The role of pH in cancer biology and its impact on cellular repair, tumor markers, tumor stages, isoenzymes, and therapeutics

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Abstract

The intriguing connection between pH and cancer is explored in this manuscript. The role of pH in cancer biology, including its impact on cellular repair, tumor markers, tumor stages, isoenzymes, and therapies, is highlighted. pH variations can affect cellular repair processes, potentially leading to cancer development. Changes in pH also disrupt various cellular functions, such as enzyme activity and DNA modifications, impacting cancer biology. The acidic tumor microenvironment resulting from pH changes promotes tumor growth and affects surrounding normal tissue. Additionally, pH variations influence specific isoenzymes activity, aiding in cancer diagnosis and targeted therapies. Targeting the pH microenvironment in cancer treatment shows promise, utilizing strategies like pH-sensitive nanoparticles and inhibitors. However, considerations must be made regarding normal cell impact and systemic pH balance. An innovative approach involving a glucose derivative, glucosodiene, inhibits tumor glucose metabolism and restores cellular pH balance. Understanding the intricate relationship between pH and cancer provides insights for diagnostics and treatments. Further research in this field can lead to innovative approaches to combat cancer and improve patient outcomes.

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1. Introduction

Cancer a multifaceted disease poses significant challenges in medicine. Research has unveiled various factors influencing cancer development. [1] The role of pH in cancer biology has attracted attention, as this manuscript explores its impact on cellular repair, tumor markers, tumor stages, isoenzymes, and therapies. Cellular repair is vital for tissue integrity, but errors in an alkaline environment may contribute to cancer development. [2] The Warburg effect highlights cancer cells' metabolic behavior, leading to an acidic tumor microenvironment that affects cellular functions. [3] Tumor development stages exhibit distinct pH dynamics, with acidic extracellular destruction and alkaline intracellular replication. Isoenzymes, influenced by pH variability, may aid in self-correction and produce unique tumor markers. [4] Exploiting the pH gradient holds promise for inhibiting cancer growth. Targeting the acidic tumor microenvironment using pH-sensitive nanoparticles and proton pump inhibitors offers novel therapeutic strategies. [5] Understanding pH's role in cancer provides insights into its biology and potential advancements in diagnostics and treatments. [6]This manuscript delves into the intriguing connection between pH and cancer.

2. pH Influence on Cellular Repair and Tumor Microenvironment Dynamics

Cellular repair plays a crucial role in maintaining tissue integrity, but the replication process can lead to errors. Understanding the impact of pH on cellular repair and tumor microenvironment dynamics provides valuable insights into cancer development and progression. [7] This section explores the relationship between pH, cellular functions, and the extracellular acidic environment. [8] Intracellular alkalization is essential for cellular repair during replication, as histones, which are alkaline and positively charged, interact with DNA, which is acidic and negatively charged. [9] However, frequent repair processes increase the likelihood of replication errors, comparable to making copies of copies, leading to monoclonal errors. [10] Inducers of cancer may generate errors or indirectly activate pre-existing errors by promoting intracellular alkalization, which aids in cell repair. As cells become more alkaline intracellularly, they tend to replicate faster but become less capable of performing normal functions and producing typical products. [11] The consequence of intracellular alkalization is the expulsion of protons into the extracellular space, resulting in acidification. This acidification renders cells less responsive and resistant to normal stimuli, impacting various cellular processes. [12] pH changes can affect enzyme function, hormone-receptor binding, conversion of prohormones to active forms, hormone-carrier protein binding, tyrosine kinase activity, microRNA function, and post-transcriptional changes. [13] Furthermore, pH alterations can

influence DNA methylation, modification of histone proteins, as well as the functioning of cellular components such as membranes, receptors, pumps, channels, and transporters. Interestingly, the acidic tumor microenvironment induced by pH changes has additional implications. Vascular endothelial growth factor (VEGF), which promotes angiogenesis, exhibits higher activity in acidic environments. [14]

This suggests that solid tumors inducing changes in the extravascular pH can actually stimulate their own blood supply, facilitating their growth and progression. [15] Additionally, apoptosis, a mechanism of programmed cell death, is more active in an acidic environment. In expanding tumors, apoptosis is induced in the outer extracellular ring, contributing to the destruction of surrounding normal tissue. [16]

