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Review

Stressor-driven extracellular acidosis as tumor inducer via aberrant enzyme activation: A review on the mechanisms and possible prophylaxis

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ABSTRACT

When the extracellular pH of human body vacillates in either direction, tissue homeostasis is compromised. Fluctuations in acidity have been linked to a wide variety of pathological conditions, including bone loss, cancer, allergies, and auto-immune diseases. Stress conditions affect oxygen tension, and the resultant hypoxia modulates the expression and/or activity of membrane-tethered transporters/pumps, transcription factors, enzymes and intercellular junctions. These modifications provoke erratic gene expression, aberrant tissue remodeling and oncogenesis. While the physiological optimization of pH in tissues is practically challenging, it is at least theoretically achievable and can be considered as a possible therapy to resolve a broad array of diseases.

1. Introduction

Abnormal enzyme activation is a pivotal reason of pathologies, which include allergies, auto-immune diseases, neuropathologies, and cancers (Wong et al., 2009; Wang et al., 2015). The zymogen forms of enzymes are converted to their active forms by different stressors. Such stressors can be the reactive oxygen species (ROS), reactive nitrogen species (RNS) etc. Due to the hyper-production of these reactive free radicals, the extracellular physiological milieu turns acidic (Rajamäki et al., 2013). The resultant low pH favors the activation of a number of crucial enzymes, often triggering 'enzyme cascades'. A number of studies have reported the direct nexus between high acidic environment, hypoxia and tumorigenesis (Cao et al., 2015). Also, low pH mediating drug resistance has got adequate evidence (Wojtkowiak et al., 2011; Pellegrini et al., 2014). Insightful reviews have critically analyzed these aspects (McCarty and Whitaker, 2010; Kato et al., 2013; Peppicelli et al., 2014). Extracellular acidity is linked to brain hypoxia-ischemia as well (McDonald et al., 1998). The acidosis activates acid-sensing ion channels (proton-gated sodium channels), leading to pain and anxiety (Wemmie et al., 2013; Li and Xu, 2015; Li et al., 2016). Also, the dropped pH in the extracellular space leaches calcium from osteoclasts, leading to bone pathologies as osteoporosis and osteomalacia (Jehle and Krapf; Teti et al., 1989). Dietary acid load has been attributed to chronic kidney disease (CKD) (Scialla and Anderson, 2013). Also, depletion of muscle mass as causal of acidosis has been observed, which occurs by activated ubiquitin–proteasome system (UPS) (Jehle and Krapf, 2010; Rajan and Mitch, 2008). A range of metabolic pathologies as diabetic ketosis, trauma, sepsis, chronic obstructive pulmonary disease (COPD), brain ailments etc. have been linked to acidosis (Schwalfenberg, 2012). In this regard, this review discusses the adverse effects and mechanisms of chronic metabolic acidosis in the form of carcinogenic enzyme activation.

2. Tumorigenesis and metastasis mechanisms

Multiple metabolic pathways operate in the human body. Glycolysis, the anaerobic mechanism of glucose metabolism is predominant in tumor cells, which generates lactate (known as Warburg effect) (Dhup et al., 2012; Kato et al., 2013). Pentose phosphate pathway (PPP) produce high CO_2, which ultimately break down by carbonic anhydrase to form H^+ and $HCO3^-$ (Jiang et al., 2014).

A broad array of pumps/transporters play active role in this ionic disturbance. Some well-characterized pumps include the lactate transporter, monocarboxylate transporter, H + -ATPase, Na +/H + exchanger etc. (Kato et al., 2013). These fluctuations in pH have far-flung consequences in the body.

Tumors acquire metastatic property by angiogenesis and cell invasiveness. Cell-cell junctions shattered through Src activation via protein kinase C (PKCα) pathway facilitate the invasion. Proangiogenic growth factors such as vascular endothelial growth factor (VEGF), insulin-like growth factor I (IGF-1R), epidermal growth factor (EGF), and cytokines as IL-8 also promote it (Rofstad et al., 2006; Chen and Sharon, 2013). Lactic acid as an inducer of tumor angiogenesis has been discovered (Dhup et al., 2012).

