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Mini Review

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Fatty Allies: How Short-Chain Fatty Acids Turn the Tumor Microenvironment Against Cancer

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Abstract
Short-chain fatty acids (SCFAs), which are fatty acids with fewer than six carbon atoms, are primarily produced by gut microbiota through fermentation of dietary fibers. They interact with various receptors on target cells, including G-protein coupled receptors (GPCRs) and free fatty acid receptors (FFARs). These interactions induce significant epigenetic modifications, such as the inhibition of histone deacetylases (HDACs) and the regulation of several microRNAs (miRNAs) and long noncoding RNAs (lncRNAs). SCFAs reprogram the tumor microenvironment (TME) by promoting the recruitment and effector function of cluster of differentiation (CD)8^+ T cells and reducing regulatory T cell (Treg) activity, thereby converting the TME from an immunosuppressive to an immunoreactive state. They modulate the differentiation and activity of various immune cell subsets, including macrophages, dendritic cells (DCs), natural killer (NK) cells, neutrophils, T cells, B cells, and myeloid-derived suppressor cells (MDSCs). SCFAs also precipitate anti-growth effects in tumor cells by hampering glycolysis and enhancing fatty acid oxidation. The idea of integrating SCFAs with immunotherapy for cancer treatment has garnered considerable interest in recent years. However, more work is still needed to better understand the molecular underpinnings of the interaction between SCFAs and different cell subsets within the TME. Further investigation of issues relating to dosing, therapeutic efficacy, and safety of exogenously administered SCFAs in cancer patients, particularly immunocompromised patients, is also in order.

Keywords:
short-chain fatty acids; G protein-coupled receptors; tumor microenvironment; immunotherapy; epigenetic reprogramming

1. Introduction

SCFAs typically contain fewer than six carbon atoms. They are produced primarily through the fermentation of dietary fibers by beneficial gut bacteria in the colon. The most common SCFAs include acetate, propionate, and butyrate. The TME is a complex system consisting of immune, stromal, and tumor cells that interact to influence cancer progression [1]. Innate and adaptive antitumor immune responses within the TME are key to tumor control [2]. However, tumors often evade immunity, weakening surveillance and enabling progression [3]. Mounting evidence suggests that SCFAs play a significant role in transforming the immunosuppressive TME into one that supports effective anti-tumor immunity [4]. SCFAs mediate their effects through signaling cascades transduced via several SCFA receptors, including some GPCRs and FFARs on target cells. This leads to significant epigenetic modifications in the form of methylation and the inhibition of HDACs [5]. These changes modulate several inflammatory pathways affecting macrophage polarization, NK cell activity, DC antigen presentation, and lymphocyte (T and B cells) functional differentiation within the TME [6]. SCFAs also variably influence tumor metabolism by altering glycolysis, enhancing oxidative phosphorylation, and regulating lipid metabolism depending on the type of tumor [7]. They also modulate MDSCs, key immunosuppressive cells in the TME [8]. Although

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SCFAs present considerable therapeutic potential as they enhance anti-tumor immunity, the risk of overwhelming the immune response and/or promoting immune evasion of tumor cells cannot be discounted [9]. More research is needed to fully understand the molecular mechanisms by which SCFAs enhance anti-tumor immunity while simultaneously suppressing tumor growth. Additionally, many aspects of the clinical application of SCFAs as adjunctive therapy in cancer patients receiving immunotherapy still need to be ironed out. This minireview commences with a general introduction to SCFAs and their anti-tumor effects and concludes with some key unanswered questions regarding their basic biology and clinical utility.