The impact of pH regulators on immune cell function in the acidic tumor microenvironment (TME) and inflamed tissues can be inferred through studying the cancerous microenvironment and the inflammatory environment in the presence or disruption of cellular hydrogen ion concentration. The acidification of the TME serves as a significant immune evasion mechanism employed by cancer cells to suppress the activity of various anti-tumor immune effectors, including T cells, natural killer (NK) cells, and dendritic cells (DCs). Simultaneously, regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) accumulate and transform into immunosuppressive cells. Extracellular acidosis can be attributed to bacterial inflammation in peripheral tissues, respiratory burst activation, or proton aggregation resulting from autoimmune and allergic diseases. A low pH prolongs the lifespan of neutrophils, triggers the activation of inflammatory bodies in eosinophils and macrophages, and induces type II inflammatory responses due to mast cell activation. However, exposure of CD8 T cells and NK cells to low pH levels diminishes their activity. [Figure 1]

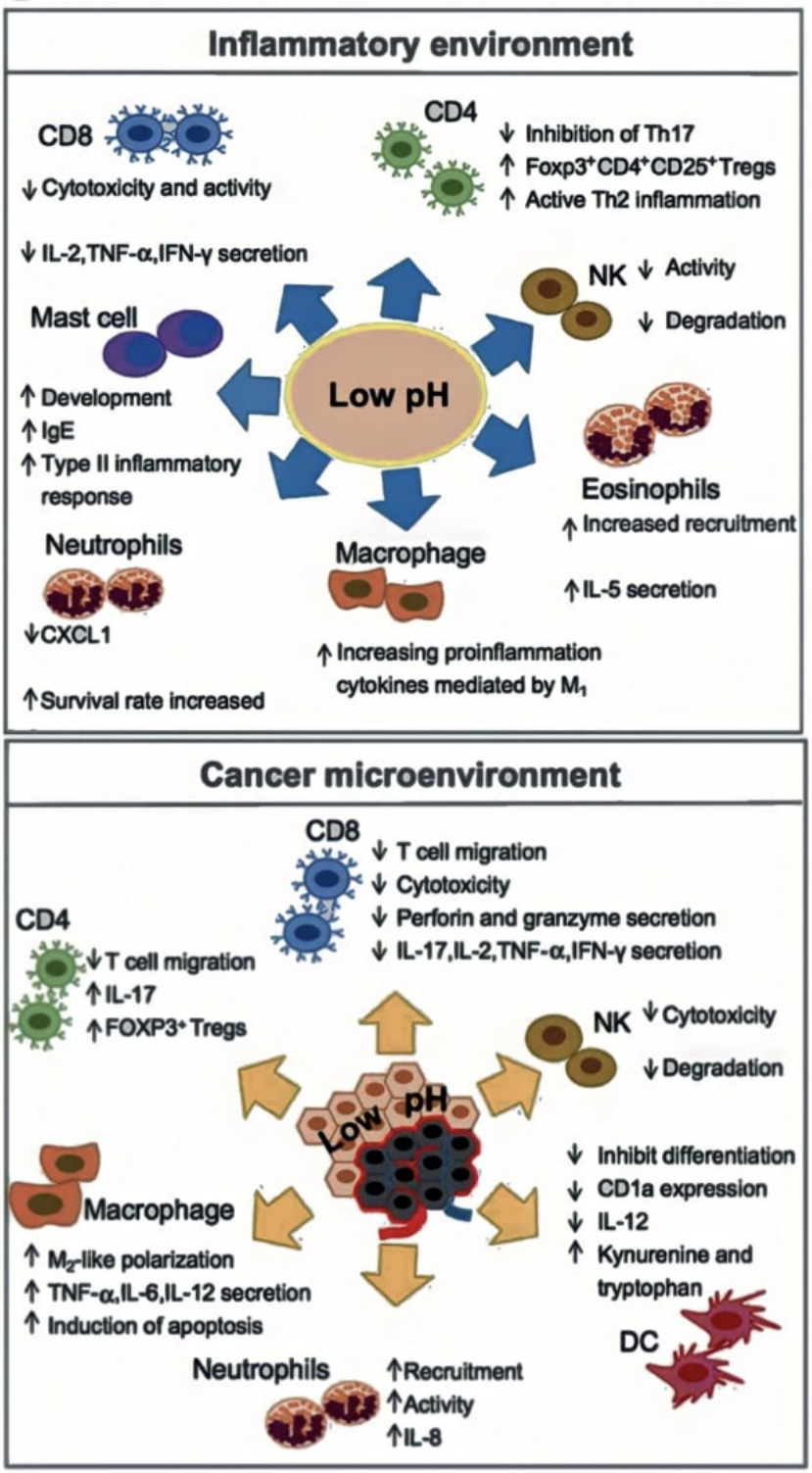

Figure 1. The cancerous microenvironment and the inflammatory environment share similarities in terms of their impact on immune cell function. In the acidic tumor microenvironment (TME), cancer cells utilize acidification as a mechanism to evade the immune system, suppressing the activity of T cells, natural killer (NK) cells, and dendritic cells (DCs). Similarly, in inflamed tissues, extracellular acidosis can occur due to bacterial inflammation, respiratory burst activation, or proton aggregation from autoimmune and allergic diseases. This low pH environment in both settings can promote the accumulation and transformation of immunosuppressive cells, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Additionally,

