Histone Deacetylases in Oncoproteins

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Reversible Nε-lysine acetylation/deacetylation is one of the most common post-translational modifications (PTM) of histones and non-histone proteins that is regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). This epigenetic process is highly involved in carcinogenesis, affecting histone and non-histone proteins' properties and their biological functions. Some of the transcription factors, including tumor suppressors and oncoproteins, undergo this modification altering different cell signaling pathways. HDACs deacetylate their targets, which leads to either the upregulation or downregulation of proteins involved in the regulation of cell cycle and apoptosis, ultimately influencing tumor growth, invasion, and drug resistance. Therefore, epigenetic modifications are of great clinical importance and may constitute a new therapeutic target in cancer treatment.

Cancer histone deacetylases p65 SIRT1

1. Introduction

Cancer is a leading cause of premature death next to cardiovascular diseases, with over 19 million new patients and 9.9 million fatalities worldwide in 2020. The latest statistics clearly show that cancer incidence and mortality have increased significantly, partly due to socioeconomic factors, including aging and population growth, as well as factors related to people's behavior and living habitat [1][2].

Cancer is defined as a disorganized cells state, where cells undergo uncontrolled division assaulting host tissue and other tissues (metastasis), annexing critical cell survival resources at the expense of healthy cells, and ultimately causing cell death [3]. These events occur due to progressive series of genetic aberrations and mutations of oncogenes and tumor suppressor genes. Genetic mutations are caused due to inherited and environmental factors and switch the normal cells toward precancerous cells, multiplying and finally evolving into cancer cells [4]. In addition to genetic changes, epigenetic changes are critical in carcinogenesis as they could cooperate with genetic abbreviations that deliver cancer phenotypes. Epigenetics could explain heritable changes in gene expression, which do not follow DNA sequence alterations. Carcinogenesis depends on both genetic and epigenetic alterations, but unlike genetic changes, epigenetic alterations are reversible. Epigenetic mechanisms include modifications on histone proteins, DNA methylation, and regulation of gene expression by non-coding RNAs and microRNAs. All these mechanisms are critical for tumor initiation, progression, and metastasis [5][6], and they have been considered innovative biomarkers or new targets in targeted therapy in various types of cancers [7][8][9][10]. Histone proteins undergo reversible acetylation by opposite working enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs). Histone acetylation by HATs is critical for providing sufficient space for

local transcription events, making chromatin active, whereas histones deacetylation by HDACs leads to chromatin deactivation [11].

In addition to histones, non-histone proteins also undergo reversible acetylation by HATs and HDACs. HDACs are critical post-translational modifiers with distinct roles in human carcinogenesis, giving a different biological effect depending on the type of tumor. They can be categorized into two groups. The first group consists of Zn^{2+} dependent HDACs, divided into four classes depending on their homology, sequence similarity, and expression patterns. Class I and IIa are comprised of four members (HDAC 1, 2, 3, 8, and HDAC4,5,7,9, respectively), class IIb possesses two members (HDAC6 and 10), and class IV only one (HDAC 11). The second group, referred to as the sirtuin family, consists of 7 members (from SIRT1 to SIRT7), which require nicotinamide adenine dinucleotide (NAD) for their activity [10]. HDACs overexpression has been confirmed in various cancers [12][13], providing evidence for the importance of their activity in cancer progression. HDACs activity is essential for controlling gene expression by deacetylation of critical for tumor suppression and tumor development transcription factors such as tumor suppressor p53 (TP53, best known as p53) [14][15], forkhead box (FOX) proteins [16], nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [17], and Myc-family proteins [18]. HDACs also affect signaling mediators, including phosphatase and tensin homolog (PTEN), signal transducer and activator of transcription 3 (STAT3) [19][20], protein kinase B (Akt) [21], and β-catenin [22], as well as other nuclear proteins like Ku70 [23] and structural proteins such as α-tubulin [24].

