ISSN: 2476-2377

Short Communication

International Journal of Cancer Research & Therapy

Briefly about Apoptosis

Siniša Franjić*

Independent Researcher

***Corresponding author**
Siniša Franjić, Independent Researcher

Submitted: 06 May 2022; **Accepted:** 18 May 2022; **Published:** 26 May 2022

Citation: *Siniša Franjić, (2022). Briefly about Apoptosis. Int J Cancer Res Ther, 7(2), 82-86.*

Abstract

Apoptosis is a type of cell death. It is also called programmed cell death because the cells follow a series of instructions that tell them how to die. These instructions allow the cell to die without damaging the healthy cells around it. A cell that dies by apoptosis is called an apoptotic cell or apoptotic body. Over time, all healthy cells age and become damaged, and some of these cells will naturally go through this type of cell death. In other circumstances, the body uses this process to get rid of cells that are no longer needed.

Keywords: Apoptosis, Cells, Proteins, Genes

Introduction

While to date cancer has been discussed simply in relation to uncontrolled cell proliferation, there's another important counter-balance to cell growth, namely that of cell death [1]. Cell death could be a natural feature of cells that happens in damaged cells, and also during development, as an example, within the foetus the development of our fingers arises from the death of the online of cells between the fingers. This process of cell death is thought as apoptosis. it's a highly regulated and biochemically defined process, distinct from simple necrosis (where cells simply spill over their contents). Cells that have extensive genetic damage often spontaneously undergo apoptosis, and in effect "commit suicide" for the greater good of the host. this is often a vital mechanism for suppressing tumour development. Indeed, the main aim of chemotherapy and radiotherapy is to induce such extensive genetic damage in tumours that the cancer cells undergo apoptosis. Cells that escape, or evade, this apoptotic process form tumours that are more resistant to chemotherapy and radiotherapy, and are related to poor prognosis.

Proteins

The changes in DNA that occur in cells that become cancerous result in changes within the expression of the many proteins, some of which play critical roles within the malignant behavior of the cells [2]. These include cyclins, proteins that function co-factors to enzymes that regulate progression through the cell cycle. Alterations that occur in cancer can cause high levels of several cyclin proteins independent of the standard signals for his or her production. In general, women with breast cancer who exhibit low levels of cyclin E expression and high levels of cyclin D1 expression are significantly less likely to die from their breast cancer than women with high levels of cyclin E and low levels of cyclin D1. African American women had higher levels of cyclin E (OR [odds ratio] = 4.3) and lower levels of cyclin D1 expression (OR = 0.5) than Caucasian women in their breast cancer cells, potentially contributing to the more serious outcome for African American women.

One of the foremost common events within the development of cancer involves the tumor suppressor protein p53 that's mutated or eliminated in over 50% of human cancers. Protein p53 may be a transcription factor that's induced when abnormal DNA is present or under cellular stress, and it results in expression of multiple proteins, including proteins that inhibit DNA replication, help repair damaged DNA, and induce programmed cell death—all functions that are designed to protect the integrity of the DNA. When the function of p53 is disrupted, cells with damaged DNA are more likely to be propagated and acquire more mistakes. The mutations within the p53 gene (TP53) that most commonly occur in tumors result in a stabilization of the protein and a loss of its ability to function as a transcription factor, in order that high levels of p53 protein reflect loss of p53 function. Patients with stage I and II breast cancers displayed no difference within the frequency of TP53 gene alterations between African Americans (20%) and Caucasians (19%), but there have been differences within the types of TP53 alterations that were encountered. When more advanced stages were included within the analysis, tumors of African Americans (OR = 1.7) more frequently displayed high levels of mutant p53 protein expression when compared to the tumors of

Caucasians. In general, tumors that display high levels of mutant p53 have a more aggressive phenotype, are less likely to retort to adjuvant therapy, and thus might contribute to the more serious outcome of African American patients.

Genes

Different genes are related to different cancers as an example the BRCA1 gene is commonly related to either breast cancer or ovarian cancer [1]. The BRCA2 gene are often related to either breast cancer or pancreas cancer. Recent studies have also shown a link between the BRCA2 gene and prostate cancer, particularly prostate cancer in younger men.

