Review Article | Emerging Therapeutics

Potential role of short-chain fatty acids in the pathogenesis and management of acute lymphocytic leukemia

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Abstract: Acute lymphocytic leukemia (ALL) is an aggressive hematological malignancy of highly proliferative lymphoblasts. ALL is the most common cancer in children, and is typically treated with combination chemotherapy. The 5-year survival of ALL improved significantly in recent decades with this treatment approach. However, certain age groups (below 2 and over 10 years of age) have much worse prognosis, and over 50% of patients with ALL experience long-term side effects proportional to the dosage of anticancer drugs. Therefore, different treatment strategies are required to improve survival in ALL and to reduce side effects of chemotherapy. Since epigenetic modifications are dominantly reversible, "epidrugs" (drugs targeting epigenetic markers) are considered for feasibility in the treatment of ALL as epigenetic modifications, and acetylation of histones was demonstrated to play a critical role in the pathogenesis of ALL. Histone deacetylases (HDACs) have been shown to be differentially expressed in several hematological malignancies, including ALL. HDAC inhibitors (HDACis) have been shown to express selective toxicity for ALL cells, but they showed limited efficacy and higher than expected toxicity in mouse models or clinical trials in ALL. The aim of this review is to examine the role of the microbiota and microbial metabolites in the mechanisms of HDAC functions, and explore the utilization of the microbiota and microbial metabolites in improving the efficacy of HDACi in ALL. HDAC regulators and natural HDACi are depleted in ALL due to microbiota change leading to a decrease in butyrate and propionate, and HDACi treatment is not effective in ALL due to their short half-life. We propose that HDACi released by the microbiota may be necessary in HDAC regulation and this process is impaired in ALL. Furthermore, the review will also consider the role of restoration of the microbiota or supplementation of natural HDACi in potentially restoring HDAC and HDACi functions.

Keywords: Leukemia; microbiota; short-chain fatty acid (SCFA); histone deacetylase (HDAC)

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Introduction

Acute lymphocytic leukemia (ALL) is a progressive hematological malignancy characterized by the proliferation of immature lymphocytes. ALL is the most common cancer in children, accounting for approximately 27% of all pediatric cancers, and is typically treated with combination chemotherapy (1). Each year, approximately 7,000 new cases and 1,500 deaths are reported in the US (2). Five-year survival of ALL improved significantly in recent decades, and is currently at around 71%. However, certain age groups (below 2 and over 10 years of age) have much worse prognosis, and over 50% of patients with ALL experience long-term side effects proportional to the dosage of chemotherapeutic drugs. Long-term side effects include early mortality, cardiac failure, infertility, cognitive impairment, obesity, fatigue, muscle weakness, decreased bone density, and increased risk of infection (3-7).

Therefore, alternative treatment approaches are urgently needed to improve survival of patients with ALL and to reduce side effects of chemotherapy. Multiple studies show that epigenetic modifications, and histone acetylation in particular, play a key role in the pathogenesis of ALL (8-10). Since epigenetic modifications are dominantly reversible, drugs targeting enzymes involved in histone acetylation became an attractive strategy for ALL treatment (8).

Histone deacetylases (HDACs) remove acetyl groups from lysines in histones, and as our group and others found, they are consistently overexpressed in ALL (8-10). Overexpression of HDACs have been associated with poor prognosis in ALL (8,11), as it leads to impaired cell development and uncontrolled growth via cyclin-dependent kinase inhibitor protein inhibition (12). HDAC inhibitors (HDACis) are chelating agents blocking HDAC function and have been observed to be efficient against ALL cells, while not damaging healthy lymphocytes. However, while HDACis have been shown to be efficient in cell culture, clinical trials and mouse studies have not been successful as HDACi showed higher than expected toxicity and reduced efficacy in ALL (8). A naturally occurring HDACi are short-chain fatty acids (SCFAs), such as butyrate and propionate (13). SCFAs are a by-product of the microbial metabolism of complex carbohydrates by the gut microbiota. We and other groups have shown that ALL is characterized by an altered gut microbiota and low SCFA levels, including butyrate, propionate, and acetate (9,10,14). SCFAs exert their effect through three mechanisms of action: (I) by HDAC inhibition via HDACs 1-11 and sirtuins; (II) via GPR41/43 G-protein coupled receptors; and (III) via GPR109A receptors impacting lymphocyte chemotaxis (*Figure 1*). This review will focus on HDAC functions, although GPR41/43 and GPR109A receptors may also play a role in the pathogenesis of bloodstream infections, a common complication in ALL (9).

