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Research Article

Dually Operative Apoptosis and Anti-Apoptosis Pathogenesis in the Integral Malignant Transformation Event

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Abstract

Determinants in the genesis of a contextually specific and integral malignant transformation event include the further implication of excessive cell cycling that specifically is influenced physically by the action of Surviving in further stabilization of microtubules and in association with other components of the cell mitotic spindle. Concurrent pro-apoptosis and anti-apoptosis events may be considered dually aberrant pathways in the pathogenesis of genomic instability and of genetic mutability/injury that further the progression of tumorigenesis and as enhanced cell cycling.

Introduction

Surviving constitutes a cell-survival mechanism that is markedly over-expressed in malignant tumor cells. This phenomenon has to be assessed within the essential pathogenesis of both abnormal apoptotic cell death and, conversely, of enhanced survival of malignant transformed cells.

Apoptosis therefore constitutes primarily a consequential dimension of abnormal pathogenesis irrespective of any considerations of persistent survival or death of embryonic and fetal affected cells during development. PCTAIRE1/CDK16/PCTK1 is critical in cancer cell proliferation and antiapoptosis and PCTAIRE1 siRNA-lipid nanoparticles may be a novel therapeutic approach in cancer [1]. Homeostatic control of developing fetal cell populations therefore has to be considered within strict parametric contexts of cells that can potentially be inherently pathologic. Beta-arrestin2 down-regulation attenuates TRAIL-induced activation of Src and ERK survival and enhanced TRAIL-induced apoptosis [2].

Thyroid hormone/Thyroid hormone receptor suppresses the pro-apoptotic protein Bim resulting in doxorubicin-induced metastasis of chemotherapy-resistant hepatocellular carcinoma [3]. In fact, therefore, enhanced survival of many types of cells in general and of neoplastic cells constitutes a basic abnormality of cellular homeostasis in its own right and comes to add another biologic level of pathologic involvement even in terms of fetal development. Protein-protein interactions modulate cancer growth and apoptosis, with over-expressed Bcl-2 family members commonly seen in numerous tumors [4].

Dual pathobiology of apoptosis/antiapoptosis

Complex detrimental consequences of anti-apoptosis and of pro-apoptotic phenomena are pathobiologic expression of various disease pathways ranging from cancer cells to the expressed enhancement of multiple cell types ranging from neurons to lymphocyte lineages. Bcl-2 expression decreases in line with excessive proliferation of trophoblast cells in hydatidiform moles and this role changes to antiapoptosis, whereas Beclin-1 is proautophagic in the pathogenesis of gestational trophoblastic disease [5].

Incremental enhancement of apoptotic cell death constitutes a core expression of the inherent disease process per se and would exhibit dynamics of pathogenic disease pathways within the expressed profiles of lesions that typically may proliferate at markedly increased rate. Release of proinflammatory cytokines induces antiapoptosis effects, an effect central to tumor promotion with non-genotoxic carcinogens such as steroid hormones, hypolipidemics and antiepileptics [6].

Mitochondria

Mitochondrial participation in apoptosis, and also of release of surviving from the intermembrane space of mitochondria is inherent manifestation of a series of abnormal pathologic pathways that are superimposed on the excessive proliferation of individual and of clones of neoplastic cells. Hence, apoptotic cell death of tumor cells comes to constitute a superimposed series of pathobiologic pathways that further contribute to the core pathogenesis linked to abnormal cell cycle control manifested in tumorigenesis. Cisplatin inhibits apoptosis of Hela cells through suppression of Bcl-2, and upregulates Bax, Fas-L, and caspase-3 activity; lysophosphatidic acid protects against cisplatin-induced apoptosis [7].