The p53 gene is that the gene most ordinarily related to a broad spectrum of cancers. This gene is responsible for coordinating the cellular response to DNA damage, be it a transient growth arrest to permit the cell to repair the DNA damage, or to instruct the cell to commit suicide via apoptosis if the damage was too great. p53 protein could be a transcription factor that switches on expression of genes that regulate the cell cycle and cause growth arrest and apoptosis. Accordingly, it's been called the guardian of the genome due to its role in indirectly maintaining the coding integrity of the genetic blueprint. Approximately half of all cancers carry an abnormal (mutated) p53 gene, and have lost the other normal copy. Every normal cell has two copies of each gene (except some genes of the Y chromosome in males). The mutation of one p53 gene, leaves the other one potentially active and ready to regulate cell growth and apoptosis. However, the mutant p53 gene makes a protein that inactivates the conventional p53 by binding to the conventional protein and inactivating the conventional p53 protein. Since the protective role of normal p53 protein is now overcome the genetic material is unstable and also the remaining normal p53 gene is deleted from its position on chromosome 17. The mutation of 1 gene followed by the loss of the remaining normal gene may be a common feature of tumour suppressor genes. The mutant p53 gene by indirectly promoting cancer behaves as an oncogene, therefore the p53 gene, can behave as both a tumour suppressor or an oncogene depending on whether or not it's mutated.

BRCA1 and BRCA2 also are tumour suppressor genes and just like the p53 gene make a protein that contains a role in switching on gene expression, and is involved with DNA repair and regulation of the cell cycle.

All tumour suppressor genes, play a modulating or inhibitory role in cell growth and differentiation. Factors that impair or damage these genes can therefore be carcinogenic.

Age

The incidence of common cancers increases with age [3]. This association is universal and is observed with the aging of any population around the world. A transparent explanation of this phenomenon is that the time-length of carcinogenesis, a stepwise process involving the activation of cellular oncogenes, and also the suppression of anti-proliferative genes (antioncogenes). It's reasonable to assume that the duration of carcinogenesis reflects the amount of stages involved within the pathogenesis of various tumors, which this number be highest for tumors whose incidence peaks late in life, like adenocarcinoma of the prostate and of the large bowel, or non-melanomatous skin cancer. within the era of chemoprevention and recognition and elimination of environmental carcinogens, an alternate possibility should be considered. These interventions may cause the prolongation of 1 or more carcinogenic steps and, in so doing; they will delay the development of cancer. as an example, the incidence of lung cancer has decreased for people less than 60, while it's increased for older individuals. As a result, the peak incidence of lung cancer has become more and more delayed. Interestingly, these changes have paralleled the incidence of smoking cessation within the Western population. during this case it's reasonable to assume that the length of carcinogenesis has increased as a results of a prolongation of the late carcinogenic stages, from reduced intensity of exposure to tobacco smoke. If this hypothesis is correct, one may expect to determine a progressive delay within the appearance of common cancer and an increased incidence of neoplasia in advanced ages.

The duration of carcinogenesis might not account completely for association of cancer and aging. The incidence of some neoplasms, like prostate and non-melanomatous skin cancer increases earlier with age, than it might be expected from the time-length of carcinogenesis alone. These findings suggest that the concentration of cells in advanced carcinogenic stages increases with the age of an organism, enhancing the susceptibility of older individuals to environmental carcinogens.

For completeness, other biological changes of aging, beside advanced carcinogenesis, may favor the development of cancer. Immunesenescence may facilitate the expansion of highly immunogenic tumors, while proliferative senescence may end in loss of cellular apoptosis, and therefore the production of tumor growth factors and proteolytic enzymes that promote the expansion and also the spreading of cancer respectively.

Does the incidence of cancer increase indefinitely with age? the solution to those question as become highly relevant with the progressive aging of the Western population and with the expansion of the oldest segment of the population (those 85 and older), that's increasing quicker than the other segment.

Causes

For generations doctors, researchers, other health workers, philosophers, unconventional practitioners and sometimes “quacks” are trying to find a single cause for all cancers, and consequently a single cure [1]. No such cause has been found and doubtless none exists. many alternative factors initiate changes in cells that result in cancer. Current evidence would suggest that each one causes of cancer act by generating damage to the genetic blueprint of cells, specifically causing mutations in proto-oncogenes and tumour

suppressor genes. In many cases the mutations in such genes will be linked on to the categories of DNA damage related to the agents that cause cancer e.g. UV-light and tobacco tar, and every has its own signature type of DNA damage, providing evidence of "direct cause and effect". Even tumour viruses cause cancer by altering the cell's genetic blueprint, either by directly altering the expression of proto-oncogenes, or indirectly, through the inactivation of tumour suppressor proteins, in effect, over-riding the genetic blueprint. Today it's believed that cancer arises from one cell that has acquired 6–12 genetic changes (mutations) in key tumour suppressor and proto-oncogenes. This explains the clonal origin of cancers, and why cancer incidence increases with age, thanks to the sequential accumulation of those mutations; and also why some familial cancers are inherited at an earlier age, as such individuals would have already got one in all these pre-disposing mutations at birth. While we will minimise our own risk of cancer by adopting a healthy life-style, we cannot completely eliminate the risk, as within all our cells are natural metabolites that may potentially cause such mutations.