while low pH levels can trigger inflammatory responses and activate certain immune cells like eosinophils, macrophages, and mast cells, it diminishes the activity of CD8 T cells and NK cells. Therefore, both the cancerous microenvironment and the inflammatory environment exhibit alterations in immune cell function due to the influence of pH regulators.

3. Alkalization and Acidification Dynamics

Tumor markers, seemingly unrelated to the tissue of origin, may be influenced by significant intracellular alkalization. This alkalization leads to increased activity of specific isoenzymes and cellular machinery. [17] Interestingly, tumor markers can also be elevated in cases of inflammation, indicating ongoing cell repair even without cancer. This suggests a potential link between cell repair and the initial stages of cancer development. [18] As the tumor mass expands, the center may experience acidification due to the shift in blood supply to the outer ring. Consequently, the center of a solid tumor can undergo apoptosis, despite being composed of different cells at an earlier stage. [19] Solid cancers exhibit variations, akin to the stages of fruit ripening, which should be considered in research to avoid conflicting outcomes [Figure 2]. [20] The outer extracellular ring becomes acidic, leading to the destruction of normal tissue and the extrusion of acid through cellular pumps, channels, and transporters. [Figure 3] Within this outer ring, an expanding alkaline intracellular ring may exist. [21] Eventually, the center of the tumor mass, observed in solid tumors, becomes significantly acidic due to reduced blood flow, leading to apoptosis and liquefaction. Therefore, pH measurements should focus on the expanding alkaline intracellular outer ring rather than averaging the entire mass. [22]

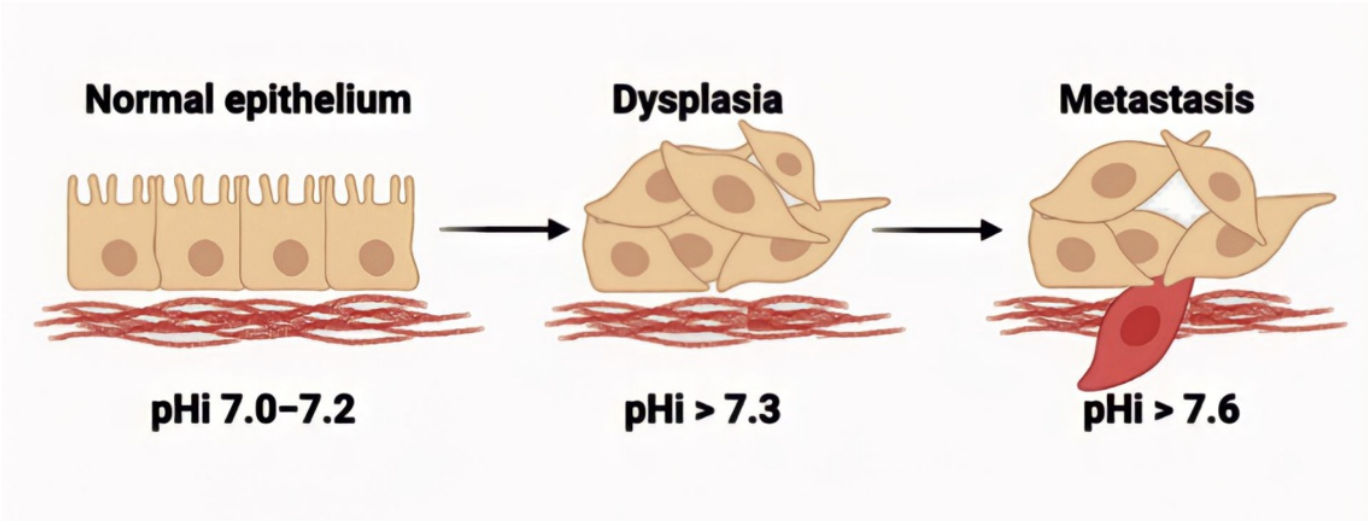

Figure 2. Solid cancers display heterogeneity similar to the maturation stages of fruits, and it is crucial to acknowledge this variation when conducting research to prevent contradictory results. One notable aspect to consider is the increased intracellular pH (pHi) observed in cancer. In normal epithelial cells, the pHi ranges from 7.0 to 7.2. However, dysplastic and metastatic cancer cells consistently exhibit elevated pHi levels.

