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Alkaliptosis: A new strategy for cancer therapy

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ABSTRACT

Cancer incidence and mortality are expected to increase with an aging population, emphasizing the need for new prevention and treatment strategies. In addition, poor prognosis and chemotherapy resistance are prevalent issues among cancer patients. Therefore, understanding the major pathways and components involved in cell death, defects in cancer-related pathways, and cell death biology in cancer will help develop new effective therapies. An unbalanced pH level can lead to cell death, unlike common knowledge. The majority of knowledge on acid-base balance differences in normal and cancer cells and gene expression patterns in the alkaliptosis pathway has the potential to be of priority for interpretation of the phenotype, particularly when considered in individualized cancer treatments. Understanding the mechanism of alkaliptosis can be a target for the development of new pharmacological therapies. Additionally, it can shed light on more effective treatments by explaining their interactions with other cell death mechanisms. This review aimed to shed light on the fundamental process of pH homeostasis in regulated cell deaths.

Keywords: Alkaliptosis, anticancer therapy, cancer, carbonic anhydrase IX, oncology, pH regulation

Cell death is a crucial mechanism tasked to eliminate the cells with damaged DNA, dysfunctional organelles, or oncogenes overexpressed. The pathways that initiate and sustain cell death are complex, genetically encoded, and protected by important regulations. Thus, although these pathways are often thought to be mutated in malignancy, there are therapies targeting these pathways to induce cell death in tumor cells.[1] In studies on spontaneous cell death, Carl Vogt[2] demonstrated the cell death in the notochord and adjacent cartilage of metamorphic frogs in 1842, after the cell theory was established by Schleiden and Schwann.[2] Cell death is a process seen in all organisms. Different classifications have been used by many researchers from past to present. Early classifications from the 1970s based on cell morphology divided cell death into apoptosis (type I), autophagy (type II), and necrosis (type III).[2] This review aimed to shed light on the mechanisms observed in cell death and their relation to pH homeostasis.

CELL DEATH

Cell death is part of physiological development. It is an ongoing process for the preservation of tissue integrity and a defense mechanism of the cell against various pathologies.[3] According to the Nomenclature Committee on Cell Death's latest guidelines in 2018, cell death can be classified into two broad categories, "accidental" and "regulated."[4] Accidental cell death (ACD) occurs as a result of severe physical (for example, excessive heat or excessive pressures) and chemical (for example, abnormal pH changes) destruction of the cell. Accidental cell death is insensitive to pharmacological or genetic intervention as it cannot be controlled and is ineffective against mechanical stimuli. Although ACD occurs secondary to tissue damage *in vivo*, it cannot be directly targeted for therapeutic interventions, as it cannot be prevented or modulated.[5] The formation of ACD is rapid, and it is thought that it does not require a special molecular mechanism.[6]

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Regulated cell death (RCD) is a genetically encoded molecular mechanism.[7] Regulated cell death is also subdivided into apoptotic and non-apoptotic main pathways (for example, ferroptosis, necroptosis, pyroptosis, and alkaliptosis), whose signal transduction and molecular mechanism are modulated differently from disease factors. Regulated cell death is a controllable cellular program that allows for genetic and biochemical changes. Regulated cell death is the primary mechanism of tumor suppression. In benign cells, it is triggered as a protective mechanism, unlike in harmful cells with uncontrolled cell division. However, tumor growth molecules known as oncogenes bring the cell closer to the death line, presenting a therapeutic window that forms the basis of standard chemotherapy practice.[8,9] Consequently, although there are barriers to ACD prevention, it can be modulated by enhancing the stress-adaptive response capacity of cells and treatment strategies by suppressing RCD pathways.[10]

