Annals of Traditional Chinese Medicine

Volume 1, Issue 1
Open Access
Review Article

Abstract

Valeric Acid (VA), a short-chain fatty acid, has garnered attention for its potential in cancer immunotherapy due to its ability to modulate key immune-regulatory mechanisms within the Tumor Microenvironment (TME). This review explores the anti-tumor effects of VA by focusing on its interaction with critical molecular targets, such as histone deacetylase 2 (HDAC2), GPR41/43 receptors, and Rho-GTPases. VA influences various immune processes, including immune cell function, cytokine production, and metabolic reprogramming. By targeting HDAC2, VA enhances immune cell recognition, restores T cell function, and improves the efficacy of immune checkpoint inhibitors. Additionally, VA's activation of GPR41/43 enhances metabolic reprogramming and inflammation modulation, boosting immune surveillance. Furthermore, VA modulates Rho-GTPases, promoting immune cell infiltration and polarization, thereby reshaping the TME and enhancing both innate and adaptive anti-tumor immune responses. Collectively, these findings highlight VA as a promising therapeutic agent in cancer immunotherapy, offering novel strategies to enhance existing treatments and overcome immune resistance mechanisms. Further research is needed to validate these effects in clinical settings.

Keywords:
Valeric acid;
Cancer immunotherapy;
HDAC2 inhibition;
Tumor microenvironment modulation.

Article Details

Received: Nov 08, 2024

Accepted: Dec 02, 2024

Published: Dec 09, 2024

Journal: Annals of Traditional Chinese Medicine

Website: www.anntcm.org

Valeric acid as a promising modulator of tumor immunity: Targeting HDAC2, GPR41/43, and Rho-GtPases in cancer Immunotherapy

Rui Han[1,2]*

[1]Department of Chinese Medicine Oncology, The First Affiliated Hospital of Naval Medical University, Shanghai 200433, P R China.

[2]Department of Chinese Medicine, Naval Medical University, Shanghai 200433, P R China.

Corresponding Author: Rui Han

Department of Chinese Medicine Oncology, Changhai Hospital Affiliated to Naval Medical University, Shanghai 200433, P R China.

Email: dianxiqiao@foxmail.com

Introduction

Cancer patients often experience poor immune function and a compromised immune environment [1-3]. Their immune systems are generally less effective at recognizing and eliminating cancer cells, which can be attributed to several factors. For example, cancer cells release specific substances, such as cytokines, growth factors, and regulatory T cells, that suppress the immune response, preventing it from effectively targeting the tumor. In addition, the tumor microenvironment (TME) plays a significant role in inhibiting the immune response. The tumor actively recruits immune-suppressive cells, such as Myeloid-Derived Suppressor Cells (MDSCs) and Tumor-Associated Macrophages (TAMs), which reduce immune activity and contribute to tumor progression. T cells, which are crucial for recognizing and destroying cancer cells, can become dysfunctional or exhausted in cancer patients. This exhaustion results in a reduced ability to target and eliminate cancer cells. Moreover, antigen-presenting cells (APCs), which present tumor antigens to T cells and initiate the immune response, may also be impaired, further diminishing T cell activation and weakening the immune defense. Chronic inflammation is another contributing factor to cancer progression. Inflammatory cytokines and chemokines produced in response to tumors create an environment that promotes tumor growth while simultaneously suppressing immune function [4].

Valeric acid, a Short-Chain Fatty Acid (SCFA) with a five-carbon structure, is primarily known for its presence in valerian root and its role in various biological processes. Recent research has highlighted its potential in cancer therapy due to its ability to modulate the tumor microenvironment and influence cellular processes related to tumor progression. Valeric acid exerts anti-tumor effects through mechanisms such as inducing apoptosis, inhibiting cell proliferation, and promoting differentiation in cancer cells. It can also influence the immune system by regulating immune cell function and inflammatory responses. As a SCFA, valeric acid is capable of modulating gene expression through histone deacetylase (HDAC) inhibition, leading to alterations in chromatin structure and

the activation of tumor suppressor genes. This epigenetic modulation enhances the body's immune response against cancer cells and reduces the ability of tumors to evade immune detection. Additionally, valeric acid has been shown to affect the metabolic activity of cancer cells, limiting their energy production and slowing down tumor growth. Its role in influencing the gut microbiome and systemic inflammation further contributes to its potential anti-tumor properties, making valeric acid an intriguing compound for further research in cancer prevention and treatment [5-7].

