Mini-review

The Applied Biology & Chemistry Journal
https://www.theabcjournal.com
eISSN: 2582-8789

Role of acidic tumor microenvironment in tumor pathogenesis and targeting

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Received September 05, 2020
Revised September 25, 2020
Accepted September 26, 2020
Published September 29, 2020

Abstract: Extensive efforts are going on to understand the molecular mechanisms behind tumor initiation, progression, and invasion and find novel targets for cancer treatment. The physiological state of the tumor microenvironment (TME) is crucial to every step of tumor cell growth and angiogenesis. Cancer cells are rarely in contact with each other. The intervening medium between the cancer cells, immune cells, and other cells become acidic, which significantly affects cancer pathogenesis. It could be a novel targeting marker and may help treat tumors. Even after extensive research in this area, the nature of molecular alterations and the basic mechanisms in the tumor microenvironment remains unclear. Based on recent studies of TME, this mini-review bids a more inclusive overview of the role of TME in cancer cell growth. Also, it helps to understand the potential of TME for therapeutic interventions.

Keywords: acidic pH; immune escape; immunomodulation; tumor microenvironment

Introduction

Cancer is the continuous growth of cells without proper self-regulation. Undoubtedly, cancer cells' metabolic pathways are reprogrammed to enhance and support the neoplastic behavior. Reprogramming of cancer cells metabolic pathways make cancer cells generally results in continuous cell growth and modulation of cells to local cell populations. One of the critical consequences of continuously growing cancer cells is that this results in lactic acid production. The lactic acid production leads to acidic niche formation around the tumor cells, referred to as tumor microenvironment (TME). It is more on a network of interacting cells with various cell populations under acidic conditions. It is noteworthy that all the tumor areas are not equally acidic or uniform in the cell population [1]. A tumor contains a heterogeneous population of cells, including cancer cells, normal cells, immune cells, and stromal cells. Apart from the cells' population, various signaling molecules, extracellular matrix (ECM), and mechanical issues also interfere with this [2]. The TME can provision the tumor growth, guard the tumor from host immune system, substitute restorative resistance, and sustain metastases [3].

The cancer cells' vital issue is that they advance to become aggressive tumors, which may have escaped the immune system. This escape is made by making a tumor-immune environment that permits the lesion to escape from the immune blitz. Cells use glucose as a source of energy and, under the aerobic environment, leads to pyruvate formation. While growing, cancer cells shift their metabolisms to lactic acid production, also referred as the 'Warburg effect' [4]. Collectively due to the metabolic activity of growing cancer cells and low perfusion of cells have acidic microenvironments. This acidic microenvironment and inefficient transport of waste products further exert physical constraints on cancer cells. Both the factors not only modulate cancer cell growth but the immune response and alkaline chemotherapeutic drugs also [5]. Tumor pH can vary as low as pH 6.4. Chronic pH has been reported to induce metastatic behavior in many tumors. Low pH has also been shown to contribute to the resistance against the drugs [6]. In contrast, several studies on acidic pH suggested that an acidic tumor microenvironment can enhance tumor cells' chemosensitivity [7].

Tumor microenvironment: a necessity or evil

Despite much research, what remains in question is whether the acidic environment is good or bad for cancer cells or their targeting. Cancer treatment lacks a distinct difference between a cancer cell and a normal cell. It is noteworthy that the tumor microenvironment is different in terms of both hypoxic and acidic features in many tumors [8]. This difference could be exploited as a treatment strategy. Acidic pH leads to the reprogramming of cells metabolic and gene expression pathways activated explicitly under acidic conditions [9]. Therefore, targeting these pathways, especially for cancer treatment, could be a novel approach. It has been shown that under acidic environments, many cancer drugs are more active, and acidic microenvironments can be exploited for drug targeting [10].

Many nanoparticles have joined the anti-cancer drug team, which delivers medications based on pH variations [11].

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Citation: Sharma V, Bawa C, Vatsyan KC (2020). Role of tumor microenvironment in tumor pathogenesis and targeting. *T Appl. Biol. Chem. J*; 1(1):34-40. https://doi.org/10.52679/tabcj.2020.0005

Recent research has shown that under an acidic microenvironment, cancer cell physiology can be moved towards apoptosis [12]. In comparison, many studies have shown that acidic microenvironment can cause metastasis [13].

