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BCL-2: pro-or anti-oxidant?

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1. ABSTRACT

Bcl-2 is recognized as an oncoprotein via its ability to impede death signaling by sequestrating pro-apoptotic proteins such as Bax and Bak as well as preserving mitochondrial outer membrane integrity. Recently, a growing body of evidence has evaluated the role of Bcl-2 in intracellular redox regulation and its downstream effects on life and death decisions in cancer cells. On the backdrop of these findings, we discuss here the classical anti-apoptotic role of Bcl-2 in malignant cells, and review the significance of Bcl-2-mediated regulation of tumor redox status. We discuss recent evidence that underscores a paradigm shift in the way cellular redox status impacts cell fate decisions via the effect of Bcl-2 on mitochondrial physiology. The ability of Bcl-2 to promote, modulate and optimize mitochondrial respiration under different redox states highlights the importance of mitochondrial bioenergetics, ROS and the roles they might play in the onset and/or maintenance of oncogenesis.

2. INTRODUCTION

In order to circumvent the extensive and highly intricate defensive networks that the human body has evolved over generations to deal with the various immunological breeches, highly proliferative cancer cells have adapted and developed a wide-ranging arsenal of death evading mechanisms, which not only render them unrecognizable by immune cells for clearance-despite the stark differences from normal somatic cells-but also prime them for survival under a multitude of conditions.

As perturbations in programmed cell death often set the stage for malignancies, the most prominent being apoptosis, there is a vested interest in seeking to understand the control mechanisms for potential therapeutic value that may be derived. Apoptosis plays an important role in normal development and physiological processes such as embryogenesis, immune responses and tissue homeostasis,

deregulation of which leads to devastating outcomes such as autoimmunity, degenerative diseases and cancer (1).

3. BCL-2 FAMILY AND CONTROL OF CELL DEATH

Bcl-2 was one of the earliest regulators of apoptosis discovered in tumor cells, an oncoprotein produced via chromosomal translocation in human follicular lymphoma (1). Later, functional data on Bcl-2 revealed its pro-survival and protective activity against cell death, rather than the ability to drive cell proliferation (2, 3). Bcl-2 is largely localized to the endoplasmic reticulum, nucleus, and mostly to the outer membrane of the mitochondria. Literature over the years has exhaustively demonstrated the physical nature of Bcl-2's anti-apoptotic activity, which acts by sequestering pro-apoptotic proteins such as Bax and Bak at the mitochondria. The latter two are responsible for the formation of oligomers on the mitochondrial outer membrane and thereby perturbing their integrity, resulting in the release of cytochrome *c* to the cytosol, a key event leading to the eventual activation of the intrinsic pathway of apoptosis (4, 5).

Impairment to engage apoptosis to eliminate cells with malfunctioning cell cycle controls not only preserves these aberrant cells but also allow metastasis-causing mutations to roll forward and exacerbate their effects. The snowballing accumulation of mutations further accentuates the function of Bcl-2 as a death brake, conferring a heightened level of chemoresistance (6-8).

The traditional role of Bcl-2 has always been focused on the interactions between the two antagonizing factions of Bcl-2 family of proteins such as Bcl-2/Bcl-xL against Bax/Bak, with the bout-winning parameters defined on a molecular signaling basis which govern several areas from cell death execution to mitochondrial morphology and physiology. More recently, autophagy has also been implicated. However, with the emphasis on mitochondrial bioenergetics and tumor cell metabolism in recent years, several landmark reports have highlighted the unique function of p53 on glycolysis and mitochondrial respiration as well as redefining the biological activity of proteins such as HIF-1 and their regulatory effects on cytochrome *c* oxidase (COX), the terminal complex of the mitochondrial electron transport chain (9-11).

4. BCL-2 AND CELLULAR REDOX STATUS

Bcl-2 was first shown to play a role in altering the redox status of cancer cells by enforcing a slight pro-oxidant state in the intracellular milieu, which has been demonstrated to promote an environment conducive for survival (12). Indeed, studies have revealed that low levels of reactive oxygen species (ROS) are required in proliferative signaling, contrasting widely-held notion that ROS is responsible solely for detrimental and deleterious purposes (13-15). Slight elevations in superoxide (O_2^-) or hydrogen peroxide (H_2O_2) has been shown to trigger growth responses in a variety of cell types and involving a multitude of proteins and pathways from kinase and transcription factor activation to inactivation of phosphatases (16). Through oxidative modification, these molecules are able to initiate, alter or attenuate the various proliferative pathways by acting on the players involved. Removal of these much-maligned molecules by shoring up anti-oxidant defenses has been shown to reverse or decelerate the growth-inducing properties of low levels of ROS (13). However, it is important to note that ROS does not promote proliferation in a linear increasing fashion. An excessive level of ROS is bound to induce oxidative stress and eventual cell death.