Here, we summarize and discuss recent mechanisms by which Valeric Acid (VA) regulates anti-tumor immunity, focusing on therapeutic targets such as HDAC2, GPR41/43, and Rho-GTPase, providing new insights and perspectives for the potential application of VA in cancer immunotherapy.

Therapeutic target of VA: HDAC2

Histone deacetylase 2 (HDAC2) is an important member of the histone deacetylase family, which plays a crucial role in regulating gene expression through the removal of acetyl groups from histones. HDAC2 is involved in chromatin remodeling and transcriptional repression, influencing a wide array of cellular processes such as proliferation, differentiation, and apoptosis. In the context of cancer, HDAC2 has been linked to the modulation of tumor progression, immune evasion, and the tumor microenvironment (TME). Recent evidence has present that HDAC2 can be significantly regulated by VA, making HDAC2 a potential therapeutic target of VA [8].

HDAC2 and immune evasion mechanisms

HDAC2 has been implicated in driving immune evasion in tumors by influencing the expression of immune regulatory molecules and modulating immune cell function [9,10].

Regulation of immune checkpoint molecules

HDAC2 has been shown to directly regulate the expression of immune checkpoint molecules such as PD-L1. Through deacetylation of histones at the PD-L1 promoter, HDAC2 represses or promotes its transcription depending on the cellular context. High PD-L1 expression in tumor cells inhibits T cell function by engaging with PD-1, leading to immune suppression and allowing tumors to escape immune surveillance [9,10].

Downregulation of antigen presentation

HDAC2 activity has been linked to the downregulation of major histocompatibility complex (MHC) molecules, which are essential for presenting tumor antigens to cytotoxic T cells. By repressing the transcription of MHC class I molecules, HDAC2 can limit the ability of tumor cells to be recognized by the immune system, contributing to immune escape mechanisms in the TME [11].

Modulation of tumor-associated immune cells

HDAC2 plays a key role in modulating the activity of various immune cells within the tumor microenvironment, influencing both immune suppression and activation [11].

Regulation of Myeloid-Derived Suppressor Cells (MDSCs): MDSCs are a critical population of immune suppressive cells in the TME, and HDAC2 has been implicated in promoting their accumulation and suppressive activity. HDAC2 drives the expression of factors that attract MDSCs to the tumor site and supports their immune-suppressive functions, including the inhibition of T cell activation.

Influence on Regulatory T Cells (Tregs): HDAC2 also modulates the activity of Tregs, which suppress effector T cell responses and contribute to immune evasion in tumors. HDAC2 promotes the expansion and suppressive function of Tregs by influencing the transcription of key regulatory genes that maintain Treg identity and function. This, in turn, creates an immunosuppressive TME that supports tumor growth [12].

HDAC2 and inflammatory cytokine production

HDAC2 regulates the production of pro-inflammatory and anti-inflammatory cytokines, which shape the immune landscape of the TME.

Suppression of pro-inflammatory cytokines: HDAC2 can repress the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-12, which are critical for mounting effective anti-tumor immune responses. These cytokines help recruit and activate immune cells like dendritic cells (DCs), natural killer (NK) cells, and cytotoxic T cells. By repressing these cytokines, HDAC2 can dampen the immune response and allow tumors to evade immune-mediated destruction.

Promotion of anti-inflammatory cytokines: HDAC2 has also been linked to the upregulation of anti-inflammatory cytokines such as IL-10 and TGF-β, which contribute to the immunosuppressive nature of the TME. These cytokines help maintain the function of Tregs and MDSCs, further promoting tumor immune evasion and inhibiting effector immune responses.