In contrast to the above studies, an acidic environment can convince the cells to over-express the proteins, either providing resistance or decreasing drugs' efficiency [14]. Recently Lotz *et al*. 2015 revealed that an acidic environment could result in the p-glycoprotein mediated efflux of drugs [15]. The role of acidic pH in metastasis of the tumor can be understood as an important parameter as the reversal of pH has been documented for the spontaneous inhibition of cancer cell growth. These studies are also supported by Thomson *et al.*, which demonstrated that reversal of acidic pH could improve antitumor activity and enhance the immune response [16]. Similarly, the proton pump inhibitors are also shown to improve the antitumor activity by inhibiting the tumor acidic environment [17]. Pepicelli *et al.* 2015 demonstrated that acidic pH could manage the mesenchymal stem cells to promote cancer progression [18]. Collectively the acidic pH around the tumor has dual behavior by supporting metastasis and proving a niche for drug targeting.

Tumor microenvironment mediated angiogenesis and metastasis

Angiogenesis is the physiological property of cells forming new blood vessels from pre-existing vessels. Angiogenesis involves chemical signals which affect the migration, growth, and differentiation of the most significant components of blood vessels, endothelial cells. Cancer cells need continuous feeding and cannot grow beyond a specific size without the involvement of blood vessels; therefore, the role of the tumor environment and angiogenesis also seem to be very important in cancer growth. The crucial factors that activates angiogenesis includes vascular endothelial growth factor (VEGF) together with pro-angiogenic factors comprising basic fibroblast growth factor (bFGF), matrix metalloproteinases (MMP), transforming growth factor-α (TGF-α), platelet-derived growth factor (PDGF), placenta growth factor (PlGF), angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), and hepatocyte growth factor (HGF) [19]. The tumor microenvironment modulates cell physiology and generates glioma stem cell phenotypes. Tumor cells are generally shown to enhance the release of protease in an extracellular environment. For example, the lysosomal enzymes usually are active under acidic pH and are also secreted by some tumor cells [20].

In many cases, the acidic pH has been demonstrated to disrupt cell junctions by Src mediated pathways [21]. Undoubtedly, acidic TME induces metastasis and angiogenesis by interfering with molecular signaling mechanisms associated with cell recruitment and vascular construction. In athymic nude mice, acidic extracellular pH promotes metastasis, while cells grown at acidic pH show heightened production of pro-angiogenic factors [22]. Sutoo *et al.* have shown that the acidic pH could augment the metastatic potential of the lung cancer cells, which was evidenced by the MMPs [23]. Acidic pH can also induce invasive phenotypes in the tumor cells. Huang *et al.* recently suggested that acidic extracellular pH can lead to prostate cancer cell metastasis by exercising that VEGF induces vasculogenesis [22]. It has been demonstrated that the tumor cells promote angiogenesis by VEGF and IL-8 [24].

Human glioblastoma cells under acidic extracellular pH induce VEGF ERK1/2 MAPK signaling pathway [25]. Acidic environment implicated in increased enhanced transcription factor AP, NF-κB, including HIF [25]. Expression of both AP and NF-κB has been proven to induce VEGF expression in an acidic environment. Cells cultured at acidic pH possess more invasive and angiogenic potential by MMPs. Among MMPs, mmp9 is associated with phospholipase D-mitogen-activated protein kinase signaling [26]. Extracellular acidification has also been linked with altered lysosome trafficking, which can further potentiate the cell's ability to secrete peripheral lysosome culminated with degrading enzymes. Recently Giusti *et al.* revealed that cancer cells could secrete cathepsin B loaded vesicles under acidic environments, promoting experimental metastasis [27]. In addition to the above factors, ATP-dependent transporters have also been shown to promote the secretion and activation of proteolytic enzymes, especially MMPs [28].

Acidic microenvironment and immune escape

Tumor microenvironments are acidic due to the anaerobic respiration of quickly multiplying cells in cancer cells. Many studies have established the production of lactic acid and its role in the immune association. Recently many studies correlated acidosis with altered immune response. An acidic environment can act on heterogeneous populations of cells, which can collectively affect the functions of the immune system, including T cells, neutrophils, macrophages, and dendritic cells. The heterogeneous population of cells present in the TME includes the T cells and B cells, macrophages, and other cells. Alteration of the tumor environment can encompass the downregulation of major histocompatibility complex (MHC) or the initiation of immune inhibitory cytokines and chemokines [29]. The combined effect of these can directly affect T cell anergy, expansion, and activation of immune suppressive cell populations such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSC).