2. Immunomodulatory Effects of SCFAs in the TME

2.1. SCFAs and Innate Immunity

Innate immunity is the first line of defense against tumors, detecting damage- and tumor-associated molecular patterns (DAMPs, TAMPs) to trigger inflammation and immune surveillance [10]. SCFAs modulate innate immune cells in the TME in several ways that affect tumor progression. In general terms, macrophages can polarize into an M1 (pro-inflammatory) or an M2 (anti-inflammatory) state. SCFAs such as butyrate and propionate tend to promote M1 polarization through transcriptional and epigenetic regulation [11]. They upregulate the expression of tumor necrosis factor-alpha (TNF-α), interleukin-12 (IL-12), interferon gamma (IFN-γ), nitric oxide (NO), while suppressing the expression of several M2 markers, including arginase 1 (ARG1), IL-10, and tumor growth factor-beta (TGF-β), and inhibiting HDAC from blocking tumor-promoting genes [9,12,13]. In DCs, SCFAs enhance the expression of major histocompatibility complex-II (MHC-II), CD80, and CD86, which facilitate T cell antigen receptor (TCR) and the co-stimulatory receptor CD28 engagement, thereby boosting T-cell priming [14,15]. In some contexts, SCFAs have been shown to promote the rise of tolerogenic DCs, increase IL-10 production, and reduce IL-12 production, thus contributing to immune evasion [16]. SCFAs can enhance NK cell cytotoxicity by upregulating the expression of natural killer group 2 member D (NKG2D), perforin, and granzyme B, and by improving NK's metabolic fitness through mitochondrial biogenesis and fatty acid oxidation [17]. HDAC inhibition further amplifies the expression of NK effector genes [18]. Neutrophils are also modulated by SCFAs through various chemokines, including CXCR1 and CXCL2. For example, SCFAs enhance the capacity of neutrophils to generate reactive oxygen species (ROS) and perform phagocytosis, but whether they affect neutrophil extracellular trap (NET) formation (NETosis) remains unclear [19,20]. SCFAs modulate immune cell migration, chemokine and cytokine release, and inflammatory signaling in the TME, primarily through their ability to interact with innate receptors, including toll-like receptors (TLRs) and GPCRs (GPR41, GPR43, GPR109A) [21].

2.2. SCFAs and Adaptive Immunity

Several studies have elaborated on the capacity of SCFAs to modulate T and B lymphocytes through epigenetic regulation, metabolic reprogramming, and cytokine signaling [22]. By inhibiting HDACs and altering metabolism, SCFAs enhance $CD8^+$ T cell differentiation and the production of IFN-γ, granzyme B, and perforin for cytotoxic activity, and promote the generation of adaptive memory for sustained tumor immunosurveillance [23,24]. Moreover, SCFAs promote T helper 1 (Th1) differentiation, thereby enhancing IFN-γ and IL-2 production, suppressing Th2 cytokines, eventually reducing IL-4 and IL-5, and modulating Th17 activity in a way that maintains anti-tumor immunity while limiting pathogenic inflammation [18,25,26]. Butyrate and propionate promote the expansion of forkhead box P3 $(Foxp3)^+$ regulatory T (Treg) cells through histone deacetylase (HDAC) inhibition, thereby contributing to immune tolerance. However, they may contribute to the development of an immunosuppressive TME, especially when excessive accumulation of Tregs occurs [27]. While SCFA-induced Tregs may mitigate chronic inflammation associated with tumorigenesis, the fact that they can precipitate immunosuppressive effects calls for caution when considering their therapeutic utility. SCFAs enhance cytotoxic T lymphocyte (CTL) survival and function, and hence promote CTL-mediated tumor eradication through their ability to support metabolic adaptability (mitochondrial function and fatty acid oxidation), especially in nutrient-deprived TME [28]. They also reduce T cell exhaustion by decreasing the expression of programmed cell death protein 1 (PD-1), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), and lymphocyte activation gene 3 (LAG-3). Combined, these effects are believed to improve patient responsiveness to checkpoint blockade and to expand the T cell memory pool [29,30]. SCFAs also seem to modulate humoral immunity within the TME by, for example, promoting B cell proliferation and enhancing isotype (IgA/IgG) switching [31]. So far, little is known regarding the effects of SCFAs on the differentiation or activity of TME immunosuppressive regulatory B cells (Bregs) [32].