REGULATED CELL DEATH

It is defined as the pharmacologically or genetically interfered (to some extent kinetically) form of cell death that occurs by inducing one or more signaling molecules. Intracellular or extracellular microenvironment communication is impaired in mammalian cells resulting in one of the many signal transduction cascades that can lead to cell death. Each of such RCD pathways is initiated by substantial and linked molecular mechanisms. Regulated cell death types cover a variety of morphological features, ranging from completely necrotic to fully apoptotic. It can also be detected on an immunomodulatory scale, ranging from anti-inflammatory to pro-inflammatory and immunogenic.[4] The impact of RCD on those metazoans, as mentioned above, has been proven by genetic and biochemical processes. A robust death mechanism is required to maintain normal tissue homeostasis and healthy embryonic development.[11] Excessive necrosis can worsen tissue damage in the heart, liver, and brain cells and affect the prognosis of the injury depending on ischemia and the degree of perfusion impairment.[12] Apoptosis, which eliminates dysfunctional cells under physiological and pathological conditions, is a well-known RCD type. In addition, the difference of cancer from normal cells is the ability to avoid apoptosis, which causes aggressive proliferation and leads to treatment resistance. Regulated cell death has been described in various ways in the past. The RCD pathways play an active role in different molecular and cellular processes. The induction of cellular and humoral immune responses varies between RCD pathways. Current genetic and biomolecular research shows that there is significant plasticity in these RCD pathways, which can provide the basis for a tangible approach to treatment strategies.[13] Understanding the relationship between the molecular mechanisms of RCD has had a major impact on biology and cancer research.[14] Further studies are needed to identify and maintain irreversible critical points of each of the RCD pathways, and to reveal the role of excess or incomplete RCD. According to recent studies, the old dichotomy is no longer accepted.[15] Other non-apoptotic forms of RCD, such as necroptosis, pyroptosis, ferroptosis, entotic cell death, entotic cell death, parthanatos, lysosome-dependent cell death, autophagy-dependent cell death, and alkaliptosis, have also been demonstrated.[16,17]

ALKALIPTOSIS

Alkaliptosis is a newly discovered cell death mechanism. It is a pH-dependent form of RCD that differs from other pathways. Tang et al.[14] defined alkaliptosis as N-acetyl cysteine-mediated, acidic pH environment-prevented, drug-induced cell death. The mechanism by which the alkalization of the cell microenvironment with sodium hydroxide in culture causes cell death with the contribution of nuclear factor-kappa B (NF-κB) was described in a study.[18]

Unlike other non-apoptotic forms of cell death, such as ferroptosis and necrosis, alkaliptosis is a sequential molecular mechanism. Alkaliptosis can be stopped by NF-κB upregulation. In addition, the Nrf2/HO-1 signaling pathway can be stimulated to activate pro-inflammatory and apoptosis-inhibitory genes.[19] There is still abundant information to be discovered regarding the over or under-expression of the Nrf2/HO-1 signaling system, which has antiapoptotic effects.[20]

Cancer cells have significantly unbalanced pH since they have higher pHi and lower pHe compared to healthy cells. Our knowledge of the effect of unbalanced pH activity on the cancer cell's

characteristics such as proliferation, metastasis, and metabolic adaptation, which determine its aggressiveness, has increased with the help of today's researchers. It was demonstrated that the unbalanced pH of cancers induces a specific cellular behavior by affecting the structure and function of pH sensitive proteins defined as pH sensors.[21] Recent findings have demonstrated that the ability of the cancer cell to proliferate can be impaired by suppressing the increase in pH.[21]

Even if the kidney or lung injury and metabolic alkalosis formula is removed in acid-base disturbances, the importance of alkaliptosis for the pathogenesis of the disease remains unclear. Another uncleared factor is the location of core effector molecules in the alkaliptosis mechanism.[22] Alkaliptosis, its importance, and its relationship with the core effector molecule in the progression of the disease are not yet fully illuminated.