2. HDACs Deacetylate NF-κB Family Member p65 Modulating Its Tumor-Suppressive Functions

The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) family is known as an important regulator of gene expression involved in inflammatory processes, cell proliferation, and apoptosis [25]. The NF-κB network consists of five protein monomers (p65, p52, p50, RelB, cRel) that can form homodimers or heterodimers that bind to DNA [26]. NF-κB function is affected by HAT-mediated acetylation and HDAC-mediated deacetylation of p65 [17][27][28][29].

2.1. p65 Activity Is Modulated by SIRT1 and SIRT2 That Inhibits Cell Cancer Growth

MYST1, a member of the MYST family containing a HAT domain, acts as a coactivator of NF-κB in PCa cells [17]. SIRT1 interacts with MYST1 and downregulates its autoacetylation forming the MYST1–p65–SIRT1 complex. Simultaneously, MYST1 interacts with p65 and androgen receptor (AR) to regulate tumor behavior. Due to mutually exclusive MYST1 interactions, both complexes act opposite to each other (MYST1–p65–SIRT1 act as a repressor complex, while MYST1–p65–AR as an activator complex), controlling the acetylation of lysine 16 on histone H4 (H4K16Ac) involved in the regulation of cancer progression. MYST1–p65–SIRT1 complex represses apoptotic pathways enhancing cell proliferation and metastasis, while MYST1–p65–AR complex upregulates p21 protein expression leading to G_2M phase arrest during cell cycle progression, resulting in the inhibition of PCa growth[17]. In human glioma tumors and cell lines, SIRT2 deacetylates p65 at lysine 310 and inhibits miR-21 transcription through blocking p65 binding to the miR-21 promoter, suppressing the growth of glioma cells[27].

2.2. Downregulation of SIRT7 Gene Decreases Expression of NF-κB and Inhibits the Growth and Invasiveness of Cancer Cells

The downregulation of *SIRT7* decreases the expression of NF-κB and its target proteins, including anti-apoptotic Bcl-xl, Bcl-2, and Mcl-1, and increases pro-apoptotic proteins, such as caspase-3, Bad, and BAX, inhibiting the growth and invasiveness of endometrial cancer cells[28]. In contrast to SIRT7, the ectopic expression of nuclear HDAC6 in NSCLC cells inhibits cancer invasiveness by the deacetylation of p65, which, in turn, decreases its binding to the matrix metalloproteinase-2 (MMP2) promoter and reduces *MMP2* expression[29].

2.3. HDIs Regulate Expression of NF-κB Partly through Inhibition of HDACs Activity

In liver cancer cells, the inhibition of class I HDACs by a natural compound called hydroxygenkwanin (HGK) increases p65 acetylation at K310, promoting its activation and ultimately upregulating the expression of its downstream tumor suppressor genes (such as *DR5*). Since the acetylation of p65 at K310 could be considered an indicator of p65 anti-cancer activity, the marked increase in the p65-Ac level after HGK treatment indicates the anti-cancer potential of this compound. [30].In turn, in myeloma cells, the use of CUDC-907 compound, a dual inhibitor for HDACs 1/2/3/10 and PI3K, leads to the reduction in p65 expression in a CUDC-907-dependent manner. As the upregulation of NF-κB activity corresponds with chemoresistance, the decrease in NF-κB expression could be a valuable target in anti-myeloma treatment [31]. Additionally, the therapeutical efficiency for CUDC-907 has been proven for human T-cell leukemia virus type 1 (HTLV-1)-driven adult T-cell leukemia (ATL). CUDC-907 inhibits the expression of multiple pro-survival proteins and also inhibits NF-κB expression [32]. The downregulation of NF-κB is also observed when another HDI is used. The use of romidepsin (HDAC1/2 inhibitor) causes a significant enhancement of CYLD, a negative regulator for NF-κB, in an HCC mice model, which partly explains the NF-κB downregulation. In conclusion, romidepsin suppresses the early stage of HCC. The suggested mechanism could be associated with the tumor-suppression activity of romidepsin through the deregulation of critical cancer-related proteins, including NF-κB [33]. In line with these observations, the subsequent finding indicates that the activation of the NF-κB signaling pathway is observed in Kaposi's sarcoma (KS), an endothelial spindle-shaped cell tumor induced by KS-associated herpesvirus (KSHV), when HDAC1 is downregulated. In detail, an oncogenic protein called KSHV-encoded viral FLICE-inhibitory protein (vFLIP) leads to the degradation of the histone deacetylase complex subunit (SAP18), a component of the histone deacetylase complex, which includes, among others, HDAC1 and HDAC2. Meanwhile, transcription factor Nanog, known as an HDAC1 promoter, is inhibited by vFLIP, which resulted in HDAC1 downregulation. Ultimately, the downregulation of the SAP18/HDAC1 complex increased p65 acetylation, activating the NF-κB signaling pathway and thus inducing cancer progression and angiogenesis [34].