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2.3. SCFAs and MDSCs

The TME is an immunosuppressive niche that promotes tumor growth and immune evasion [33]. MDSCs, key TME components, suppress T cell activity and promote Treg expansion through several mediators, including ARG1, inducible nitric oxide synthase (iNOS), ROS, and TGF-β [34]. Targeting MDSCs is thus a promising strategy in cancer immunotherapy. Gut microbiota-derived SCFAs (acetate, propionate, and butyrate) modulate immunity through SCFA receptors (GPCRs) GPR41, GPR43, GPR109A, and through the inhibition of HDACs [35, 36]. These pathways affect immune cell differentiation and function, including that of MDSCs [37]. The effects of SCFAs on MDSCs are context-dependent. For example, butyrate and propionate promote MDSC expansion and immunosuppressive activities by enhancing ARG1 and iNOS expression [38]. Conversely, SCFAs may reprogram MDSCs toward less suppressive phenotypes. Butyrate-driven HDAC inhibition and GPR109A signaling have been linked to reduced MDSC-mediated suppression and improved anti-tumor immunity [39,40]. SCFAs also shape MDSC metabolism, influencing glycolysis, oxidative phosphorylation, and fatty acid metabolism. Butyrate, in particular, promotes oxidative metabolism and mitochondrial function, potentially impairing MDSC suppressive activity [41,42]. Understanding these paradoxical effects of SCFAs on MDSC regulation may help identify novel strategies to enhance anti-tumor immunity.

2.4. SCFAs and Tumor Cell Metabolism

Being metabolically adept enables cancer cells to sustain growth, resist apoptosis, and evade immunity [43]. SCFAs, as key metabolic modulators in the TME, influence glucose and lipid metabolism, mitochondrial function, and redox balance [44,45]. Generally, cancer cells favor aerobic glycolysis (Warburg effect) for adenosine triphosphate (ATP) production. SCFAs counter this by downregulating the production of the glycolytic enzymes hexokinase 2 (HK2) and pyruvate kinase M2 (PKM2) and reducing glucose uptake and lactate output [46]. SCFAs also activate the AMP-activated protein kinase (AMPK), inhibiting the mammalian target of rapamycin (mTOR) signaling and curbing anabolic growth [47]. SCFAs enhance oxidative phosphorylation, shifting energy production from glycolysis and limiting tumor proliferation. In lipid metabolism, SCFAs suppress lipogenesis by downregulating the expression of sterol regulatory element-binding protein-1 (SREBP-1) and fatty acid synthase (FASN) [48,49], while promoting fatty acid oxidation (FAO) via peroxisome proliferator-activated receptor-gamma (PPAR-γ). These effects increase ATP production and reduce lipid accumulation, which is a characteristic feature in several aggressive, chemoresistant tumors [50]. SCFAs also prevent lipid droplet buildup, a hallmark of invasive cancers. SCFAs support mitochondrial function by fueling the tricarboxylic acid (TCA) cycle, boosting nicotinamide dehydrogenase "nicotinamide adenine dinucleotide (*NAD*) + hydrogen" (NADH) and ATP production, and restoring mitochondrial health in normal cells [51,52]. They regulate oxidative stress by increasing antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPx), protecting normal cells while enhancing ROS in tumor cells [53]. Additionally, SCFAs upregulate the expression of peroxisome proliferator-activated receptor γ coactivator 1 alpha (PGC-1α), promoting mitochondrial biogenesis and counteracting metabolic dysregulation [54].