The abrogation of proper cellular redox regulation has been attributed a role in cancer onset and progression, with a slight pro-oxidant milieu being commonplace in many tumor types (14, 15). The link between pro-oxidant state and tumorigenesis is corroborated by the involvement of O_2^- in cellular transformation. This association can be negatively regulated by an O_2^- scavenger, MnSOD, which is often found to be compromised or lowly expressed in tumor cells. Enforced expression of MnSOD reverses or decelerates the progression of the invasive phenotype (17-21). Increased activity of O_2^--producing systems and the involvement of growth signaling networks also lent weight to the pro-oxidant theory of tumorigenesis (22, 23).

The notion that ROS has deleterious effects on cells is largely accredited to the observation obtained when cells treated with death stimuli, produced and strewn out a tremendous amount of ROS but more interestingly, in the event of hypoxia, the death signals are still able to transcend through this condition, suggesting that ROS might not be crucial molecules for death execution after all (24-26). On the contrary, low level induction of intracellular ROS such as O_2^- has been shown to inhibit apoptosis in tumor cells in different systems and irrespective of trigger (12, 23, 27-35). In this regard, various studies have demonstrated the apoptosis-inhibitory nature of slightly elevated O_2^- and lowering the species by overexpressing O_2^- scavenger such as SOD resulted in the onset of cell death (32). Clearly, the biological effects conferred by ROS are greatly dependent on the intracellular level and the type of oxygen species involved.

Further studies have gone on to show the intricate balance between intracellular O_2^- and H_2O_2, which is required to incline the tumor cell to either survival or death. Slight elevation in intracellular O_2^- with no appreciable increase in H_2O_2 preserves cell viability through inactivation of the apoptotic pathway (27, 28, 36). Heightened levels of intracellular H_2O_2 leads to a corresponding reduction in O_2^-, creating a reduced environment conducive for apoptosis (36). Incidentally, treatment with anti-cancer drugs also triggers the production of H_2O_2, resulting in oxidative stress and killing (37). Excessive ROS in the form of H_2O_2 brings about the modification of many key cellular components such as cardiolipin, a mitochondrial membrane lipid, which when modified, leads to the formation of compromised membrane integrity and the leakage of cytochrome *c*, triggering the onset of apoptosis (38). The exact

mechanisms by which O_2^- and H_2O_2 promote survival and death respectively are still not well understood although oxidative modifications of apoptosis-associated proteins such as caspases have been implicated (32, 39-41).

5. BCL-2, MITOCHONDRIAL RESPIRATION AND ROS

Bearing the role of ROS in mind, particularly O_2^- and H_2O_2, the effect of Bcl-2 in promoting tumor cell survival has been delineated for further exploratory work in another perspective, from the standpoint of ROS and mitochondrial bioenergetics. On second thoughts, an intracellular pro-oxidant milieu and Bcl-2 may not be such odd bedfellows after all, considering that Bcl-2 is localized to the membranes of mitochondria, ER and nuclear envelope, which are all major sites of ROS production. Conventionally, literature has often described Bcl-2 as an anti-oxidant protein, where its expression is usually coupled to heightened anti-oxidant defenses such as increased expression and activity of SOD enzymes (35). Nonetheless, recent groups have stepped forth to dispute this notion by providing evidence to show that Bcl-2 itself does not induce or exhibit anti-oxidant features in the cell. Rather, it leads to the formation of a pro-oxidant intracellular milieu, which in turn triggers the various anti-oxidant defense systems. This pro-oxidant state has been ascribed as one of the ways in which Bcl-2 facilitates the cell to cheat death. More importantly, this pro-oxidant, survival-enhancing feature of Bcl-2 suggests a specificity for O_2^-, whereby inhibition of a O_2^--producing NADPH oxidase by DPI or disruption of Rac1-mediated O_2^- by introducing a dominant negative form of Rac1, abolished the death inhibition in a Bcl-2 overexpressing background upon treatment with various death-inducing stimuli (12). These reports not only provided an alternative opinion of ROS, away from the traditionally-held notion of detriment to a more balanced and insightful view of the possible effects of ROS in carcinogenesis depending on the levels and species involved; but also soundly established an emerging role for Bcl-2 in terms of death inhibition by facilitating a mild pro-oxidant intracellular milieu through an increase in production of O_2^-.