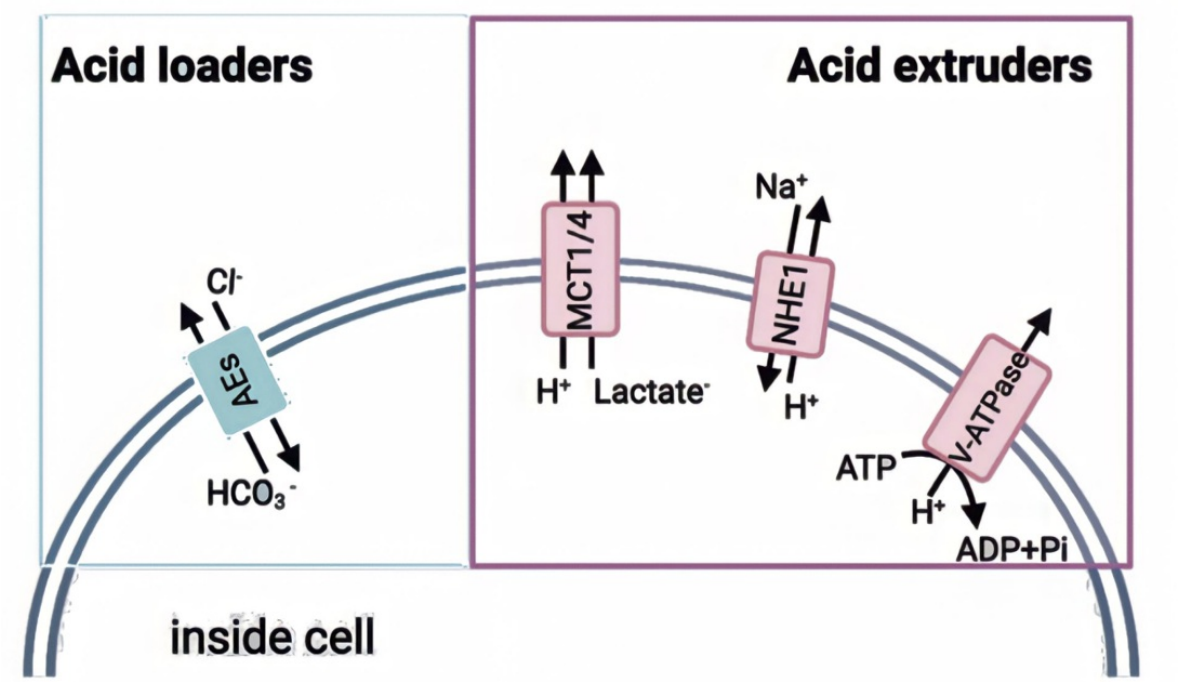

Figure 3. The acidic environment within the outer extracellular ring triggers tissue damage, causing the release of acid through cellular pumps, channels, and transporters. The dysregulation of acid loaders (specifically, anion exchangers (AE1)) and acid extruders (such as the sodium proton exchanger (NHE1), monocarboxylate transporters (MCTs), and plasma-membrane resident vacuolar ATPases (V-ATPases)) has been associated with the dysregulated intracellular pH in cancer cells.

4. Isoenzymes and pH Variability

The existence of isoenzymes raises questions about their purpose and why multiple isoenzymes are present instead of a single enzyme for a specific function. Episodic regional pH variability could provide an explanation, although it remains largely unknown. [23] Larger organisms exhibit pH variations in different organs and organelles in response to normal physiological conditions. For instance, the stomach and duodenal area in humans have significant pH differences. [24] Similar pH variability may occur in organs like the liver, which acts as the chemical enzyme manufacturing plant of the body. If pH levels vary episodically during specific physiological situations, certain isoenzymes may become more functional due to their variable optimum pH levels. [25] Optimum pH levels have historically been used to differentiate between different isoenzymes. Organisms may utilize specific isoenzymes to restore homeostasis under particular conditions, representing an attempt at self-correction. The concentration of isoenzymes can vary depending on the environment. [26] Enzymes can originate from one or multiple gene loci, and their expression can be influenced by various factors, including pH levels. In the context of cancer, the altered pH environment could lead to changes in the expression and activity of specific isoenzymes. This alteration could result in the production of different products, including tumor markers, which can be utilized for diagnostic purposes. [27]