2.5. SCFAs and the Expression of miRNAs and lncRNAs in TME

Beyond immune regulation, SCFAs, mainly butyrate, propionate, and acetate, are involved in regulating the expression of several gene sets in different cell types within the TME through HDAC inhibition and chromatin remodeling [55]. Among the genes that are regulated by SCFAs are several miRNAs and lncRNAs, which subsequently regulate tumor progression, immune evasion, and metabolic reprogramming [56,57]. For example, SCFAs have been reported to upregulate the expression of tumor-suppressive miRNAs like miR-34a, which inhibits Wnt/β-catenin and Notch signaling [58], miR-200 family, which blocks epithelial-mesenchymal transition (EMT) and enhances chemosensitivity [59], miR-146a, which reduces inflammation and M2 polarization [60], miR-124, which boosts $CD8^+$ T cell cytotoxicity, and miR-155, which promotes M1 polarization and T cell activation [61]. Moreover, several SCFAs were reported to downregulate the expression of oncogenic miRNAs, including miR-21, miR-181a, miR-222/221, and miR-27a, all of which promote tumor growth, immune suppression, and/or metabolic reprogramming [62–65]. SCFAs also regulate lncRNAs by upregulating tumor suppressors like the maternally-expressed 3 gene (MEG3; induces apoptosis) [66], nuclear paraspeckle assembly transcript 1 (NEAT1; modulates immunity), *growth arrest-specific transcript 5* (GAS5; enhances T cell function) [67], tumor suppressor candidate 7 (TUSC7; inhibits proliferation) [68], and *long intergenic non-protein coding RNA, and p53 induced transcript* (LINC-PINT; activates p53 signaling) [69]. At the same time, SCFAs have been reported to downregulate the expression of several oncogenic lncRNAs, including

metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), *HOX transcript antisense RNA* (HOTAIR), *small nucleolar RNA host gene 16* (SNHG16), *urothelial cancer associated 1* (UCA1), and plasmacytoma variant translocation 1 (PVT1), which drive metastasis, immune evasion, and chemoresistance [70–74]. In short, SCFAs regulate key lncRNAs in the TME, contributing to tumor suppression by enhancing immunity and disrupting oncogenic signaling.

3. Standing Questions and Future Perspectives

There is ample evidence to suggest that integrating SCFAs with immunotherapy enhances treatment outcomes in colorectal cancer (CRC), breast cancer, melanoma, lung cancer, and hepatocellular carcinoma (HCC), but not in glioblastoma, prostate, and ovarian cancer. This suggests that the anti-tumor effects precipitated by SCFAs could be cancer type-dependent, which raises the question of how cancers that respond positively to SCFA plus immunotherapy differ from those that do not. Focusing on this question may help identify cellular and molecular correlates that will inform future work on the therapeutic utility of SCFAs. One of the critical aspects to investigate here is the expression patterns of SCFA receptors and the integrity of the pathways initiated by SCFA receptor signaling in different types of cancer. Similarly related to this issue is whether specific effects precipitated by SCFAs in target cells of the TME can be assigned to specific SCFA receptors. SCFA-induced HDAC inhibition affects many genes, some of which play important roles in modulating the TME in favor of tumor regression. Searching for other genes that are subject to HDAC inhibition-dependent regulation should help in further appreciating the full extent of the anti-tumor effects of SCFAs within the TME. The absence of specific biomarkers for assessing the therapeutic value of SCFAs further complicates the issue.

SCFAs play a crucial role in the differentiation and function of various immune cell subsets. The exact mechanism(s) underlying the immunomodulatory effects of SCFAs, particularly as they relate to macrophage polarization and Th cell differentiation, have yet to be elucidated. A detailed understanding of how SCFAs drive the differentiation of MDSCs is also pivotal to realistically assessing the risks of SCFA-based therapy in cancer patients. Exploring the therapeutic utility of SCFA-induced differentiation of MDSCs in inflammatory and autoimmune diseases also merits further investigation.