Current HDACi approved for the treatment of hematological malignancies include Vorinostat (Zolinza)-approved in 2006 for the treatment of cutaneous T-cell lymphoma; Romidepsin (Istodax)-approved in 2009 for the treatment of cutaneous T-cell lymphoma; Belinostat (Beleodaq)-approved in 2014 for the treatment of peripheral T-cell lymphoma; and Panobinostat (Farydak)-approved in 2015 for the treatment of multiple myeloma (8,15).

All the above-mentioned drugs are pan-HDACis, as they target all HDACs. In the treatment of ALL they show significant anti-cancer effect, but in mouse models and clinical trials indicated higher than expected toxicity and low efficacy (15).

Pan-HDAC have not been successful in ALL, likely because different HDACs have different oncogenic and oncosuppressor roles. For example, HDAC1–2 can play an oncosuppressive role in leukemia initiation, while HDAC3 has pro-oncogenic functions in multiple phases of leukemogenesis (16). While HDACs have been reported to be consistently overexpressed in ALL, it only involves the minority of all HDACs. HDAC1–4 and HDAC6–9 have been verified as overexpressed in ALL either in cell culture, or animal models or clinical samples (17). Therefore, these reports suggest that while HDAC inhibition offers a promising molecular pathway, a selective HDACi would be of primary importance for the successful management of ALL (8,11). The U.S. Food and Drug Administration (FDA) approved HDACi (Vorinostat, Panbinostat, Romidepsin, Belinostat) are pan-HDACis, and that may be the reason of their lack of success in clinical trials in ALL as they inhibit oncosuppressor and pro-oncogenic HDAC alike. Butyrate and propionate are selective inhibitors primarily of HDAC3, and HDAC8, while acetate inhibits HDAC5 and HDAC9 (15). A comprehensive review of HDACi receptor specificity can be found in Ceccacci *et al.* (15).

The microbiota in ALL

There are approximately 40 trillion microbes, dominantly bacteria, inhabiting the human body, and they are commonly referred to as the human microbiota. The microbiota performs several important physiological