Subsequently, our group demonstrated that the mitochondria are responsible at least in part, for the pro-oxidant state caused by Bcl-2. Mitochondria, being the powerhouse of the cell's energy needs where molecular oxygen is readily reduced to water for the generation of ATP in a coupled process known as oxidative phosphorylation, are major producers of ROS. It is widely accepted that electron transport between the mitochondrial respiratory complexes is not a completely efficient process and a significant amount of electrons leak from the chain to react with readily available molecular oxygen in the vicinity to form singlet oxygen, otherwise known as superoxide (42, 43). Bcl-2 which is almost ubiquitous at the mitochondria has rarely been linked to the bioenergetics aspect of the mitochondria. In this respect, by measuring the enzymatic activity of COX, which is the rate-limiting complex of the electron transport chain, leukemic tumor cells overexpressing Bcl-2 were found to display increased COX activity and oxygen consumption, which correlated with the increase in O_2^- production. Similar observations were obtained in cervical carcinoma cells. Despite better coupled mitochondrial respiration, Bcl-2 overexpressing tumor cells continued to display elevated oxygen consumption and O_2^- levels, suggesting that increased O_2^- generation is indeed a function of heightened mitochondrial respiration and not due to uncoupling. Increased mitochondrial respiration suggests an increased tendency to leak electrons for the generation of O_2^- as a by-product (44).

Decrease in expression of Bcl-2 by siRNA is able to reverse this pro-oxidant effect. Along similar lines, reduction of mitochondrial respiration through the partial inhibition of COX is able to reduce O_2^- levels in Bcl-2 overexpressing cells to that of non-transfected cells, further substantiating the impact of Bcl-2 on pro-oxidant state through mitochondrial respiration. Serendipitously, induction of excessive mitochondrial ROS led to a down-regulation of COX activity in tumor cells overexpressing Bcl-2, whilst their non-overexpressing counterparts headed in the opposite direction. This phenomenon corresponded to maintenance of intra-mitochondrial O_2^- levels in the Bcl-2 cells whereas the levels in non-overexpressing cells continue to mount despite existing oxidative stress (44).

This unique observation seems to suggest a novel feature of Bcl-2 in the regulation of ROS production within the mitochondria, especially O_2^-. Though it is often reported that cancer cells display altered metabolism traits, preferentially utilizing glycolysis rather than mitochondrial oxidative phosphorylation for the generation of ATP, otherwise known as the Warburg effect (45), an enforced increase in expression of anti-apoptotic Bcl-2 might improve mitochondrial respiration to serve the dual purposes of further enhancing energy production as well as generating more O_2^- as a by-product to provide a slight pro-oxidant milieu inadvertently. Stress stimuli such as substrate/serum deprivation, oxygen depletion or direct ROS inducers triggered a homeostatic response from Bcl-2 to reduce mitochondrial respiration, evident from COX activity; hence, compounding of O_2^- to a deleterious level on top of existing oxidative stress can be avoided, while striving to maintain the basal energy requirement and slight pro-oxidant milieu necessary for survival. Studies seem to put forward the notion of Bcl-2's ability to optimize both the energy needs and redox status of the cell under different growth conditions, modulating and adjusting the mitochondrial bioenergetics parameters to attain an environment best tailored for the survival of the cancer cell. The exact mechanism with which Bcl-2 carries out this function is still under discussion and investigation.

Under a Bcl-2 background, this unusual phenomenon coupled with the Warburg effect provides a formidable protective barrier to the cancer cell when treated with ROS-inducing or oxygen-based chemotherapeutics that aims to stimulate death and mitochondrial dysfunction by bringing about an overwhelming amount of ROS within the cell. The model proposed could also possibly explain why some tumor models have more dominant mitochondrial respiration function than others (46-51). This

emerging role provides an added incentive to target Bcl-2 from a bioenergetics perspective when evaluating chemoresistance or considering potentially novel treatments for cancer.

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