HDAC2 and T cell function

HDAC2 influences the activation and function of T cells, which are key players in the anti-tumor immune response.

Inhibition of T cell activation: HDAC2 represses the expression of genes critical for T cell activation and differentiation, such as those involved in the IL-2 signaling pathway. By limiting the production of IL-2, a cytokine essential for T cell proliferation and survival, HDAC2 impairs the expansion of cytotoxic T lymphocytes (CTLs), reducing the immune system's ability to target and eliminate tumor cells.

Regulation of T cell exhaustion: HDAC2 has been implicated in promoting T cell exhaustion, a state where T cells lose their ability to function effectively against tumors. This is achieved through the upregulation of exhaustion markers such as PD-1, CTLA-4, and TIM-3 on T cells. By driving T cell exhaustion, HDAC2 reduces the effectiveness of anti-tumor immune responses, allowing tumors to progress unchecked [12,13].

Potential of HDAC2 modulation in cancer therapy

By targeting HDAC2, tumor outcomes can potentially be improved through the following mechanisms:

Enhancing the efficacy of immune checkpoint inhibition: Since HDAC2 promotes the expression of immune checkpoint molecules such as PD-L1, targeting HDAC2 could enhance the efficacy of Immune Checkpoint Inhibitors (ICIs), such as anti-PD-1/PD-L1 therapies. Inhibiting HDAC2 in combination with ICIs may increase the immunogenicity of tumors by reducing PD-L1 expression and improving antigen presentation. This would enable T cells to recognize and attack tumor cells more effectively, potentially overcoming resistance to immune checkpoint blockade therapies.

Restoring T cell activation and function: Targeting HDAC2 may help restore T cell function by reversing T cell exhaustion and improving T cell activation. HDAC2 inhibition may reduce the expression of exhaustion markers on T cells, such as PD-1 and CTLA-4, thus restoring their cytotoxic activity and enhancing the immune response against tumors. In addition, by inhibiting HDAC2, the production of key cytokines like IL-2 can be enhanced, promoting the activation and proliferation of effector T cells. This can lead to more robust immune-mediated tumor destruction.

Modulating the tumor microenvironment: Targeting HDAC2 may help reshape the tumor microenvironment by reducing immune suppression and enhancing anti-tumor immune activity. Inhibiting HDAC2 can reduce the recruitment and activity of immunosuppressive cells such as MDSCs and Tregs, allowing effector T cells and NK cells to infiltrate the tumor and exert their anti-tumor functions. Moreover, HDAC2 inhibition may lead to increased production of pro-inflammatory cytokines like TNF-α and IL-12, which can boost immune cell recruitment and activation within the TME.

Synergizing with other cancer therapies: HDAC2 inhibitors can be combined with other cancer therapies such as chemotherapy, radiotherapy, and adoptive cell therapies to enhance their effectiveness. HDAC2 inhibition can sensitize tumors to chemotherapy or radiotherapy by enhancing the immune system's ability to recognize and destroy tumor cells. This is particularly important in tumors that exhibit resistance to conventional therapies due to immune suppression. In CAR-T or TCR-T cell therapies, inhibiting HDAC2 can enhance the persistence and function of adoptively transferred T cells, improving their ability to eliminate tumor cells.

Therapeutic target of VA: GPR41/43 (FFAR3/FFAR2)

GPR41 and GPR43 are free fatty acid receptors primarily activated by short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate. SCFAs are metabolic products of the gut microbiota and have been shown to play important roles in regulating gut immunity, metabolism, and systemic immune responses. By modulating GPR41 and GPR43, these SCFAs can influence anti-tumor immune responses, providing new potential targets for cancer therapy. GPR41 and GPR43 are also the potential therapeutic targets of VA in regulating anti-tumor immunity [14].

