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Review

Anti-cancer effects of naturally derived compounds targeting histone deacetylase 6-related pathways

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ABSTRACT

Alterations of the epigenetic machinery, affecting multiple biological functions, represent a major hallmark enabling the development of tumors. Among epigenetic regulatory proteins, histone deacetylase (HDAC)6 has emerged as an interesting potential therapeutic target towards a variety of diseases including cancer. Accordingly, this isoenzyme regulates many vital cellular regulatory processes and pathways essential to physiological homeostasis, as well as tumor multistep transformation involving initiation, promotion, progression and metastasis. In this review, we will consequently discuss the critical implications of HDAC6 in distinct mechanisms relevant to physiological and cancerous conditions, as well as

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AP, activator protein; AR, androgen receptor; BAX, Bcl-2-associated X protein; Bcl, B-cell lymphoma; BUZ, ubiquitin-binding domain; CDK, cyclin-dependent kinase; CLIP, cytoplasmic linker protein; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; CYLD, cylindromatosis; DD, deacetylase domain; DMB, dynein motor binding; DNMT, DNA methyltransferase; EA, ellagic acid; EB, end binding protein; EC, endothelial cell; EGCG, (−)-epigallocatechin-3-gallate; EGFR, epidermal growth factor receptor; EMT, epithelial-to-mesenchymal transition; ER, estrogen receptor; ERK, extracellular signal-regulated kinase; ERST, endoplasmic reticulum stress-tolerance; FADD, Fas-associated protein with death domain; FDA, Food and Drug Administration; FLICE, FADD-like IL-1 β-converting enzyme; FLIP, FLICE inhibitory protein; GBM, glioblastoma; GR, glucocorticoid receptor; GSK, glycogen synthase kinase; HAT, histone acetyltransferase; HCC, hepatocellular carcinoma; HDAC, histone deacetylase; HDAC6i, HDAC6 inhibitor; HDACi, HDAC inhibitor; HIF, hypoxia-inducible factor; HMGN, high mobility group nucleosomal binding domain; HSF, heat shock transcription factor; HSP, heat shock protein; ICD, immunogenic cell death; IIp, invasion inhibitory protein; IL, interleukin; JAK, Janus kinase; LCoR, ligand-dependent nuclear receptor co-repressor; MAPK, mitogen-activated protein kinase; MM, multiple myeloma; MMP, matrix metalloproteinase; MST, mammalian STE20-like kinase; MT, microtubule; mTOR, mammalian target of rapamycin; NES, nuclear export signal; NLS, nuclear localization signal; Nrf, nuclear factor erythroid 2-related factor; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PP, protein phosphatase; Prx, peroxiredoxin; PTEN, phosphatase and tensin homolog; PTM, post-translational modification; RhoB, Ras homolog family member B; RUNX, runt-related transcription factor; SAHA, suberoylanilide hydroxamic acid; SE14, cytoplasmic retention domain; SFN, sulforaphane; SIRT, sirtuin; SMRT, silencing mediator for retinoid or thyroid-hormone receptor; SRSF, serine and arginine rich splicing factor; STAT, signal transducer and activator of transcription; Tau, tubule-associated unit; TGF, transforming growth factor; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; TPPP, tubulin polymerization-promoting protein; TSA, trichostatin A; TSG, tumor suppressor gene; UA, ursolic acid; UDCA, ursodeoxycholic acid; VCP, valosin-containing protein; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; ZBG, zinc binding group.

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Chemical compounds studied in this article:
FK228 (PubChem CID: 5352062)
PXD101 (PubChem CID: 6918638)
SAHA (PubChem CID: 5311)
LBH-589 (PubChem CID: 6918837)
tubacin (PubChem CID: 6675804)
tubastatin A (PubChem CID: 49850262)
ACY-1215 (PubChem CID: 53340666)
ACY-241 (PubChem CID: 53340426)
(−)-epigallocatechin-3-gallate (PubChem CID: 65064)
aceroside VIII (PubChem CID: 21637600)
curcumin (PubChem CID: 969516)
ellagic acid (PubChem CID: 5281855)
genistein (PubChem CID: 5280961)
20(S)-Rh2 (PubChem CID: 119307)
salirepol (PubChem CID: 188287)
butyrate (PubChem CID: 264)
sulforaphane (PubChem CID: 5350)
trichostatin A (PubChem CID: 444732)
ursodeoxycholic acid (PubChem CID: 31401)
ursolic acid (PubChem CID: 64945)

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the anticancer properties of synthetic, natural and natural-derived compounds through the modulation of HDAC6-related pathways.

Contents

1. Introduction

Tumorigenesis is a multistep process whereby normal cells are transformed into malignant cells leading to an abnormal tissue growth. Such transformational events are associated with major biological changes shared by most neoplastic cells called hallmarks of cancer (see for review [1]). It is now widely accepted that besides mutations, the deregulation of epigenetic mechanisms, referring to heritable changes in gene expression that do not involve DNA sequence modifications, participate in the acquisition of the underlying causes of the cancer hallmarks [2].

Growing evidence highlight the essential role of lysine acetylation of histone and non-histone proteins in the coordination of