3. Signal Transducers and Activators of Transcription (STATs)

Signal transducers and activators of transcription (STATs) constitute a family of proteins (STAT1-4, STAT5A, STAT5B, and STAT6) responsible for regulating gene expression. Activation of STAT proteins occurs due to their

phosphorylation by receptor-associated Janus kinases followed by protein dimerization, transportation of formed dimers to the nucleus, and their binding to DNA within the promoter regions. This, in turn, results in the expression of multiple genes. However, STATs activation can also inhibit specific genes, such as those encoding matrix metalloproteinases and genes involved in cell cycle progression. Therefore, they play the role of a linker connecting multiple signal transduction pathways, and they are essential in many biological processes such as cellular growth, differentiation, apoptosis, and immunity. Increased STAT3 activity is observed in more than 50% of malignancies, including breast, ovarian, lung, prostate cancer, leukemia, and lymphoma [35].

3.1. HDAC1 and HDAC4 Inhibit STAT3 Activity and Interfere with Its Stability

STAT3 is acetylated by histone acetyltransferase p300 at lysine 49 and 87. HDAC1, on the other hand, is involved in the deacetylation process, resulting in the inhibition of STAT3 transcriptional activity in human prostate cancer (PC3) cell lines [36]. Furthermore, HDACs 1 and 4 are responsible for the deacetylation of STAT3 to either terminate STAT3 transcriptional activity or maintain the deacetylated form of STAT3[37].

3.2. SIRT1 and Its Activators Affect STAT3 Transcriptional Function

SIRT1 deacetylates STAT3, which promotes the degradation of STAT3 and leads to the suppression of tumorigenesis in renal cell carcinoma (RCC) [38]. SIRT1 inhibits RCC proliferation by deacetylating and thus destabilizing STAT3, which in turn leads to the inhibition of *FGB* gene expression. The *FGB* gene encodes the fibrinogen Bβ chains, and it constitutes a target gene for STAT3. Overexpression of FGB protein resulting from an increased STAT3 expression is observed in patients with RCC, and it is associated with tumor progression and poor prognosis [38]. Depletion of SIRT1 increases STAT3 acetylation and phosphorylation as well as upregulates matrix metalloproteinase 13 (MMP-13) protein in gastric cancer (GC) both in vivo and in vitro, which, together with other metalloproteinases such as MMP-2 and MMP-9, play an important role in cancer cell invasion via the degradation of the extracellular matrix. The activation of STAT3/MMP13 signaling after SIRT1 depletion suggests that SIRT1 may work as a tumor suppressor[19].

Additionally, using SIRT1 activators, SRT501 and SRT2183, results in the growth, inhibition, and induction of apoptosis in malignant lymphoid cells through the upregulation of growth arrest DNA-damage-inducible protein GADD45 gamma (GADD45G). This, in turn, is due to the inhibition of binding of NF-κB/STAT3 complex to the GADD45G promoter [39]. Nevertheless, the mechanism of SIRT1 activation using the compounds mentioned above remains a matter of dispute. The most likely and accepted mechanism of action of these activators is the allosteric mechanism consisting of conformational changes within the N-terminal domain of SIRT1. This leads to better binding of SIRT1 to its substrates [40]. In line with these findings, SIRT1 activators seem to be a promising tool in anticancer treatment. In research focused on gastric cancer (GC), the use of SIRT1 activator resveratrol (RSV) resulted in a significant reduction in *STAT3* and *c-myc* gene expression as well as the expression of phosphorylated (STAT3-P) and acetylated (STAT3-Ac) forms of STAT3. RSV significantly decreases cell viability and facilitates senescence in GC cell lines as compared to the normal gastric cell line [41]. Correspondingly, new

SIRT1 activators: SRT2183 and SRT501 induce the deacetylation of STAT3, apoptosis, and growth arrest in malignant lymphoid cells with the constitutively activated STAT3 signaling pathway [39].