PH-DEPENDENT CANCER CELL BEHAVIORS

Acid-base homeostasis must be maintained for a healthy cellular physiology and metabolic activity. How cell death is induced in response to changes in pH is not clear. Disruption of pHi and pHe homeostasis promotes cell proliferation, resistance to immune response, and avoidance of cell death. It also determines the progression of cancer by enabling cell migration and metastasis to other organs or tissues. Researchers' concentration on sensors has revealed the importance of the basis of pH-dependent cell formation in cancer cell biology. Structurally high pHi of cancer cells provides most of the growth factor independent proliferation of cancer and selective advantages to avoid apoptosis. In addition, many mechanisms that affect pHi dependent on cell proliferation, and it is known that a pHi level above 7.2 increases the rate at which the cell enters the S phase, the G2/M phases, and the progress of the cells induced by the growth factor. Therefore, stimulation of critical points in the cell cycle will not only aid the proliferation of cancer cells with abnormally increased pH but also is likely to cause genetic defects. Constant high pHi in cancer cells causes a robust resistance to apoptosis. Our understanding of apoptosis, which regulates the pH sensor, is limited, and pH dynamics possibly co-modulate multiple proteins to control this process. The studies aiming to limit cancer progression intend to augment cell death associated with mitochondria. Identification of an pHi sensor that shows changes by inhibiting or inducing drug-dependent pH-related pathways may increase the chances of treatment success.[23,24] Increased pH stimulates glycolysis and inhibits gluconeogenesis due to the pH sensitive activity of glycolytic enzymes.[25]

Cancer cell metastasis occurs via an unstable pH and some other factors. A study demonstrated a pHi dependent molecular basis by showing that an increase or decrease in pH controls different stages of cell migration.[26] The findings highlight the specificity of pH signals and the ability of pH to regulate multiple processes involved in complex cell behavior.

THE ROLE OF CARBONIC ANHYDRASE IX IN CANCER

Oxygen deprivation of the cell can have dramatic consequences, altering every scale from cancer cell function to gene expression, genetic stability, cell proliferation, and survival.[27] Due to hypoxia, cancer cells use anaerobic glycolysis rather than oxidative phosphorylation for their energy requirements. Decreased pHe is observed as a result of lactic acid and carbon dioxide production, which leads to the development of an acidic environment in the tumor microenvironment with glycolytic metabolism. Since the cell's maintenance of vital functions is sensitive to small changes in pHi, its ability to adapt to these limiting conditions will determine the fate of the cell. Carbonic anhydrase IX (CA9) protein is one of the valuable factors in the cell's adaptation to changing conditions.[28,29]

Carbonic anhydrase IX is activated due to the need to neutralize pHi against the acidic environment of the cell microenvironment. Its most distinctive feature is to regulate the pH of cancer cells exposed to the acidic environment caused by lactic acid.[30]

NUCLEAR FACTOR KAPPA B'S FUNCTION IN CANCER

The nuclear factor kappa B (NF-κB) pathway involved in the inflammatory response is generally

considered to be the post-survival signaling pathway. Nuclear factor kappa B ensures cell survival by transactivating many pro-inflammatory and anti-apoptotic genes. The increase in NF-κB function causes alkaliptosis by suppressing CA9, a member of the carbonic anhydrase family.[31] It is the focus of attention in cancer research, as the mechanisms that mediate the formation of inflammation contain similar characteristics to tumor formation. Nuclear factor kappa B proteins are key players in innate and adaptive immune responses that play an active role in cell proliferation, mediate apoptosis suppression, enhance cell migration and transactivating ability, and they can also be induced.[32] Nuclear factor kappa B is functional in many cell types to ensure normal functioning of both malignant cells and healthy cells.[33] Most of the increased NF-κB activity observed in malignancy occurs as a result of the upregulation of cytokines that activate inhibitory-B kinase, such as tumor necrosis factor and interleukin-1.[34] Tumor formation is a complex process divided into three steps: tumor formation, tumor growth and adaptation to the microenvironment, and tumor spread. Nuclear factor kappa B is generally regarded as a key regulator in all of these steps.[35]