Studies by different groups suggested that the tumor-immune environment can be actively manipulated to revert to a pro-inflammatory Type I environment, which will allow the activation of antigen-presenting cells (APC) and the initiation of cytokines such as IFN-ɣ, TNF-α, and IL-2 that are related with cancer atrophy [30]. Multiple immunomodulatory approaches are currently being actively evaluated, which could be used alone or in combination with vaccination and T-cell therapy to eradicate cancer [31]. These approaches generally concentrated on remodeling the tumor immune environment and stimulating an effective antitumor immune response. These strategies include the activation of APCs via stimulation of toll-like receptors

(TLRs) and elimination of immunosuppressive cell populations (Tregs and MDSC), leading to heightened local cytokine production and a Th1-polarized microenvironment that favors tumor cell atrophy by cytotoxic T cells [32]. The T cells are known to be involved in the early killing of tumor cells.

The generation of an acidic environment can interfere with both antigen recognition as well as immune cell performance. The acidic environment generally influences these cells by downregulation of essential cytokines involved in immune defense. A recent study suggested an acidic microenvironment can lead to the downregulation of IFN-ɣ and TNF-α in T cells [33]. Furthermore, many studies have documented that acidic pH can lead to decreased MHC performance [34]. MHC is a significant molecule in T cell-mediated immune response. Another type of essential cell residing in the TME is tumor-associated macrophages. These cells are chiefly responsible for the secretion of various immunosuppressive cytokines and also IL-10 and TGF-β, which inhibit CD4 and CD8 cells [35].

Additionally, the tumor-associated macrophages are also known to enhance Treg cells' population, making the tumor microenvironment immune suppressive. A recent study suggested that lactic acid-induced acidic microenvironment can inhibit MCT-1 and cytotoxic T lymphocyte cell functions [36]. The acidic tumor microenvironment has also been correlated with enhanced apoptosis induction and decreased IL-2, IFN-ɣ production by T cells [37]. Extracellular lactic acid generates anaerobic glucose metabolism shown to overpower the activity of T cells.

In fact, many studies suggested that under acidic pH conditions, the transcription factor participated in the enhanced depression of effector molecules like IFN-ɣ are downregulated [38]. Acidic pH has been shown to suppress the function of cytotoxic leukocytes by downregulating P38 and JNK mediated pathways [38]. *In vitro* studies on the impact of acidic tumor microenvironment also supported the compromised performance of Immune cells. A recent study suggested impaired cell proliferation and decreased the expression of IL-2 receptor CD25 in T cells and TCR components [39]. Many tumor investigations reported the reduced performance of T cells by modulation of the tumor microenvironment depleting T regulatory cells. Recent studies predicted that acidic pH could promote the tumor progression suppressing Th1 lymphocytes and stimulating the Th2 lymphocytes [40]. Although up to now, there is no sufficient direct evidence that the impaired activity of T cells is due to the acidic tumor environment, however, growing evidence is favoring the role of TME in immune escape.

The motility of leukocytes was significantly reduced in the presence of the acidic pH. Many studies suggested that acidic pH can affect the microtubule mobility and TCR components leading to T cells anergy [41]. Acute exposure to acidic pH can induce apoptosis in T cells. However, there are contradictions in studies regarding the chemotaxis of immune cells acidic pH. Recently it has been shown that the diminution of Tregs, IL-2, and diphtheria toxin can significantly impede tumor growth in a breast cancer mouse model [42]. It has also been shown that in breast cancer mouse model, tumor growth can also be inhibited by topical treatment with imiquimod cream [43]. Tumor-associated macrophages are the key population of cells present in the tumor microenvironment. There are many contradictions in the literature regarding the behavior of tumor-associated macrophages in acidic tumor microenvironments. Many studies pointed out that acidic pH can attract macrophages at the tumor site and convinced tumor-associated macrophages to promote the tumor [44]. This study was further supported by the evidence suggesting that neutralization of tumor pH restore the T cells response and lead to the secretion of effector cytokines [45]. Tumor-associated macrophages are shown to promote the induction of iNOS, and the NF-κB mediated signaling pathways [46].