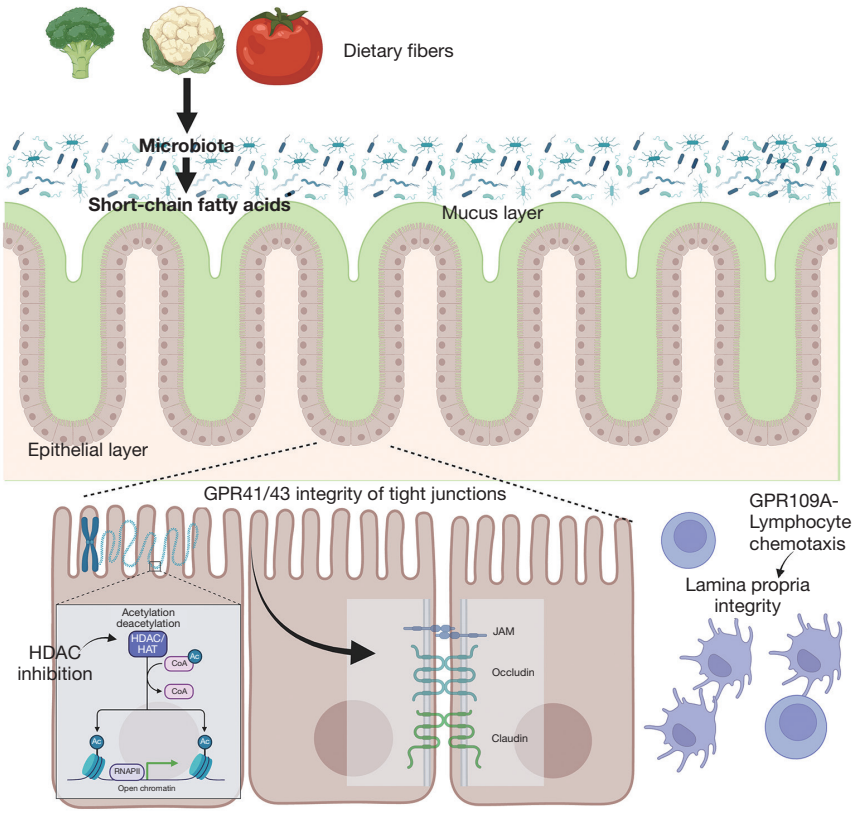

Figure 1 Schematic representation of how SCFAs exert their effect on the host. SCFAs are microbial metabolites derived from the microbiota by degrading dietary fibers in the intestinal tract. SCFAs can bind to GPR41/43 receptors to provide nutrient source to intestinal epithelial cells, which affect intestinal barrier function. SCFAs can also bind to GPR109A receptors to influence lymphocyte migration and the integrity of the lamina propria. Lastly, SCFAs are natural inhibitors of HDAC, which regulate the transcriptional activity of the cell in tandem with HAT by adding/removing acetyl groups on histone terminals. The image was created with Biorender.com. HDAC, histone deacetylase; HAT, histone acetyltransferase; Ac, acetyl; CoA, coenzyme A; RNAPII, RNA polymerase II; JAM, junctional adhesion molecule; SCFA, short-chain fatty acid.

functions from training the immune system to colonization resistance, among others (14,18). Over 95% of the microbiota is located in the intestinal tract, composed of around 200 species per person, and >90% of the gut microbiota belongs to three phyla: *Firmicutes*, *Bacteriodetes*, and *Actinobacteria* (18). Apart from taxonomical compositions, microbial diversity is an important metric when evaluating microbiota changes, as decrease in diversity limits the breadth of microbial functions.

It is well established that the taxonomic composition of the microbiota changes in ALL (14). However, it has to be considered in human studies that the human microbiota is very versatile, and displays broad differences depending on diet, health status, age, geography, drug use, among other factors. Even more importantly, most patients with ALL undergo prophylactic antibiotic therapy that severely change microbiota compositions, and selecting appropriate control population may be challenging. Variability and antibiotic prophylaxis are likely the key reasons why there has been little consistency in microbiota changes in patients with ALL [reviewed in (14)].

Therefore, microbiota studies in animal model systems under more controlled environmental conditions may shed light on changes in the microbiota and its function in ALL (9). Nevertheless, increase in opportunistic pathogens such as *Staphylococcaceae*, *Streptococcaceae*, and *Enterococcus* have been consistently reported (19-23) along with decreased microbial diversity in ALL both in clinical settings (20,23-25) and in mouse models (9,26).

HDACi in cancer therapy

Histones

Epigenetic alterations play an important role in the pathogenesis of ALL (27). Amongst those, histone modifications, especially acetylation of histones demonstrated direct clinical significance (8,27,28). Histones are a class of highly conserved proteins rich in lysine and arginine residues, whose primary role is to organize and tightly package genomic DNA into chromatin structure. Histones protect genomic DNA from becoming tangled and undergoing DNA damage. In relation to that, histones also play major roles in regulating gene expression and DNA replication via directing DNA packaging. There are five main types of histones: H1, H2A, H2B, H3, and H4, and these proteins assemble together to form a nucleosome. Due to their arginine and lysine-rich structure, histones possess a positive charge which makes it possible to interact with negatively charged DNA molecules. This interaction leads to the formation of the histone-DNA complex, which forms the fundamental building blocks of chromatin (15).

This tight packaging of genomic DNA by histones restrict access for transcription factors and other regulatory elements, creating a repressive state called heterochromatin characterized by limited gene expression. However, epigenetic modifications of histones, such as acetylation, can alter chromatin structure and allow increased access to genes leading to a more open state with increased transcription called euchromatin.

