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Review

Modulatory roles of glycolytic enzymes in cell death

Claudia Cerella [a], Mario Dicato [a], Marc Diederich [b,*]

[a] Laboratoire de Biologie Moléculaire et Cellulaire de Cancer, Hôpital Kirchberg, 9, rue Edward Steichen, L-2540 Luxembourg, Luxembourg
[b] Department of Pharmacy, College of Pharmacy, Seoul National University, Seoul 151-742, Republic of Korea

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ABSTRACT

Cancer cells depend on an altered energy metabolism characterized by increased rates of both glycolysis and glutaminolysis. Accordingly, corresponding key metabolic enzymes are overexpressed or hyperactivated. As a result, this newly acquired metabolic profile determines most other cancer hallmarks including resistance to cell death. Recent findings highlighted metabolic enzymes as direct modulators of cell death pathways. Conversely, key mediators of cell death mechanisms are emerging as new binding partners of glycolytic actors; moreover, there is evidence that metabolic regulators re-localize to specific subcellular compartments or organelles to modulate various types of cell demise. The final outcome is the resistance against cell death programs. Current findings give a new meaning to metabolic pathways and allow understanding how they affect cancer-specific pathological alterations. Furthermore, they shed light on potentially targetable functions of metabolic actors to restore susceptibility of cancer cells to death. Here, we discuss an emerging interplay between cell metabolism and cell death, focusing on interactions that may offer new options of targeted therapies in cancer treatment involving more specifically hexokinases and glyceraldehyde-3-phosphate dehydrogenase.

Contents

Abbreviations: ANT, adenine nucleotide translocase; APAF-1, apoptotic protease activating factor-1; ATG5, autophagy related 5; ATP, adenosine triphosphate; Bak, Bcl-2 homologous antagonistic killer; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma-2; Bcl-xL, B-cell lymphoma extra-large; Bid, BH3 interacting-domain death agonist; 3-BP, 3-bromopyruvate; BSO, L-buthionine sulfoximine; CICD, caspase-independent cell death; DOG, 2-deoxyglucose; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HIF-1, hypoxia inducible factor-1; HK, hexokinase; NF-κB, nuclear factor-κB; MCT, monocarboxylate transporter; MOMP, mitochondrial outer membrane permeabilization; NAD, nicotinamide adenine dinucleotide; OMM, outer mitochondrial membrane; PKM2, pyruvate kinase M2; RIPK1/3, receptor-interacting protein kinases 1 and 3; TNFα, tumor necrosis factor alpha; STAT, signal transducer and activator of transcription; XIAP, X-linked inhibitor of apoptosis.

* Corresponding author.
E-mail addresses: marcdiederich@snu.ac.kr, marc.diederich@lbmcc.lu (M. Diederich).

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1. Introduction

It is an old notion that cancer cells exhibit an altered metabolic profile but it is an emerging fact that metabolic reprogramming occurs in early steps of carcinogenesis essential for the establishment of many other cancer hallmarks [1,2]. Resistance to cell death is one of the aberrations developed by cancer cells mostly investigated for therapeutic purposes. Beside apoptosis, the discovery of the existence of many other cell death modalities has further fuelled investigations to discover more effective therapeutic agents selectively reducing cancer cell survival. The variety of cell death pathways so far classified has generated the immediate hypothesis that cancer cells displaying resistance to apoptosis might maintain the ability to shift to alternative death pathways when exposed to stress or damaging conditions. Therefore, drug discovery aimed to identify new cytocidal compounds triggering cell death beyond apoptosis. However, this is just one side of the coin. The current knowledge on the intracellular signaling events modulating these additional non-apoptotic forms of cell death is revealing a highly dynamic interplay with apoptosis: non-apoptotic cell death modalities may even take place in cancer cells challenged with chemotherapeutic agents known as canonical inducers of apoptosis, whenever the execution of the apoptotic program is prevented [3]. These findings reveal an elaborate capacity of cells to switch from one cell death pathway to another: this reprogramming naturally allows physiological cell death, but most often the inability to activate these alternative cell death pathways (slower compared to apoptosis) are now well recognized as an additional and relevant cause of chemoresistance and tumor relapse. Accordingly, efforts are required to identify novel strategies targeting those alternative pro-survival mechanisms as well as their interplay with well-established apoptotic cell death programs.