Surviving isoforms

The isoforms derived from the surviving gene and molecule are manifestation of incremental progression of the cancer pathogenic pathways that paradoxically contribute to malignant transformation of clonally proliferating tumor cells. Defining criteria in terms of neoplastic cell cycling are themselves further manifestation of the essential progression of the integral tumor lesion in spite of often significant indices of enhanced apoptotic cell death of some or many of the cells in a neoplastic lesion. Ubiquitination of pro- and

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antiapoptotic proteins are regulated tightly by ubiquitin E3 ligases and deubiquitinases, modulating apoptosis and cell survival [8]. Exogenous Hydrogen sulfide promotes liver cancer cell proliferation, anti-apoptosis, angiogenesis and migration via amplified activation of Nuclear Factor-kappaB pathway; hydrogen sulfide implicates p38 MAPK/ERK1/2-COX2 pathways in C6 glioma cells [9], inducing cell proliferation and anti-apoptosis.

Cell cycling pathogenesis

The pathogenic roles of surviving as a marker of poor prognosis in neoplastic lesions appear to contribute materially to cell cycling abnormalities as evidenced by close physical association with various mitotic spindle components. The determined progression of the individual tumor lesion is further enhanced also by increased apoptotic rate of some of the tumor cells in a manner linked to the accumulation of genetic injury in subsets of the tumor cell population. Such pathogenic forms of genomic injury in the face of subset enhancement of apoptotic cell death would arise due to the development of abnormal outcomes of cell cycle events. Signal transducer and activator of transcription 3 (STAT3) inhibits DNA damage induced by ultraviolet light and also increases the expression of ATR in A431 cells and downregulates the transcription of micro-RNA-383 promoter in skin epithelial cells [10].

Pathway duality

A duality in pathogenic pathways in neoplastic cells is centered on the cell cycling events that implicate parallel series of events that are promoting in different subsets of tumor cells at the onset and during progression of both apoptosis and anti-apoptosis. Cytoprotective processes activated in cancer cells that are chemoresistant are rational targets for research; reversing cytoprotective processes of miR-634 may be broadly useful in cancer therapy [11]. The loss of apoptotic tumor cells therefore comes to contribute to pathogenic pathways in cell cycling events.

This essential coupling of apoptosis and anti-apoptosis pathways with excessive proliferative rates of neoplastic cells is evidence for the initiation of genomic instability and injury that goes beyond the contextual formulation of increased tumor cell numbers. Under hypoxic conditions HIF-1 induces metabolic reprogramming and antiapoptosis, with upregulation of CD147 and MCT-4 in glycolytic reprogramming [12].

Tumorigenesis

Apoptotic cell death of tumor cells is therefore another component in the malignant transformation phenomenon underlying tumorigenesis. The antitumor action of PS-341 that inhibits the proteasome is limited by antiapoptosis pathways, which in turn is possibly induced by activated Nuclear Factor-kappaB [13]. The premise of concurrently evolving apoptosis and anti-apoptosis is therefore suggestive of dual pathway pathogenesis that both paradoxically lead to abnormalities of cell cycling. Tumor hypoxia is linked to upregulation of Livin, a member of the family Inhibitors of apoptosis proteins, with the development of therapy resistance in glioblastoma [14].

Such aberrant cell cycling is linked also to differentiation and de-differentiation schemes in the presence of inflicted genomic injury. The individual tumor is therefore a role-evolving system of potential pathways that concurrently implicate the apoptotic cell death phenomenon in terms also of enhanced anti-apoptotic rates. Sirtinol, a specific inhibitor of the NAD(+)-dependent deacetylase Sirt1, attenuates proliferation and is pro-apoptotic in non-small-cell lung cancer cells [15].

Such complex series of events in individual tumor cells and also in inherent clones of proliferating tumor cells carries forward the progression of neogenesis beyond simple dynamics of enhanced cell cycling. A novel nelarabine-resistant cell line shows reduced drug incoporation within DNA and also antiapoptosis in leukemic cells [16].

The intrinsic nature of the malignant transformation event is expressed within the paradoxical attempts at homeostatic control of cell cycling and cell survival and such integral phenomenon is exhibited within contexts of excessive mitotic spindle formation and the consequent frequent emergence of aneuploidy. Enhancer of zeste homolog 2 correlates positively with vascular endothelial growth factor in clear cell renal cell carcinoma and enhances antiapoptosis and cell cycling in 786 renal cancer cell line [17].