Regulation of immune cell metabolism and function

SCFAs activate GPR41 and GPR43 to directly regulate the metabolism and function of immune cells, particularly enhancing the anti-tumor activity of T cells through butyrate and propionate [9,15].

Metabolic reprogramming: SCFAs, through the activation of GPR41/43, can reprogram the metabolism of T cells and other immune cells. For instance, butyrate, acting as a histone deacetylase (HDAC) inhibitor, can influence the transcriptional state of T cells, increasing their production of anti-tumor cytokines like IFN-γ. This metabolic reprogramming enables T cells to more effectively recognize and eliminate tumor cells.

Inhibition of regulatory T cells (Tregs): Tregs are suppressive immune cells that promote immune escape within the tumor microenvironment. SCFAs, by modulating GPR41/43, inhibit the expansion and activity of Tregs, allowing effector T cells to dominate within the tumor environment, thereby enhancing the anti-tumor immune response.

Regulation of inflammatory responses and the tumor microenvironment

The Tumor Microenvironment (TME) is often populated by immunosuppressive cells and associated inflammatory responses. Modulating GPR41 and GPR43 can regulate immune cell-mediated inflammation, reshaping the TME to strengthen anti-tumor immunity [16,17].

Enhancing neutrophil and macrophage activity: SCFAs, through GPR43 activation, promote the chemotaxis and activity of neutrophils, inducing them to produce reactive oxygen species (ROS), which can kill tumor cells. Additionally, macrophages are influenced by SCFAs, polarizing towards the M1 type and increasing the production of pro-inflammatory cytokines, such as TNF-α and IL-12, which enhance anti-tumor effects.

Modulation of the tumor microenvironment: SCFAs regulate immune cell activity within the TME, reducing the number of immunosuppressive cells (such as Tregs and M2 macrophages) and enhancing the anti-tumor function of effector T cells and neutrophils. SCFAs can also decrease lactate accumulation in the TME, mitigating immune suppression.

Regulation of gut microbiota and their metabolic products

The gut microbiota plays a critical role in regulating the host immune system. By modulating GPR41/43, SCFAs can enhance the metabolism of the gut microbiota, further improving the host's immune status. Through influencing the composition of the gut microbiota, the GPR41/43 signaling pathway can regulate systemic immune responses. Research has shown that a diet rich in fiber increases the production of SCFAs, which activate GPR41/43 and boost anti-tumor immunity [18].

Potential of GPR41/43 in anti-tumor therapy

Based on evidence present above, by modulating the GPR41/43 signaling pathway, tumor treatment outcomes could be effectively improved through the following mechanisms:

Enhancing the efficacy of immune checkpoint inhibitors: Immune checkpoint inhibitors (e.g., PD-1, CTLA-4 antibodies) have shown significant efficacy in treating various cancers. However, some patients develop resistance or show no response to such therapies. Studies have shown that SCFAs, by activating GPR41/43, can enhance the function of effector T cells and reduce the number of Tregs, thus improving the tumor's sensitivity to immune checkpoint inhibitors. Therefore, GPR41/43 could be a powerful co-target for immune checkpoint inhibition therapy.

Targeting gut microbiota modulation: By targeting GPR41/43, host immune status can be improved through diet or fecal microbiota transplantation (FMT). For instance, increasing a fiber-rich diet can elevate SCFAs levels, thereby activating GPR41/43 and enhancing anti-tumor immune responses. This strategy of modulating the gut microbiota to indirectly enhance anti-tumor immunity holds potential, especially in patients with weakened immune function.

Targeting metabolic pathways to improve the tumor microenvironment: By targeting GPR41/43, metabolic changes in the TME can be regulated. For example, by reducing lactate accumulation, GPR41/43 can decrease immunosuppressive effects and improve the function of effector T cells. Additionally,

SCFAs through the GPR41/43 signaling pathway can promote the metabolic adaptation of immune cells, improving their persistence and function within the TME.