Metabolic alterations are associated with both activation and inhibition of selected metabolic pathways; cancer cells rely on the switch to aerobic glycolysis (Warburg effect), with the consequent hyperactivation and over-expression of the enzymes catalyzing this metabolic process [4]. A body of evidence indicates that glycolytic enzymes are highly multifunctional protein, with additional functions conferred by specific domains. Differential intracellular activities of these glycolytic enzymes is further demonstrated by their re-localization to subcellular compartments, including the nucleus, the plasma membrane and the mitochondria [5–7], although glycolytic enzymes are expected to primarily act at the cytosolic level. Recent findings highlight novel, emerging roles for glycolytic enzymes in modulating cell death mechanisms, related or not to apoptosis. We are extending our knowledge beyond the strict energetic function of glycolytic enzymes.

As this topic is complex and still many pieces are lacking to get the definitive scenario, we will focus our attention here on modulatory activities of key glycolytic enzymes to reveal their unexpected direct abilities to regulate cell death and to offer targets for novel therapeutic strategies.

2. Apoptosis and its backup cell death pathways

Apoptosis is the most frequent form of death triggered in response to physiological stimuli as well as to a variety of stresses inducing cell damage [8]. The stimulus determines the nature of the early signaling events leading to the death commitment: (cell death receptors clustering *vs.* Bak (Bcl-2 homologous antagonistic killer)/Bax (Bcl-2-associated X protein) activation and outer mitochondrial membrane permeabilization (MOMP); this dual modality to achieve cell death commitment, is termed extrinsic or intrinsic apoptotic pathway, respectively [9,10]. Both pathways eventually converge into caspase activation and acquisition of a number of common morphological and biochemical features including DNA fragmentation and laddering and the exposure of phosphatidyl serine on the plasma membrane. Crosstalks between these two pathways exist, further potentializing cell demise. Caspase-8 may truncate BH3 interacting-domain death agonist (Bid), triggering its re-localization to mitochondria, where it activates Bax and triggers the mitochondrial pathway [11]. Caspase-8, in turn, is a known substrate of caspase-3 [12].

The multistep nature of apoptotic signaling has unveiled a delicate balance between pro-survival and pro-death stimuli. During carcinogenesis, many pathological alterations of these cell death pathways promote a persistence of mutated cells; importantly, this unbalance also interferes with anti-cancer therapies determining chemoresistance and favoring tumor relapse. Over the last 15 years, alternative cell death pathways have been discovered; the characterization of the mediators and the mechanisms implicated in these additional processes highlighted an important crosstalk with apoptotic signaling [10]. The emerging scenario suggests that under physiological conditions and in order to maintain homeostasis, a cell primed to die will sequentially activate differential cell death programs, especially if the apoptotic pathways remain silent for one reason or another. Accordingly, such backup cell death pathways allow compensating apoptosis deficiency [10,13–15] and are caspase-independent.

Necroptosis is the best-characterized type of regulated necrosis [16], as we have knowledge about the implicated molecular signaling pathway; furthermore, we dispose of specific pharmacological inhibitors to study it. Characterizing feature of necroptosis is the activation of the receptor-interacting protein kinases 1 and 3 (RIPK1 and RIPK3) [17]. RIPK1 activity may be efficiently blocked by necrostatin 1 and its analogues [18]. Initially described as a type of cell demise triggered by tumor necrosis factor alpha (TNFα) [19], necroptosis has been considered for a long time as a sort of backup cell death associated with defective physiological or extrinsic apoptosis. Nowadays, this scenario becomes more elaborated as stressing agents, including genotoxins or anti-cancer drugs also trigger necroptosis [20,21]. These findings imply that necroptosis is not exclusively activated by endogenous stimuli.

As an alternative to necroptosis, caspase-independent cell death (CICD) can be activated downstream to MOMP. This mechanism is inducible by several chemotherapeutic agents whenever caspase activation is blocked (*i.e.*, in presence of chemical caspase inhibitors or ectopic downregulation of caspase modulators) [3]. Green and collaborators were particularly active in identifying the hallmarks of this form of cell death, which shares both apoptotic features and at the same time peculiar non-apoptotic characteristics including absence of phosphatidylserine exposure or DNA laddering [15]. Many signaling events controlling this pathway remain to be elucidated; moreover, there is a need of molecular tools to detect and monitor CICD. Interestingly, cells undergoing CICD display a high level of vacuolization with autophagosome formation, reminiscent of autophagy.

Autophagy represents a pleiotropic mechanism between survival and death; a body of evidence highlights its interplay with all cell death modalities [22,23]. Although this process is an old acquaintance, recent investigations reveal its true role and meaning in the modulation of cell death mechanisms. The initial concept was that this process might play a pro-survival role, through its ability to degrade and recycle internal cellular components. More, recently, identification of a growing number of autophagic markers and the possibility to easily monitor them has shown that autophagy is frequently triggered in cells undergoing different forms of cell death [10,24]. First, it has been gradually accepted that a paroxystic activation of autophagy may culminate *per se* into a distinctive cell death modality: autophagic

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