4. Conclusions

The gut microbiota metabolizes dietary fibers to produce SCFAs. Consumption of fiber-rich foods should, by definition, increase the concentration of SCFAs in the blood and tissues. However, determining the amount of fiber-rich food required to produce therapeutic levels of SCFAs remains unclear, making it difficult to calculate the appropriate dietary intake. Further, a detailed understanding of the pharmacokinetics and pharmacodynamics of SCFAs is still lacking. Moreover, tissue infiltration by SCFAs needs to be further investigated, especially in the case of hypoxic cores of solid tumors. Would too much SCFAs in the circulation and/or the TME overwhelm the anti-tumor immune response? Could insufficient SCFA levels contribute to immune tolerance and hinder rejection? Assessing the impact of dysbiosis resulting from antibiotics or chemotherapy, for example, on the type and concentration of SCFAs produced in cancer patients warrants further investigation.

Abbreviations

AMPK	AMP-activated protein kinase
ARG1	arginase 1
ATP	adenosine triphosphate
Bregs	regulatory B cells
CD	cluster of differentiation
CTL	cytotoxic T lymphocyte
CXCL1	C-X-C motif chemokine ligand 1
DAMPs	damage-associated molecular patterns
DC	dendritic cell
EMT	epithelial mesenchymal transition
FAO	fatty acid oxidation
FASN	fatty acid synthase
FFARs	free fatty acid receptors
Foxp3	forkhead box P3
GAS5	*growth arrest-specific transcript 5*
GPCRs	G-protein coupled receptors
GPx	glutathione peroxidase
HDACs	histone deacetylases
HK2	hexokinase 2 (HK2)
HOTAIR	*HOX transcript antisense RNA*
IFN-γ	interferon gamma
IL	interleukin
iNOS	inducible nitric oxide synthase
LAG-3	lymphocyte activation gene 3
LINC-PINT	*long intergenic non-protein coding RNA, and p53 induced transcript*

lncRNAs	long noncoding RNAs
M1	pro-inflammatory
M2	anti-inflammatory
MALAT1	metastasis-associated lung adenocarcinoma transcript 1
MDSCs	myeloid-derived suppressor cells
MEG3	maternally-expressed 3 gene
MHC-II	major histocompatibility complex-II
miRNAs	micro RNAs
mTOR	mammalian target of rapamycin
NADH	nicotinamide adenine dinucleotide hydrogen
NEAT1	nuclear paraspeckle assembly transcript 1
NET	neutrophil extracellular trap
NK	natural killer
NKG2D	natural killer group 2 member D
NO	and nitric oxide
PD-1	programmed cell death protein 1
PGC-1α	peroxisome proliferator-activated receptor γ coactivator 1 alpha
PKM2	pyruvate kinase M2
PPAR-γ	peroxisome proliferator-activated receptor-gamma
PVT1	plasmacytoma variant translocation 1
ROS	reactive oxygen species
SCFAs	Short-chain fatty acids
SNHG16	*small nucleolar RNA host gene 16*
SOD	superoxide dismutase
SREBP-1	sterol regulatory element-binding protein-1
TAMPs	tumor-associated molecular patterns
TCA	tricarboxylic acid
TCR	T cell antigen receptor
TGF-β	tumor growth factor-beta
Th	T helper
TIM-3	T-cell immunoglobulin and mucin-domain containing-3
TLRs	toll-like receptors
TME	tumor microenvironment
TNF-α	tumor necrosis factor-alpha
Treg	regulatory T cell
TUSC7	tumor suppressor candidate 7
UCA1	*urothelial cancer associated 1*

Author Contributions

M.H. conceived the idea, B.R., M.W.M., A.S.J., T.M.K., and J.S.A.S. collected articles, prepared the first draft, B.R. and M.H. reviewed and edited the manuscript. All authors confirm that they have agreed to the submission and publication of this manuscript in [Cancer immunology connect].

Availability of Data and Materials

The data used in this study were obtained from publicly available repositories: [PubMed, google scholar, google search]. No new datasets were generated during the current study.

Conflicts of Interest

The authors declare no conflicts of interest.

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