Therapeutic target of VA: Rho-GTPases

Rho-GTPases are small GTP-binding proteins that regulate multiple cellular processes, including cytoskeletal organization, cell migration, proliferation, and survival. They play key roles in the behavior of immune cells within the Tumor Microenvironment (TME), influencing the immune response to tumors. Rho-GTPases, particularly members such as RhoA, Rac1, and Cdc42, modulate various functions of Dendritic Cells (DCs), macrophages, and T cells, making them critical regulators in the anti-tumor immune response. Below is an analysis of how Rho-GTPases regulate anti-tumor immunity and their potential applications in cancer therapy [18].

Regulation of immune cell migration and activation

Rho-GTPases are essential for controlling the migration and activation of immune cells in response to tumor cells. By orchestrating the remodeling of the actin cytoskeleton, Rho-GTPases regulate how immune cells navigate through tissues to reach the tumor site.

Dendritic cell migration and antigen presentation: Rho-GTPases, particularly Rac1 and Cdc42, are critical for dendritic cell migration to lymph nodes, where they present tumor antigens to T cells. This activation of T cells is essential for initiating an effective anti-tumor immune response. Rac1 and Cdc42 promote actin polymerization at the leading edge of dendritic cells, enhancing their ability to migrate towards chemotactic signals.

T cell activation and cytoskeletal remodeling: Rac1 is crucial for T cell activation by mediating T cell receptor (TCR) signaling. Once activated, Rac1 promotes cytoskeletal rearrangements in T cells, facilitating their migration and increasing their ability to exert cytotoxic functions against tumor cells. Inhibiting Rac1 has been shown to impair T cell responses, underscoring its importance in maintaining an effective anti-tumor response.

Regulation of macrophage polarization and function

Rho-GTPases, particularly RhoA and Rac1, regulate macrophage polarization, which plays a critical role in shaping the tumor microenvironment [19].

M1 and M2 macrophage polarization: Macrophages can polarize into two main phenotypes: M1, which is pro-inflammatory and anti-tumor, and M2, which is anti-inflammatory and promotes tumor growth. RhoA and Rac1 regulate the cytoskeletal dynamics associated with macrophage activation. RhoA activation promotes M1 polarization, leading to enhanced production of inflammatory cytokines such as TNF-α and IL-12, which support anti-tumor immune responses. Conversely, inhibition of RhoA can lead to M2 macrophage polarization, which favors tumor growth and immune suppression.

Tumor-Associated Macrophages (TAMs): In the TME, Rho-GTPases regulate the function of TAMs, which are often skewed towards the M2 phenotype, supporting tumor progression. Targeting RhoA or Rac1 in TAMs may shift their polarization towards the M1 phenotype, improving their anti-tumor activity and reducing immune suppression within the TME.

Regulation of T cell migration and effector functions

T cells must efficiently migrate to the tumor site and exert their cytotoxic functions to eliminate tumor cells. Rho-GTPases, especially Rac1 and Cdc42, are involved in modulating these processes [20].

T cell trafficking to tumor sites: Rho-GTPases regulate the trafficking of cytotoxic T lymphocytes (CTLs) to the tumor site. Rac1 plays a crucial role in the chemotaxis of T cells toward chemokines released by tumor cells or immune cells in the TME. By controlling actin dynamics, Rac1 ensures that T cells can efficiently migrate through the extracellular matrix to reach the tumor and exert their cytotoxic effects.

Effector T cell functions: In addition to controlling migration, Rho-GTPases regulate the cytotoxic functions of T cells. Rac1 and Cdc42 contribute to the formation of the immunological synapse between CTLs and tumor cells, allowing the delivery of cytotoxic granules that induce tumor cell death. Deficiency in Rho-GTPase signaling impairs the ability of T cells to kill tumor cells effectively.