TARGETING ALKALIPTOSIS FOR CANCER TREATMENT

A screening of a small-molecule compound library targeting G-protein coupled receptors for cytotoxic activity on a human pancreatic cancer cell line led to the identification of JTC-801, a new synthetic selective opioid receptor-like 1 receptor antagonist.[36] It contributes to the treatment via induction of a unique pH-dependent form of RCD that we term alkaliptosis. The induction of alkaliptosis by JTC801 partly requires NF-κB activation. These unexpected properties reveal new opportunities for pH-dependent cancer therapy by induction of alkaliptosis.[36] It is known that the down-regulation of inhibitors of NF-κB kinase subunit beta and NF-κB induces alkaliptosis.[37] Treatment with JTC801 induces alkaliptosis in cancer cells by activating NF-κB, which represses the expression of the CA9 gene, whose product regulates pH balance in cells.[37] Increased tumor levels of CA9 mRNA or protein have been associated with shorter survival times in patients with pancreatic, kidney, and lung cancer.[37] Administration of JTC801 inhibited the growth of xenograft tumors, orthotopic tumors, lung metastases of mice, and slowed the growth of tumors in mice.[37]

In summary, JTC801 induces alkaliptosis, pH-dependent cell death, specifically in cancer cells such as pancreatic adenocarcinoma cells, by reducing the expression of CA9.[38] Levels of CA9 are increased in human cancer tissues. The use of JTC801 may be viable in the treatment of pancreatic cancer. However, studies on other types of cancer are limited.

CANCER

The dynamic balance between proliferation and cell death is known as homeostasis. If altered, various pathologic processes such as carcinogenesis can take place. In cancer cells, pHi is increased compared to normal cells, while pHe is decreased. This reversal in the pH gradient of cancer cells is an early event in cancer development and increases during neoplastic progression.[39,40]

Cancer, a complex genetic disease ensuing from mutations of oncogenes or tumor suppressor genes resulting in the alteration of key signaling pathways, has been well known to have numerous links to programmed cell death (PCD). Explaining PCD in disease conditions is imperative as it not only gives new insights into the pathogenesis of such conditions but also will help the development of new targeted anticancer therapeutic strategies. One of the main deregulated landmarks in cancer is the imbalance between cell division and cell death. In addition, other factors that influence cell survival, proliferation, and differentiation are fundamental in cancer. Moreover, from this perspective, any alterations in cell development or cell homeostasis can lead to dysregulation, whose fate is decided by PCD, as it may shift the balance between cell death and cell survival, depending on the trophic conditions of the cell. However, in addition to being a solution, PCD can also be the cause of the problem.[41,42]

CANCER THERAPY

Conventional cancer therapies aim to permanently eliminate tumor cells from the organism; however, they can induce severe

side effects on healthy cells and multiple organ dysfunction, often with chronic consequences. Off-target toxicity is exerted on the cardiovascular system, neural cells, liver, kidney, bone marrow, and other organs. One of the most common side effects of chemotherapy is the non-specific antiproliferative activities of the anticancer drugs on leukocytes and lymphocytes, which can induce the suppression of the immune system with a consequent higher susceptibility to infections.[43] Current anticancer strategies deal with reactivation of cancer cell death signaling routes to induce tumor regression.[44] Today, the studies are investigating the mechanisms that regulate other underexplored forms of cell death and how these pathways could be mapped and integrated with each other.[45] Knowledge on the link between cell death and cancer will enable us to predict in a more refined manner the carcinogenic process, and therefore, pave the way for a personalized approach to the disease. While tumor cell death may occur in response to therapy, the selection, growth, and dissemination of resistant cells can ultimately be fatal.[46]

CHALLENGES IN CANCER TREATMENT

The most obvious factors are low socioeconomic status.[47,48] Despite significant progress towards confronting cancer treatment, the current approach is still insufficient. Targeting single molecular abnormalities and cancer-related pathways have achieved sufficient clinical responses, modestly affecting survival in some cancers.[49] Targeting a single hallmark with a single drug is not likely to lead to a cure for cancer. Thus, the action of most cancer drugs is directed against a limited number of well-established targets, reflecting the difficulty involved in the identification and validation of new targets crucial to the disease.[50] Combination therapy, a treatment modality that combines two or more therapeutic agents against several molecular alterations or cancer hallmarks, is a promising therapeutic strategy to treat cancer in the near future, similar to the human immunodeficiency virus treatment. Defects in cell death pathways are nearly ubiquitous among cancer types; therefore, targeting the cell death components can be used as a comprehensive treatment strategy for a broad range of cancers. However, understanding the differences between the cell death pathway defects in each type of cancer can offer a more tailored approach to choosing treatments to enhance cell death in a specific and effective way.