HDACs

HDACs are enzymes that regulate gene expression and chromatin structure by removing acetyl groups from histone terminals. Acetylation and deacetylation of histones are a dynamic process leading to alterations in chromatin structure and gene expression, and are completed by histone acetyltransferases and HDACs, respectively. Acetylation of histones, an addition of acetyl groups to lysine residues by histone acetyltransferases neutralize the positive charge of histones, allowing a more open chromatin structure and increased gene expression. On the other hand, HDACs remove acetyl groups from lysine residues, restoring positive charge to histone, that leads to a more compact chromatin structure and repressed gene expression. HDACs are categorized based on their structure and enzymatic activity. Class I, II, and IV HDACs are zinc-dependent enzymes, while class III HDACs, also known as sirtuins, require nicotinamide adenine dinucleotide (NAD^+) as a cofactor (15). HDACs have been found overexpressed in several cancer types, including leukemias (8,29), which led to the theory that HDAC inhibition may play a role in cancer treatment.

HDACis and their use in cancer therapy

HDACs are differentially expressed in several solid tumors (30-34), and HDACi were shown a strong anticancer activity *in vitro* (35-38). However, expression differences of HDAC genes can be bidirectional which may be due to the involvement of HDACs in a multitude of cell functions (28). For example, in breast cancer only HDAC2 and 3 were associated with clinicopathological signs while HDAC1 was not (31), or as it was shown in promyelocytic leukemia mouse model, HDAC1 can act as an oncosuppressor in tumorigenesis, while also facilitate the disease as an oncogene in tumor maintenance (28). These data suggest that broad range HDACi may inhibit innate antitumor mechanisms, and a more tailored inhibition of HDACs are necessary for targeted therapies.

HDAC studies in ALL

While the methodological aspects of gene expression studies are beyond the scope of this review, it has to be noted that while only the differential expression results will be reported here, these results were obtained from different patient populations, different locations and different cell lines. Since leukemias are genetically very heterogenous and can affect multiple age groups, this aspect has to be taken into account when interpreting the results. In addition, the works reported here include a wide variety of experimental protocols, calculations, analytical methods, thresholds, and (positive and negative) controls (if any), which could all influence the final results (39-43).

With that in mind, several HDACs have been consistently reported to display an altered gene expression pattern in ALL. Moreno *et al.* reported HDAC differential expression from bone marrow samples of 94 pediatric ALL patients using Taqman real-time quantitative polymerase chain reaction (RT-qPCR) for HDACs 1–7 and 9–11 (44). The authors found HDACs 2–3 and 6–8 significantly overexpressed in ALL bone marrow, HDAC2 and HDAC8 providing the largest differential expression when compared to normal bone marrow samples. Higher expression of HDACs 1 and 4 and lower expression of HDAC5 were

shown in T-cell ALL when compared to B-cell ALL samples. Higher expression of HDAC3 has been associated with low-risk classification, and higher 5-year event-free survival. Lower HDAC3 expression implied an increase in unfavorable outcomes, while overexpression of the HDAC7 and HDAC9 genes indicated lower 5-year event-free survival and high levels of minimal residual disease.

In 93 pediatric and adolescent ALL patients aged between 2 and 20 years, Gruhn *et al.* (12) isolated leukemia cells and mononuclear cells from the bone marrow, and measured expression levels of HDACs 1–11. Using RT-qPCR, their group found HDAC1, HDAC2, and HDAC8 were significantly overexpressed when compared to donor samples, while none of the HDACs showed underexpression. HDAC1 and HDAC4 overexpression was associated with higher (>50,000/μL) initial white blood cell (WBC) count, and HDAC4 was also correlated with poor response to prednisone (12). The authors also showed that reduction of HDAC4 in cell culture improved chemotherapy response, implying a potential role for specific inhibition of HDAC in the treatment of ALL.

While most HDAC are overexpressed in ALL, HDAC7 is frequently underexpressed in ALL, particularly in B-cell ALL (45). HDAC7 is a class IIa HDAC, with a primary role in lineage commitment of B-cells as it interacts with transcription factor MEF2C in B-cell progenitors, which in turn leads to silencing of lineage-inappropriate genes and appropriate differentiation of B-cells (46). Ectopic expression of HDAC7 leads to apoptosis and downregulation of the c-Myc, a transcription factor with a wide range of functions including apoptosis, hematopoiesis, and DNA damage response. It has been demonstrated that low expression of HDAC7 in B-cell ALL samples is correlated with increased levels of c-Myc to promote apoptosis, based on a dataset of 191 samples from patients with B-cell ALL (45). The study used an expression profiling microarray targeting two HDAC7A transcript variants.