Such genomic instability may be linked to various other component pathways such as mutations of mismatch repair pathways as seen in Hereditary Non-Polyposis colorectal cancer lesions or in Lynch Syndrome patients.

Cell cycling mechanics

The mechanics of genesis of the increased rates of cell cycling in tumors is well-exemplified by survivin pathways that associate closely to various components of the mitotic spindle, including microtubules and centrosomes and kinetochores. PAK5, p21-activated kinase 5, occurs in many tumors and contributes to proliferation, anti-apoptosis and the cytoskeleton and serves as a signal molecule in tumor progression [18]. An integral manifestation of the malignant transformation process comes to be exhibited by effects of apoptosis inhibition within the pathogenic context of proliferating cells that are prone to increased apoptotic cell death that give arise in particular to genomic instability and genetic mutability/injury. Nuclear factor-kappaB transcription factors affect inflammation and immunity, apoptosis and angiogenesis; Amorfrutin A inhibits NF-kappaB activation and inhibits antiapoptosis, proliferation, invasion, angiogenesis and major inflammatory cytokines [19].

Other component pathways

Various component agents such as the pro-apoptotic Smac and the inhibitory apoptotic proteins and also ubiquitin-dependent destruction of bound caspases may evolve as determinant molecular signature pathways implicating especially a caspase-recruitment domain of Inhibitory Apoptosis Proteins. PI3-kinase/Akt activation is anti-apoptotic and hematopoietic cytokines result in expression of survivin. Vascular remodeling of endothelial cells can also develop due to the action of angiopoietin-1.

A general anti-apoptosis may arise also due to the action of fibronectin-dependent cell adhesion. Survivin may therefore be expressed in the absence of effective cell cycling. Interleukin 11 associated with vascular endothelial-cadherin and angiotensin II stimulation may enhance survivin expression, as also vascular endothelial growth factor, Interleukin-6 and Interleukin-10 in pleural effusion lymphoma cells.

Modulated levels of survivin per se may develop when levels are decreased and lead to catastrophic spindle cell events. The chromosome passenger complex binds to kinetochores and is implicated in cytokinesis and in independent modes of interaction with microtubules and mitotic spindle assembly.

Concluding remarks

Dynamic integration of dually active apoptosis and anti-apoptosis pathways is well illustrated by the evolutionary attributes of a malignant transformation event that both permits the emergence of

genomic instability and injury on the one hand but also the emergence of excessive cell cycling. Such phenomena are well-exemplified by survivin modulation of its levels of activity both in dividing and non-dividing cells. In addition, an integral and aberrant modulation of high levels of activity of both pro-apoptotic and anti-apoptotic factors allow for the realization of cell cycling events; such enhanced participants in the genesis of an essential transformation event is progressive in terms arising directly from anti-apoptosis of cells which, in turn, may be prone also, for various reasons, to apoptotic cell death.