RESEARCH PROSPECTS ON ALKALIPTOSIS

Alkaliptosis is a newly found, pH-dependent form of RCD. Tang et al.[14] first introduced the definition of alkaliptosis when they found that the N-acetyl cysteine mediated acidic pH environment protects against drug induced cell death, whereas alkalinization of cell culture medium by sodium hydroxide is more likely to induce cell death through NF-κB. This mechanism is typically different from other forms of non-apoptotic RCD including ferroptosis, pyroptosis, and necrosis. NF-κB expression can both suppress alkaliptosis and induce the Nrf2/HO-1 signaling axis to transactivate pro-inflammatory and anti-apoptotic genes;[15] however, Nrf2 inhibition has not been found to affect drug-induced cell death so far. Thus, there is still much to explore regarding the up- and down-regulators in the Nrf2/HO-1 axis that mediate protection against alkaliptosis.[32] The pathological significance of alkaliptosis in human diseases remains complicated, and the main signals of allkaliptosis need to be illuminated in the future.

Cancer is a common disease with many diagnostic possibilities and predisposing factors. It emerges as a serious health problem worldwide in terms of mortality and morbidity rates. Surgery, chemotherapy, and radiotherapy do not affect the survival rates for the long term; however, the long-term treatment of conditions significantly affects the morale and motivation due to the patients' quality of life. In addition to anticancer therapy solutions such as immunotherapy, inducing PCD in cancer cells can sometimes lead to the avoidance of the immune response and resistance to treatment. Moreover, not knowing the critical points of RCD pathways and not knowing the optimum treatment dose are among the primary causes of treatment resistance. The importance of regulating the homeostasis of cell survival and death signals is emphasized. Regulated cell death occurs in different ways according to the physiological and pathological

conditions of the cells, thus, various pathways with different results emerge following different morphological and immunological changes. The process of evolutionary communication between RCD pathways is unknown due to the biological variation. Since it is not possible to fully distinguish RCD forms, it is important to prepare standard biomarkers and determine its critical points to understand the RCD combination that occurs in pure form or mixed variants in which subgroups act together. It is thought that the establishment of fast and functional tests will greatly affect the prognosis of the disease. It should be kept in mind that RCD can play a critical role in both maintaining organism homeostasis and dysfunctional cellular death. In addition, more research is needed to determine the critical point of the non-reversal of each sub-route, and the role of underactive and overactive RCDs in human disease needs to be investigated. Although little is known about the role of intracellular alkalinization in RCD, pathological conditions associated with alkalosis have been identified. Before treatment that prevents aggressive proliferation in cancer cells, the stimulated RCD pathway must be determined, and we must resolve the defects and resistances in these cell death pathways. Many cancer treatments aim to trigger cell death that prevent tumor growth. However, the presence of genetic mutations that cause cancer limits the physiological effects of molecules that cause cell death. Personalized strategies are needed to improve the clinical response of the individual.

In conclusion, alkaliptosis is biochemically and genetically different from other apoptotic and non-apoptotic forms of RCD, and caspase activation, necrosome assembly, and lipid peroxidation reactions are not observed in alkaliptosis. Apoptosis and necrosis pathways and the suppression of ferroptosis do not restrict the alkaliptosis mechanism induced by JTC801. Alkaliptosis-regulated cell death pathway is pH-dependent, as described in recent publications, and it is seen as a new treatment strategy. It is known to be discovered as a result of the upregulation of NF-κB, which inhibits the expression of CA9. The histopathological significance of alkaliptosis and core effector molecules is still under investigation, the specific relationship has yet to be revealed. Therefore, we hope to provide a broad perspective for future studies on cancer treatment investigating the approach of alkaliptosis.

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