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3. Enzyme activations

Activated proteinases can unleash a deluge of tissue damage (Zucker et al., 2009). Once activated, the essential enzymes such as serine proteases and cysteine proteases cannot discriminate between self and non-self, burning away self-tissues (Chien et al., 2009; Laskar et al., 2012; Choudhury et al., 2013; Phillips-Mason et al., 2014). Extracellular matrix (ECM) is a viscous cocktail of proteins, proteoglycans, and glycoproteins, providing tensile strength and viscoelasticity to tissues (Lu et al., 2011). ECM proteins such as elastin, fibronectin, laminin, and type IV collagen are manipulated (Lu et al., 2011; Yue, 2014). ECM proteins are degraded by the digestive action of matrix metalloproteinases (MMPs), the zinc-dependent endopeptidases/proteolytic enzymes (Vartak and Gemeinhart, 2007). Though new discoveries are constantly changing the classifications, the substrate-activity-based clustering of enzymes appears informative (Vartak and Gemeinhart, 2007). MMPs, owing to their proteolytic activities mediate a gamut of pathologies including arthritis, atherosclerosis, ulcers, periodontal disease, brain, liver cirrhosis, fibrotic lung disease, multiple sclerosis, endometriosis, pulmonary emphysema etc. (Amălinei et al., 2010). ProMMP-9 is activated in the stomach, which can cause gastric ulcer and gastric cancer (Carneiro et al., 2009; Choudhury et al., 2013). ProMMP-2 and proMMP-8 activation in saliva causes caries. MMP-7 is expressed by tumor cells of epithelial and mesenchymal origin (Amălinei et al., 2010). Table 1 presents the pertinent data regarding the types and function of MMPs. For further information on the functional profile of MMPs, previously published works can be referred to (Klein and Bischoff, 2011). Tissue inhibitors of metalloproteinases (TIMPs), a type of extracellular proteins, regulate the MMPs. Inflammatory milieu increase TIMP-1 expression. TIMPs and MMPs are mutual inhibitory (Moore and Crocker, 2012).

Cyclooxygenase-2 (COX-2) produces prostaglandin (PGE2), the pain mediator. COX-2 elaboration increases in the presence of cytokines, growth factors, microbial lipopolysaccharides (LPS), and insect chitins (Ricciotti and FitzGerald, 2011). Aromatase is a cytochromes P450 monooxygenase that converts androgens (C19) to estrogens (C18) (Demura et al., 2007; Izawa et al., 2008). Hyper-activity of this enzyme can generate excess local estrogen, leading to perturbation of glucose, and lipid, affecting brain function, ovulation, fertility etc. COX-2 and aromatase activity are directly related (Fowler et al., 2005; Sirianni et al., 2009; Basu et al., 2015). It is important to understand that all enzymes collaborate and co-ordinate to run the human systems and their functions. Perturbation of one can shake the others as well. The inflammatory enzymes COX-2 and aromatase require phospholipase C, and protein kinase C, among other array of enzymes for their functions.

Glycosidases embrace a broad array of enzymes and they can activate in sub-optimal pH. Heparanase can express, degrading the proteoglycan heparan sulfate in the basement membrane and ECM, contributing to tumor invasion and metastasis (Koliopanos et al., 2001; Takaoka et al., 2003; Zheng et al., 2010).

Focal adhesion kinase (FAK) is a tyrosine kinase, with role in cell adhesion, growth, proliferation (via the Ras/ERK/MAPK pathway), angiogenesis and migration etc. Tumorous tissues have higher expression of FAK, which regulate protein scaffoldings (Stevenson et al., 2012). Src family kinases (SFKs), a group of non-receptor tyrosine kinases, also play critical role in cell adhesion, invasion, proliferation, and angiogenesis. SFKs comprise nine family members (Src, Fyn, Yes, Blk, Yrk, Fgr, Hck, Lck and Lyn) that share similar structure and function. Overexpression of SFKs occurs frequently in tumor tissues (Kim et al., 2009; Guarino, 2010). SFKs interact with FAK for tumor cells invasion (Guarino, 2010). Kinases manipulate structural proteins like integrins, actins, GTPase-activating proteins, scaffold proteins (p130CAS and paxillin). Angiogenic growth factors as EGFR and the VEGF serve as tyrosine kinase receptors. The mammalian target of rapamycin (mTOR), a serine/threonine kinase, is activated by diverse stimuli, including growth factors, and signaling pathways as PI3K, mitogen-activated protein kinases (MAPK) and 5′ AMP-activated protein kinase (AMPK) (Pópulo et al., 2012).The Ras-MAPK pathway is

Table 1
Types of MMPs, their common names, and pathological functions.

Types of MMP	Other names	Activated in/secreted by	Pathologies	References
MMP-1	Collagenase	–	Melanoma Colorectal cancer Arthritis	(Carneiro et al., 2009; Amălinei et al., 2010; Choudhury et al., 2013)
MMP-2	Gelatinase	Chondrocytes	Dental caries Leukaemia	
MMP-3	Stromelysin	Bone	Rheumatoid arthritis	
MMP-7	Matrilysin	Epithelial and mesenchymal cells	Tumors	
MMP-8	Collagenase	Chondrocytes	Dental caries Melanoma Wound	
MMP-9	Gelatinase	Stomach	Adenocarcinoma Chronic obstructive pulmonary disease (COPD)	
MMP-10	Stromelysin	Macrophages	Head and neck cancer Cystic fibrosis	
MMP-11	Stromelysin	–	Tumor Invasive breast carcinoma	
MMP-12	Metallo-elastase	Bronchoalveolar lavage	Skin cancer Squamous cell carcinoma of the vulva Chronic obstructive pulmonary disease (COPD)	
MMP-13	Collagenase	Human tooth pulp	Breast carcinoma	
MMP-20	Enamelysin	–		
MMP-26	Endometase	–	Breast cancer Wound	
MMP-28	Epilysin	Gingival tissues Testis Keratinocytes	Gastric cancer	
MMP-14, −15, −16, −17, −24 and −25	Membrane-anchored MMPs	–	Cancer	