References

1. Yanagi T, Tachikawa K, Wilkie-Grantham R, Hishiki A, Nagai K, Toyonaga E et al. "Lipid nanoparticle-mediated siRNA transfer against PCTAIRE1/PCTK1/Cdk16 inhibits in vivo cancer growth" Mol Ther Nucleic Acids 5: 327.
2. Qi Z, Qi S, Gul L, Shen L (2016) "Beta-arrestin2 regulates TRAIL-induced HepG2 cell apoptosis via the Src-extracellular signal-regulated signaling pathway" *Mol Med Rep* 4: 263-270.
3. Chi HC, Chen SL, Cheng YH, Lin TK, Tsai CY, et al. (2016) "Chemotherapy resistance and metastasis-promoting effects of thyroid hormone in hepatocarcinoma cells are mediated by suppression of FoxO1 and Bim pathway" *Cell Death Dis* 7: 2324.
4. Beekman AM, O'Connell MA, Howell LA (2016) "Identification of Small-Molecule inhibitors of the antiapoptotic protein myeloid cell leukemia-1 (Mcl-1)" *ChemMedChem* 11: 840-844.
5. Wargasetia TL, Shahib N, Martaadisoebrata D, Dhianawaty D, Hernowo B, et al. (2015) "Characterization of apoptosis and autophagy through Bcl-2 and Beclin-1 immunoexpression in gestational trophoblastic disease" *Iran J Reprod Med* 13: 413-420.
6. Riegler T, Nejabat M, Eichner J, Stiebellehner M, Subosits S, et al. (2015) "Proinflammatory mesenchymal effects of the non-genotoxic hepatocarcinogen Phenobarbital: a novel mechanism of antiapoptosis and tumor promotion" *Carcinogenesis* 36:1521-1530.
7. Sui Y, Yang Y, Wang J, Li Y, Ma H, et al. (2015) "Lysophosphatidic acid inhibits apoptosis induced by cisplatin in cervical cancer cells" *Biomed Res Int* 2015:598286.
8. Asaoka T, Ikeda F (2015) "New insights into the role of ubiquitin networks in the regulation of antiapoptosis pathways" *Int Rev Cell Mol Biol* 218: 121-158.
9. Zhen Y, Zhang W, Liu C, He J, Lu Y, et al. (2015) "Exogenous hydrogen sulfide promotes C6 glioma cell growth through activation of the p38 MAPK/ERK1/2-COX-2 pathways" *Oncol Rep* 34: 2413-2422.
10. Liao XH, Zheng L, He HP, Zheng DL, Wei ZQ, et al. (2015) "STAT3 regulated ATR via microRNA-383 to control DNA damage to affect apoptosis in A431 cells." *Cell Signal* 27: 2285-2295.
11. Fujiwara N, Inoue J, Kawano T, Tanimoto K, Kozaki K, et al. (2015) "miR-634 activates the mitochondrial apoptosis pathway and enhances chemotherapy-induced cytotoxicity" *Cancer Res* 75: 3890-3901.
12. Ke X, Chen Y, Wang P, Xing J, Chen Z, et al. (2014) "Upregulation of CD147 protects hepatocellular carcinoma cell from apoptosis through glycolytic switch via HIF-1 and MCT-4 under hypoxia" *Hepatol Int* 8: 405-414.
13. Lee KH, Jang AH, Yoo CG (2015) "17-Allylamino-17-Demethoxygeldanamycin and the enhancement of PS-341-induced lung cancer cell death by blocking the NF-KappaB and PI3K/Akt pathways" *Am J Respir Cell Mol Biol* 53: 412-421.
14. Hsieh CH, Lin YJ, Wu CP, Lee HT, Shyu WC, et al. (2015) "Livin contributes to tumor hypoxia-induced resistance to cytotoxic therapies in glioblastoma multiforme" *Clin Cancer Res* 21: 460-470.
15. Fong Y, Lin YC, Wu CY, Wang HM, Lin LL, et al. (2014) "The antiproliferative and apoptotic effects of sirtinol, a sirtuin inhibitor on human lung cancer cells by modulating Akt/beta-catenin-Foxo3a axis" *ScientificWorldJoural* 2014: 937051.
16. Yamauchi T, Uzul K, Nishi R, Shigemi H, Ueda T, et al. (2014) "Reduced drug incorporation into DNA and antiapoptosis as the crucial mechanisms of resistance in a novel nelarabine-resistant cell line" *BMC Cancer* 14: 547
17. Xu ZQ, Zhang L, Gao BS, Wan YG, Zhang XH, et al. (2015) "EZH2 promotes tumor progression by increasing VEGF expression in clear cell renal cell carcinoma" *Clin Transl Oncol* 17: 41-49.
18. Wen YY, Zheng JN, Pei DS (2014) "An oncogenic kinase: putting PAK5 forward" *Expert Opin Ther Targets* 18: 807-815.
19. Shi H, Ma J, Mi C, Li J, Wang F, et al. (2014) "Amorfrutin A inhibits TNF-alpha-induced NF-kappaB activation and NF-kappaB-regulated target gene products" *Int Immunopharmacol* 21: 56-62.