Since STAT3 regulates the expression of proinflammatory genes, the inhibition of its activity against cytokines secreted by Th17 cells should be emphasized. However, the role of Th17 cells in neoplasms remains controversial and elusive, as they exhibit oncogenic properties in certain types of malignancies yet suppress the development of other tumors. Th-17 cells secrete, among others, IL-17A and IL-17F proinflammatory cytokines, and STAT3 can directly regulate their expression by binding to their promoter regions. The treatment of patients affected by metastatic colon cancer with metformin (SIRT1 agonist) revealed decreased acetylation of STAT3, impeded Th17 cell differentiation, and reduced secretion of IL-17A cytokine by Th-17 cells. Additionally, in vivo studies showed that the use of metformin resulted in reduced tumor growth in a SIRT1-dependent manner [42]. These findings indicate that SIRT1 may function as a tumor suppressor in the tumorigenesis of different cancers, and SIRT1 activators constitute potential therapeutic tools that may be considered for cancer treatment in the future.

4. Myc Family

Another group of oncoproteins that are post-translationally regulated via acetylation and deacetylation consists of three members in the Myc family that are encoded by *c-myc*, *l-myc,* and *n-myc* genes [43]. Myc proteins regulate genes involved in cell proliferation, differentiation, intercellular communication, and cell cycle control. Dysregulation of Myc gene expression or protein stabilization is found in many types of cancers [44]. c-Myc binds to the promoter of SIRT1 and increases SIRT1 expression. SIRT1 interacts and deacetylases c-Myc, decreasing its stability, which suggests that SIRT1 plays a role in tumor suppression [45]. On the other hand, the binding of SIRT1 to the carboxyterminal domain of c-Myc and its deacetylation by SIRT1 leads to the increased formation of c-Myc/myc-associated factor X (Max) heterodimers, which, in turn, facilitates the transactivation of c-Myc[46]. The formation of the C-Myc/Max heterodimers is necessary for the recognition of the target gene promoter by the C-Myc protein, and thus, it constitutes a necessary condition for the proper performance of its function as a transcription factor. One of the C-Myc target genes is the *hTERT* gene encoding the human telomerase reverse transcriptase, responsible for the synthesis of the telomerase catalytic subunit. Interestingly, TERT enables the binding of C-Myc to the target gene promoter and plays a crucial role in its stabilization [47]. Furthermore, the active C-Myc/Max complex induces expression of the *NAMPT* gene encoding nicotinamide-phosphoribosyltransferase. This, in turn, leads to an increase in NAD^+, which is a cofactor for SIRT1, resulting in an increase in the level of the SIRT1 protein [48].

The anticancer effect of the SIRT1 inhibitor comes from the decreased expression of c-Myc target genes, which leads to suppressed proliferation and induction of cell cycle arrest at the G1/S phase in leukemic cells [46]. Similarly, the use of SIRT2 specific inhibitor: TM (thiomyristoyl lysine compound) stimulates c-Myc ubiquitination and its degradation in various cancer cell lines depending on the sensitivity of cells to TM. Interestingly, a negligible effect of TM action is observed both in non-tumor cells and in tumor-free mice, indicating a greater dependence of cancer cells on SIRT2, which may indicate SIRT2 as a potential therapeutic target [49]. Mao and colleagues revealed that

the use of nicotinamide (NAM), the precursor for the synthesis of NAD^+, leads to the inhibition of SIRT1 activity and thus decrease in the C-Myc protein expression[46].

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