Regulation of Natural Killer (NK) cell functions

Natural killer (NK) cells are critical components of the innate immune response against tumors. Rho-GTPases regulate NK cell-mediated cytotoxicity and their ability to infiltrate the tumor. RhoA and Rac1 modulate NK cell migration towards tumor cells and their subsequent cytotoxic response. Similar to T cells, NK cells require Rac1 to form an effective immunological synapse, allowing them to release perforin and granzymes that kill tumor cells. Targeting Rho-GTPases to enhance NK cell function could improve their anti-tumor activity, particularly in immunosuppressive TMEs.

Potential of Rho-GTPase modulation in cancer therapy

Modulating the Rho-GTPase signaling pathway offers several promising strategies for improving cancer therapy outcomes [21].

Enhancing immune cell infiltration and function: In many cancers, poor infiltration of immune cells into the tumor is a key factor contributing to immune escape. By targeting Rho-GTPases, particularly Rac1, immune cell migration and infiltration into the tumor can be enhanced.

Improving T cell and NK cell trafficking: Activating Rac1 in T cells and NK cells may enhance their ability to infiltrate tumors. This strategy could be combined with immune checkpoint inhibitors (such as anti-PD-1 or anti-CTLA-4 antibodies) to improve T cell presence in tumors, thereby enhancing the overall anti-tumor immune response.

Overcoming tumor-associated immunosuppression: By reprogramming TAMs through RhoA inhibition, immune suppression within the TME can be reduced. This could shift the immune balance within tumors from a pro-tumor to an anti-tumor state, leading to better therapeutic outcomes [22].

Targeting immune cell cytoskeletal dynamics

Since Rho-GTPases play a crucial role in controlling cytoskeletal dynamics, targeting them may improve immune cell function in tumors [23].

Enhancing effector T cell functions: Rho-GTPase modulation could improve the formation of the immunological synapse in

T cells and NK cells, increasing their cytotoxic activity against tumors. Inhibiting negative regulators of Rho-GTPase signaling, such as RhoA, may further amplify T cell effector functions, leading to enhanced tumor clearance.

Improving antigen presentation by dendritic cells: Targeting Rac1 and Cdc42 in dendritic cells could improve their ability to migrate, present antigens, and activate T cells, boosting the initiation of adaptive immune responses against tumors.

Combining with existing immunotherapies

Rho-GTPase modulators could be combined with existing cancer immunotherapies, such as immune checkpoint inhibitors or CAR-T cell therapy, to improve their efficacy [24,25].

Combination with immune checkpoint blockade: Rho-GTPase modulation could improve the efficacy of immune checkpoint inhibitors by enhancing the infiltration and function of T cells and other immune effectors. For instance, enhancing Rac1 activity in tumor-infiltrating lymphocytes may increase their ability to overcome tumor-mediated suppression [25-27].

Improving CAR-T cell therapy: CAR-T cell therapy could benefit from Rho-GTPase modulation, as enhancing Rac1 and Cdc42 signaling in CAR-T cells may improve their migration, persistence, and cytotoxic activity within the TME [28-30].

HDAC2, GPR41/43, and Rho-GTPases all play critical roles in regulating anti-tumor immunity within the Tumor Microenvironment (TME). HDAC2 is involved in immune evasion, cytokine production, and immune cell function, and its modulation can enhance immune cell recognition, restore T cell function, and improve the efficacy of immunotherapies like immune checkpoint inhibitors. Targeting HDAC2 offers a promising strategy for reprogramming the TME and enhancing anti-tumor immunity. Similarly, GPR41 and GPR43 regulate anti-tumor immunity through metabolic reprogramming, inflammation modulation, and gut microbiota regulation, helping the immune system better recognize and eliminate tumors. Modulating the GPR41/43 pathway or Short-Chain Fatty Acid (SCFA) levels could be a new direction in cancer immunotherapy, enhancing the efficacy of existing therapies. Additionally, Rho-GTPases are key regulators of immune cell migration, polarization, and effector functions within the TME. Modulating Rho-GTPase signaling can improve immune cell infiltration, reprogram the TME, and enhance both innate and adaptive immune responses, offering a promising approach to improve cancer immunotherapies and overcome immune resistance mechanisms in tumors.