5. Therapeutic Implications Targeting the pH Microenvironment

Understanding the role of pH in cancer development and progression has significant therapeutic implications. Researchers have investigated strategies to target the acidic microenvironment of tumors as a potential approach to inhibit cancer growth. [28] Several approaches have been explored, including pH-sensitive nanoparticles, proton pump inhibitors, and carbonic anhydrase inhibitors. [29] These approaches aim to exploit the pH gradient between the acidic extracellular tumor environment and the relatively alkaline intracellular environment to deliver targeted therapies. Additionally, modulating pH levels within cancer cells could impact their growth and survival. [30] By targeting the mechanisms involved in cellular pH regulation, it may be possible to disrupt the favorable conditions for cancer cell proliferation. However, it is crucial to consider the potential impact on normal cells and overall systemic pH balance when developing such therapies. [31] Regarding the understanding of hydrogen ion strategies and cancer development, there is a new theory for treating cancerous tumors through metabolic activity.[32][33][34] This theory involves synthesizing alkaline glucose isomers using a reaction between dextrose and sodium bicarbonate, resulting in a glucose derivative with alkaline properties known as glucosodiene.[35] Glucosodiene [36] can potentially inhibit glucose metabolism within the tumor, known as the Warburg effect, and restore the pH balance within the body's cells. It has shown success in documented cases, including the first reported case of complete healing from metastatic triple-negative breast cancer in the bones in less than a month. [37] Especially after documenting safety [38] It is suggested that glucosodiene may cause tumor shrinkage, possibly due to its control over glucose metabolism, which in turn may activate the P53 enzyme, providing an ideal target for cancerous tumors through its metabolic activity.

6. Discussion

The investigation into the influence of pH on cellular repair and tumor microenvironment dynamics revealed compelling insights. Cellular repair, crucial for maintaining tissue integrity, can be affected by pH variations. Intracellular alkalization, necessary for efficient cellular repair, may contribute to replication errors and cancer development. The expulsion of protons into the extracellular space during alkalization leads to the acidification of the tumor microenvironment, impacting cellular functions. pH changes can affect enzyme function, hormone-receptor binding, and various cellular components, highlighting the widespread impact of pH on cancer biology. Moreover, the acidic tumor microenvironment induced by pH changes can promote tumor growth and stimulate angiogenesis, while apoptosis is more active in an acidic environment, contributing to the destruction of surrounding normal tissue. The alkalization and acidification dynamics observed in tumor development stages resemble the stages of fruit ripening. The presence of specific tumor markers, influenced by intracellular alkalization, suggests a potential link between cell repair and early stages of cancer development. The acidification of the tumor center due to reduced blood flow results in apoptosis and liquefaction, emphasizing the importance of considering pH measurements in the expanding alkaline intracellular outer ring.

Isoenzymes and their association with pH variability provide further insights into cancer progression. Episodic regional pH variability in organs may influence the activity of specific isoenzymes, contributing to self-correction and the production of different products, including tumor markers. Understanding the altered pH environment's impact on isoenzymes expression and activity can aid in cancer diagnosis and targeted therapies. The therapeutic implications of targeting the

pH microenvironment in cancer treatment are significant. Strategies such as pH-sensitive nanoparticles, proton pump inhibitors, and carbonic anhydrase inhibitors aim to exploit the pH gradient between the tumor microenvironment and intracellular space for targeted therapy delivery. Modulating pH levels within cancer cells could disrupt their favorable growth conditions. However, it is crucial to consider the potential impact on normal cells and systemic pH balance when developing such therapies. Additionally, the novel approach involving glucosodiene, a glucose derivative with alkaline properties, shows promise in inhibiting glucose metabolism within tumors and restoring cellular pH balance. Glucosodiene has demonstrated success in documented cases, indicating its potential as a therapeutic target for cancer treatment.

7. Conclusion

Understanding the intricate relationship between pH and cancer offers valuable insights into cancer biology, diagnostics, and therapeutic strategies. The influence of pH on cellular repair, tumor markers, tumor development stages, and isoenzymes highlights the multifaceted nature of pH dynamics in cancer. Exploiting the pH gradient for targeted therapies presents a promising avenue for inhibiting cancer growth. Further research should focus on unraveling the underlying mechanisms and conducting rigorous clinical studies to translate these findings into effective treatments. By deepening our understanding of pH-related dynamics in cancer, we can pave the way for advancements in cancer diagnosis, treatment, and ultimately improve patient outcomes.

Statements and Declarations

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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