SCFAs as HDACi in ALL

As mentioned earlier, SCFAs are microbial metabolites with several physiological functions, including regulation of cell cycle and inhibition of HDACs. Microbiota-derived HDACi include SCFAs propionate, butyrate (both selectively inhibiting HDAC3 and 8), and acetate (selective inhibitor of HDACs 5 and 9) (15). However, there have been limited studies concerning their activities in ALL.

Pivaloyloxymethyl butyrate (AN-9)

AN-9 is a butyric acid prodrug that is metabolized by intracellular esterases to release butyrate. AN-9 displays improved pharmacokinetics to butyrate due to its increased permeability across cell membranes (47) and exhibits anti-tumor activity *in vitro* and *in vivo* (48). AN-9 has been shown to possess an effective antiproliferative and cytotoxic activity against multiple ALL cell types, including cells resistant to doxorubicin and refractory ALL (49), and only has been tested in preclinical studies.

Valproic acid

Valproic acid is an SCFA with HDACi activity (a pan-HDACi), which has been used as an anti-epileptic medication and treatment for bipolar disorder and post-traumatic stress disorder (PTSD) for decades. Valproic acid *in vitro* inhibits proliferation and induces apoptosis and hyperacetylates histone H4 proteins in ALL cell line (50). In the same study, valproic acid was also demonstrated to reduce the spread of the tumor in a B-cell ALL xenograft mouse model and inhibited leukemia-induced splenomegaly without significant toxicity detected in the animals (50).

Potential role of changes in the microbiota in ALL

It has been repeatedly demonstrated in clinical samples from patients with ALL and in ALL mouse models that the microbiota undergoes drastic changes in ALL, and the changes in the microbiota are consistently characterized by a decrease in microbial α-, and β-diversities [reviewed in (14)]. Since not every member of the microbiota can produce SCFAs, changes in the microbiota lead to changes in SCFA levels as well. It has been shown that levels of butyrate, propionate, and acetate significantly decrease in ALL, and replenishing these SCFAs ameliorate the consequences of the disease (9).

As discussed above, SCFAs are natural HDACis, which can enter the circulation and cross the blood-brain barrier, and apart from their nutritional value, they also participate in a broad range of cellular functions (8). We and other groups have shown that microbiota changes in ALL lead to a decrease of natural HDACis butyrate, propionate, and acetate (9,14). An intriguing hypothesis would be to assert that the depletion of natural HDACi may participate in the pathophysiological development of lymphocytes and in the pathogenesis of ALL. Firstly, as natural HDACi

with limited or no toxicity, a decrease of SCFAs can result in irregularities in cell cycle development. Secondarily, SCFAs have very selective inhibitory capacity for HDACs, which could circumvent the limited efficacy of pan-HDACs, such as Givinostat, seen in the treatment of ALL. Thirdly, natural HDACs such as butyrate are provided in a continuous low dose (compared to treatment dosage) by the microbiota, which could lead to improved treatment efficacy; while HDACi drugs typically are administered in higher dose but have short half-life. Lastly, a combinative effect of SCFAs along with traditional chemotherapy should be more extensively explored in ALL (51).

Conclusions

As of the writing of this review (October 2023), there is no active clinical trial directed at ALL using SCFAs. Valproic acid has been involved in a phase 2 trial in acute myeloid leukemia (AML) and myelodysplastic syndrome with decitabine therapy (NCT00414310). Preliminary data indicate higher remission and slightly higher adverse effects for the valproate (VPA)-treated group, but no peer-reviewed paper has been published. Phase 2 studies have been conducted in AML with phenylbutyrate acid, but no results have been published (NCT00006240, NCT00004871). Further studies in cell and animal models of hematological malignancies will be required to fully utilize the potential of SCFAs either as a monotherapy or in combination with chemotherapy for improved treatment of ALL.

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Footnote

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1806/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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