Initiation

EtOH-induced (Ethanol) ROS (Reactive oxygen species) production and lipid peroxidation are important issues because they induce genetically programmed cell death (apoptosis) [4]. Initiation of apoptosis can begin by the extrinsic pathway or the intrinsic pathway. The intrinsic pathway begins within the cell and may be initiated with DNA damage, oxidative stress directed against the mitochondrial membrane, and/or the transcription of oncogenes that, in turn, promote transcription of proapoptotic genes within the Bcl-2 (B cell lymphoma 2 protein) family of genes. within the intrinsic pathway, DNA damage can promote the synthesis of p53, and elevated p53 levels promote the expression of proapoptotic Bcl-2 family genes, including Bax (Bcl-2-associated X protein), BH-3-only proteins including Noxa (Latin for damage), and PUMA (p53-upregulation modulator of apoptosis). Increased Bax, Noxa, and PUMA levels and oxidative damage directed against the mitochondrial membrane all have the ability to cause mitochondria to release cytochrome c from mitochondria into the cytoplasm. Upon crossing into the mitochondria, several reactive aldehydes, including HNE (4-hydoxynonenal), HPNE (4-hydroperoxy-2-nonenal), and ONE (4-oxo-2-nonenal), are known to cause increased mitochondrial membrane permeability and are related to the discharge of cytochrome c from the mitochondria into the cytoplasm. Increased cytoplasmic cytochrome c levels facilitate the formation of activated apoptosomes (active apoptosome: APAF-1 (Apoptotic protease activating factor-1), caspase-9, and cytochrome c). Activated caspase-9, within activated apoptosomes, cleaves and activates effector (killer) caspases including caspase-3, caspase-6, and caspase-7. Caspase-3 could be a protease that cleaves any protein with a DEVD sequence (aspartic acid-glutamic acid-valine-aspartic acid) and has been used as a marker of EtOH-induced apoptosis within embryos. Thus, the rapid destabilization of the mitochondrial membrane is a component of the intrinsic pathway.

The extrinsic pathway is initiated at the cell membrane with the activation of receptor proteins that possess death domains (death-inducing signaling complex; DISC). The binding of a ligand, like tumor necrosis factor, Fas-ligand, TRAIL-ligand, or Apo 3-ligand, or the deprivation of a growth factor causes the activation of membrane receptors that possess death domains (DISC), and EtOH-induced apoptosis via the Fas-ligand receptor is additionally well documented. DISC signaling activates variety of adaptor molecules including FADD and caspase-8. Caspase-8 cleaves proteins that have IETD domains (isoleucine-glutamic acid-threonine-aspartic acid). Activated capase-8 activates effector (killer) caspases (caspase-3, caspase-6, and caspase-7) and/or cleaves a BH-3 protein called Bid (BH-3-interacting death domain). Once cleaved, truncated Bid will incorporate into the mitochondrial membrane and promote the discharge of cytochrome c. Once within the cytoplasm, cytochrome c will activate apoptosomes and effector caspases including caspase-3, caspase-6, and caspase-7. it's also known that EtOH-induced apoptosis can proceed through the activation of cell membrane-bound death-inducing signaling complexes (DISC), annexin-V involvement, poly(ADP-ribose) polymerase (PARP) involvement, p53 involvement, and PUMA (p53-upregulation modulator of apoptosis) involvement. Thus, ethanol can stimulate apoptosis by both the extrinsic pathway, which then spreads to mitochondrial dysfunction.