Macrophages under acidic environments are correlated with enhanced expression of arginase 1. Arginase has been previously established to decrease and inhibit the T cell's activation and proliferation [47]. Macrophages have also been shown weak to antibacterial response in acidic pH conditions. However, acidic microenvironments are positively co-related with neutrophil activation [48]. Many studies are suggested that acidic environments lead to the activation of neutrophils. Acidic environments can activate the CD18, Calcium, and ERK-mediated pathways in neutrophils [49]. Recently, Som *et al.* demonstrated that acidic stress leads to the enhanced expression of OCT4 in fibroblasts and the reprogramming of the tumor-associated stromal cells [50].

Therapeutic aspects of the acidic environment

An acidic microenvironment favorably modulates cancer therapies such as hyperthermia, radiotherapy, and chemotherapy. It modulates chemotherapeutic with weak acid and weak base characteristics. Most studies suggest that an acidic environment can enhance cancer cells' drug uptake and increase cancer cells' susceptibility towards medicine [51]. Recently resveratrol has been shown to be more effective under acidic conditions [52]. Even combined therapy, including chemotherapy and hyperthermia, seems more promising in an acidic environment. Quercetin is a heat shock protein 70 (HSP70) inhibitor and has been found most effective under low pH conditions [53].

Generally, it is a big problem in cancer treatments that it is very tough to find novel targets. However, it is very well established that tumor microenvironment can be cancerous; therefore, the genes working under the acidic environment can be a therapeutic target for cancer. Many studies have exhibited the enhanced sensitivity of cancer cells under acidic pH; however, several others contradict it, confirming the decreased efficacy of standard chemotherapeutic drugs in cancer treatment [54]. Recently, research suggests the reduced effectiveness of mitoxantrone and topotecan in cancer treatment under an acidic environment [55]. Doxorubicin is less effective under acidic pH against breast cancer cells [56]. However, the studies associated with alkalization of tumor microenvironment *in vivo* showed

recovery in tumor progression. These studies are supported by many patient studies, also. Currently, many studies are exploiting the acidic pH-sensitive drug delivery systems. Recently poly (L-histidine)-b-poly (ethylene glycol) has been shown [57]. Patients under treatment of 5-fluorouracil (5FU) and cyclophosphamide have revealed improved effectiveness under the acidic pH conditions to enhance the cytotoxicity of doxorubicin in drug-resistant tumors [51]. Probably multiple mechanisms can be responsible for the decreased efficacy of drugs. One study opinion is that acidic pH can modify the expression of many genes responsible for the uptake of drugs [58]. Alternatively, it may be conceivable that acidic pH can alter the chemistry of drugs and decreases drug efficacy. However, no significant literature studies reveal that either the extracellular pH or cytoplasmic pH affects drugs' effectiveness. Recently Lázaro *et al*. revealed that PEG-coated nanoparticles could deliver the anti-cancer drug in acidic pH mediated pathways [59]. These studies suggested that such medications can lead to tumor localized accumulation of drugs and enhanced anti-cancer treatments. Salinomycin, an ionophore antibiotic, has been shown to be more effective in chronic acidic pH conditions [60]. Many agents, which are TLR8 agonists, are shown to enhance NK cell function and ADCC. VTX-2337 is a recently appreciated novel TLR8 agonist that selectively activates myeloid DC and induces elevation of TNF-α and IL-12 levels [61].

Conclusion

Facts are very well established that tumor microenvironments may not be the cause of cancer initiation. However, they play an important role in promoting metastatic behavior and chemoresistant phenotypes in cancer cells. Therefore, the acidic environment exists in the tumor microenvironment and needs substantial attention to take the tumor more efficiently. One of the significant needs of the time is discovering novel nanoparticles, leading to acidic pH-sensitive anti-cancer leads. Further shortly, it is expected that acidic pH mediated anti-cancer agents can be developed to enhance the chemotherapy, and acidic pH can be exploited more efficiently.

Declarations

Authors Contributions

VS conceived of the presented idea for the article. VS, CB and KCV performed the literature search and data analysis. VS and CB wrote the manuscript. KCV provided critical feedback and helped to shape the manuscript.

Funding: The authors have no funding or financial relationships.

Competing Interests: The authors declare no conflict of interest.

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Citation: Sharma V, Bawa C, Vatsyan KC (2020). Role of tumor microenvironment in tumor pathogenesis and targeting. *T Appl. Biol. Chem. J*; 1(1):34-40. https://doi.org/10.52679/tabcj.2020.0005