated histones H3 and H4, as well as methylated H3K4, with concomitant loss of the "repressive" histone mark methylated H3K9. Induction of $p21^{WAF1}$ was seen coincident with cell growth arrest, as reported for SFN in colon and prostate cancer cells.[5,6] These findings are summarized in Table 1.

DIETARY HDAC INHIBITORS IN CANCER CHEMOPREVENTION

Other dietary agents such as butyrate, biotin, lipoic acid, garlic organosulfur compounds, and metabolites of vitamin E have structural features compatible with HDAC inhibition,[4] although, to date, only SFN has been tested from cells to mice to man.[11] The ability of dietary compounds to derepress epigenetically silenced genes in cancer cells has important implications for cancer prevention and therapy. However, important issues remain to be resolved, such as the possible non-selectivity of inhibition towards multiple HDACs and the various pathways regulated downstream. There is also evidence that oxidative stress can inhibit HDAC activity and enhance inflammatory gene expression, leading to a chronic inflammatory response in disorders such as chronic obstructive pulmonary disease.[12] Indeed, there is a growing realization than HDACs are implicated in multiple disease conditions, and an important area for future work will be to clarify the role of dietary HDAC inhibitors not only in cancer development, but also for cardiovascular disease, neurodegeneration, and aging.

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REFERENCES

1. Juge N, Mithen RF, Traka M. Molecular basis for chemoprevention by sulforaphane: a comprehensive review. Cell Mol Life Sci 2007;64:1105–1127. [PubMed: 17396224]
2. Myzak M, Dashwood RH. Chemoprotection by sulforaphane: keep one eye beyond Keap1. Cancer Lett 2006;233:208–218. [PubMed: 16520150]
3. Xu WS, Parmigiani WB, Marks PA. Histone deacetylase inhibitors: molecular mechanisms of action. Oncogene 2007;26:5541–5552. [PubMed: 17694093]
4. Dashwood RH, Myzak MC, Ho E. Dietary HDAC inhibitors: time to rethink weak ligands in cancer chemoprevention? Carcinogenesis 2006;27:344–349. [PubMed: 16267097]
5. Myzak MC, Karplus PA, Chung FL, Dashwood RH. A novel mechanism of chemoprotection by sulforaphane: inhibition of histone deacetylase. Cancer Res 2004;64:5767–5774. [PubMed: 15313918]
6. Myzak MC, Hardin K, Wang R, Dashwood RH, Ho E. Sulforaphane inhibits histone deacetylase activity in BPH-1, LnCaP and PC-3 prostate epithelial cells. Carcinogenesis 2006;27:811–819. [PubMed: 16280330]
7. Pledgie-Tracy A, Sobolewski MD, Davidson NE. Sulforaphane induces cell type-specific apoptosis in human breast cancer cell lines. Mol Cancer Ther 2007;6:1013–1021. [PubMed: 17339367]

8. Myzak MC, Tong P, Dashwood WM, Dashwood RH, Ho E. Sulforaphane retards the growth of human PC-3 xenografts and inhibits HDAC activity in human subjects. Exp Biol Med 2007;232:227–234.

9. Myzak MC, Dashwood WM, Orner GA, Ho E, Dashwood RH. Sulforaphane inhibits histone deacetylase in vivo and suppresses tumorigenesis in *Apc*^{min} mice. FASEB J 2006;20:506–508. [PubMed: 16407454]

10. Ma X, Fang Y, Beklemisheva A, Dai W, Feng J, Ahmed T, Liu D, Chiao JW. Phenylhexyl isothiocyanate inhibits histone deacetylases and remodels chromatins to induce growth arrest in human leukemia cells. Int J Oncol 2006;28:1287–1293. [PubMed: 16596246]

11. Dashwood RH, Ho E. Dietary histone deacetylase inhibitors: from cells to mice to man. Sem Cancer Biol 2007;17:363–369.

12. Rahman I, Marwick J, Kirkham P. Redox modulation of chromatin remodeling: impact on histone acetylation and deacetylation, NFκB and pro-inflammatory gene expression. Biochem Phamacol 2004;68:1255–1267.

Table 1

HDAC Inhibition by SFN and other structurally related isothiocyanates

Test compound(s)	Results obtained	Reference
Sulforaphane, sulforaphene, phenylbutyl isothiocyanate, phenethyl isothiocyanate, erucin, other isothiocyanates	Inhibition of HDAC activity in cell lysates from human colon cancer cells treated with various isothiocyanates; structure activity for HDAC inhibition; molecular modeling	Dashwood et al. (2006)[4]
Sulforaphane	HDAC inhibition in human colon, prostate, breast cancer lines; $p21^{WAF1}$ and bax induction; cell cycle arrest/apoptosis	Myzak et al. (2004)[5] Myzak et al. (2006)[6] Pledgie-Tracy et al. (2007)[7]
	Tumor suppression; HDAC inhibition in mice (PC-3 prostate cancer xenografts); increased histone acetylation status	Myzak et al. (2007)[8]
	HDAC inhibition and suppression of polyps in Apc^{min} mice; increased histone acetylation	Myzak et al. (2006)[9]
	HDAC inhibition in human volunteers consuming SFN-rich broccoli sprouts; increased histone acetylation in peripheral blood cells	Myzak et al. (2006)[9]
Phenylhexyl isothiocyanate	Inhibition of HDAC activity in leukemia cells; increased histone acetylation; loss of repressive histone marks; p21 induction; cell growth arrest	Ma et al. (2007)[10]