Conclusion

In conclusion, VA demonstrates significant potential in modulating anti-tumor immunity through various molecular targets, such as HDAC2, GPR41/43, and Rho-GTPases. By targeting HDAC2, VA can reprogram the tumor microenvironment (TME), reduce immune evasion, and enhance immune cell functions, thus improving the efficacy of immunotherapies like immune checkpoint inhibitors. GPR41/43 activation by VA influences metabolic reprogramming and inflammation modulation, improving the immune system's capacity to recognize and destroy tumors. Additionally, VA's impact on Rho-GTPases helps improve immune cell infiltration, polarization, and effector functions, which can reprogram the TME and enhance both innate and adaptive anti-tumor responses. Collectively, these findings suggest that VA holds promise as a therapeutic agent in cancer immunotherapy, offering novel strategies for enhancing current treatment approaches and addressing immune resistance mechanisms in tumors. Further research is needed to fully explore the therapeutic potential of VA in clinical settings.

Declarations

Ethical Approval: Not applicable.

Availability of data and materials: Not applicable.

Competing interests: The author declares no competing interests.

Acknowledgements: Not applicable.

Funding: This research was supported by "National Natural Science Foundation of China (Youth foundation) (No.82204864)" project (to Rui Han).

References

1. Zhao L, et al. Diagnostic value of cancer-testis antigen mRNA in peripheral blood from hepatocellular carcinoma patients. World J Gastroenterol. 2010; 16(32): 4072-8.
2. Zheng Z, et al. Idarubicin-loaded biodegradable microspheres enhance sensitivity to anti-PD1 immunotherapy in transcatheter arterial chemoembolization of hepatocellular carcinoma. Acta Biomater. 2023; 157: 337-351.
3. Zhou G, et al. Pharmacological Effects of Ginseng: Multiple Constituents and Multiple Actions on Humans. Am J Chin Med. 2023: 1-20.
4. Alkan SB, et al. The Evaluation of Dietary Antioxidant Capacity, Dietary Inflammatory Index and Serum Biomarkers in Breast Cancer: A Prospective Study. Nutr Cancer. 2023: 1-13.
5. Gracia MI, et al. Performance Evaluation of a Novel Combination of Four- and Five-Carbon Butyric and Valeric. Short-Chain Fatty Acid Glyceride Esters in Broilers. Animals (Basel). 2024. 14(4).
6. Li Y, et al. Non-Coding RNAs in Pancreatic Cancer Diagnostics and Therapy: Focus on lncRNAs, circRNAs, and piRNAs. Cancers (Basel). 2021; 13(16).
7. Zhang XL, et al. MCT1-mediated transport of valeric acid promotes porcine preimplantation embryo development by improving mitochondrial function and inhibiting the autophagic AMPK-ULK1 pathway. Theriogenology. 2024; 225: 152-161.
8. Serralta-Interian AA, et al. Inhibition of histone deacetylases class I improves adipogenic differentiation of human periodontal ligament cells. Cell Mol Biol (Noisy-le-grand). 2024; 70(5): 40-47.
9. Estrada-Perez AR, et al. Untargeted LC-MS/MS Metabolomics Study of HO-AAVPA and VPA on Breast Cancer Cell Lines. Int J Mol Sci. 2023; 24(19).
10. Fahmy SH, et al. Effects of histone acetyltransferase (HAT) and histone deacetylase (HDAC) inhibitors on proliferative, differentiative, and regenerative functions of Toll-like receptor 2 (TLR-2)-stimulated human dental pulp cells (hDPCs). Clin Oral Investig. 2023; 28(1): 53.
11. Taefehshokr N, et al. SARS-CoV-2 NSP5 antagonizes MHC II expression by subverting histone deacetylase 2. J Cell Sci. 2024; 137(10).
12. Andrusaite A, et al. Microbiota-derived butyrate inhibits cDC development via HDAC inhibition, diminishing their ability to prime T cells. Mucosal Immunol. 2024.
13. Bajpai P, et al. Combination of dual JAK/HDAC inhibitor with regorafenib synergistically reduces tumor growth, metastasis,

and regorafenib-induced toxicity in colorectal cancer. J Exp Clin Cancer Res. 2024; 43(1): 192.

14. Skrzypecki J, K Nieweglowska, E Samborowska. Valeric Acid, a Gut Microbiota Product, Penetrates to the Eye and Lowers Intraocular Pressure in Rats. Nutrients. 2020; 12(2).

15. Wang Y, et al. Sialic acid-based probiotic intervention in lactating mothers improves the neonatal gut microbiota and immune responses by regulating sialylated milk oligosaccharide synthesis via the gut-breast axis. Gut Microbes. 2024; 16(1): 2334967.

16. Lee AR, et al. GPR41 and GPR43 regulate CD8(+) T cell priming during herpes simplex virus type 1 infection. Front Immunol. 2024; 15: 1332588.

17. Lee YJ, SE Son, DS Im. Free fatty acid 3 receptor agonist AR420626 reduces allergic responses in asthma and eczema in mice. Int Immunopharmacol. 2024; 127: 111428.

18. Lau HC, et al. Lactobacillus acidophilus suppresses non-alcoholic fatty liver disease-associated hepatocellular carcinoma through producing valeric acid. EBioMedicine. 2024; 100: 104952.

19. Raulien N, et al. Glucose-oxygen deprivation constrains HMGCR function and Rac1 prenylation and activates the NLRP3 inflammasome in human monocytes. Sci Signal. 2024; 17(845): eadd8913.

20. Liang J, et al. Synthesis and in vitro evaluation of benzo[b]thiophene-3-carboxylic acid 1,1-dioxide derivatives as anticancer agents targeting the RhoA/ROCK pathway. J Enzyme Inhib Med Chem. 2024; 39(1): 2390911.

21. Zhang D, et al. Decreased B7-H3 promotes unexplained recurrent miscarriage via RhoA/ROCK2 signaling pathway and regulates the secretion of decidual NK cellsdagger. Biol Reprod. 2023; 108(3): 504-518.

22. Chen R, et al. Destabilization of fear memory by Rac1-driven engram-microglia communication in hippocampus. Brain Behav Immun. 2024; 119: 621-636.

23. Tanner CD, EE Rosowski. Macrophages inhibit extracellular hyphal growth of A. Fumigatus through Rac2 GTPase signaling. Infect Immun. 2024; 92(2): e0038023.

24. Doye A, et al. RAC2 gain-of-function variants causing inborn error of immunity drive NLRP3 inflammasome activation. J Exp Med. 2024; 221(10).

25. Dipankar P, et al. Functional and Therapeutic Relevance of Rho GTPases in Innate Immune Cell Migration and Function during Inflammation: An In Silico Perspective. Mediators Inflamm. 2021; 2021: 6655412.

26. Biro M, MA Munoz, W Weninger. Targeting Rho-GTPases in immune cell migration and inflammation. Br J Pharmacol. 2014; 171(24): 5491-506.

27. El Masri R, J Delon. RHO GT Pases: From new partners to complex immune syndromes. Nat Rev Immunol. 2021; 21(8): 499-513.

28. Sampson CJ, et al. The RhoGEF Zizimin-related acts in the Drosophila cellular immune response via the Rho GTPases Rac2 and Cdc42. Dev Comp Immunol. 2012; 38(1): 160-8.

29. Sarrabayrouse G, et al. Regulatory properties of statins and rho gtpases prenylation inhibitiors to stimulate melanoma immunogenicity and promote anti-melanoma immune response. Int J Cancer. 2017; 140(4): 747-755.

30. Xu H, et al. Innate immune sensing of bacterial modifications of Rho GTPases by the Pyrin inflammasome. Nature. 2014; 513(7517): 237-41.