Cancer Cells

As cancer cells grow uncontrollably during a limited space, compressive forces are generated inside the tumor [5]. The increase in growth-induced stress ends up in signicant deformation of the tumor microenvironment. Although the intratumoral region is in compression, the periphery of a tumor is in tension because of shear stresses. The peripheral tensile stress provides a smooth transition between high-compressive stresses inside the tumor and stresses within the surrounding normal tissue. In some cases, the resulting intratumoral compression will be escalated to level that results in pinching and occlusion of blood and lymphatic vessels. The compression of blood and lymphatic vessels limits the delivery of nutrient, oxygen, and medicines and might create a hypoxic microenvironment. The lack of nutrient and oxygen supply can also cause the formation of necrotic tissues inside the tumor. At the identical time, this compression is believed to protect cancer cells from the immune system of the host, allowing them to access oxygen and nutrients that are essential for tumor progression. The compression of blood vessels causes the blood ow to be decreased and vascular shunts to be formed and limits drug delivery to certain regions (especially in large tumors).

The compression also has an eect on the extracellular matrix (ECM), which, in turn, exerts forces that are capable of changing cell shape and cytoskeletal organization. Is inuences the proliferation and apoptosis of tumor cells, remodels the cytoskeleton organization, and has an effect on the migration process of cancer cells. The compressed cells undergo a phenotypic transformation, become leader cells, adhere better to the substrate (due to larger cell–substrate contact areas), and participate in an exceedingly collective or coordinated migration. The presence of a moderate level

of continuous compressive forces is benecial for cell motility and enhanced migration; however, excessive amounts are detrimental thanks to the resultant increased cell death, which is an impediment to cell migration. Cell compression changes the stromal cell function, the synthesis and organization of ECM, the gene expression, and therefore the invasiveness of the cells.

Apoptotic Cells

Besides having the ability to cause cell cycle arrest, chemopreventive compounds also can induce apoptosis [6]. Thus another method to see whether a compound has good chemopreventive or therapeutic activity is to judge its ability to induce apoptosis. The apoptotic program is characterized by certain morphological features, including loss of plasma membrane asymmetry and attachment, condensation of the cytoplasm and nucleus, and internucleosomal cleavage of DNA. In apoptotic cells, the membranous phospholipid phosphatidylserine (PS) is translocated from the inner leaflet to the outer leaflet of the plasma membrane, thereby exposing the PS to the external cellular environment. Annexin V, a 35–36 kDa Ca 2+ dependent phospholipid-binding protein includes a high affinity for PS and thus is ready to bind to apoptotic cells with exposed PS. When conjugated to fl uorochromes including FITC, Annexin V can function a sensitive searched for analysis of apoptotic cells by flow cytometry. Because externalization of PS occurs within the earlier stages of apoptosis, FITC-Annexin V staining can detect apoptosis at an earlier stage than assays supported nuclear changes like DNA fragmentation. during this way, FITC- Annexin V is often employed in conjunction with nucleic acid dye like propidium iodide (PI) to permit the investigator to identify early apoptotic cells (i.e., PI negative, FITC-Annexin V positive) from the late apoptotic cells (i.e., both PI and FITC-Annexin V positive), because only membranes of dead and damaged cells (late apoptotic cells) are permeable to PI, whereas viable cells with intact membranes exclude PI.

Cleavage of genomic DNA during apoptosis yields doublestranded, low relative molecular mass DNA fragments likewise as singlestrand breaks in high relative molecular mass DNA. These DNA strand breaks is identified by labeling the free 3′-OH termini with modifi ed nucleotides in an enzymatic reaction. The terminal deoxynucleotidyl transferase (Tdt) enzyme will add nucleotides to the 5′ ends of DNA fragments in apoptotic cells. A labeled nucleotide is employed, which may subsequently be visualized. Before fixation in ethanol, the cells are fixed in formaldehyde (typically 1 Samuel para - formaldehyde), so as to cross-link the DNA fragments into the cell and to maximise the amount of broken DNA ends. The TUNEL reaction may be a precise, fast, and nonradioactive technique to detect and quantify apoptotic cell death at one cell level in cells and tissues. By preferentially labeling DNA strand breaks generated during apoptosis, the TUNEL assay allows one to distinguish apoptosis from necrosis and from primary DNA strand breaks induced by potential chemopreventive compounds.

Proliferation

Apoptosis is an evolutionarily conserved, highly regulated mechanism for maintaining homeostasis in multicellular organisms [7]. Numerous signals are capable of modulating cell death. After a death stimulus, the signal is propagated and amplified through the activation by proteolytic cleavage of caspases, culminating within the ordered disassembly of the cell. the process may transpire through a mitochondrial-dependent or -independent pathway, looking on the death signal and cell type involved. The Bcl-2 family of proteins is situated upstream of irreversible cell damage within the apoptotic pathway, providing a pivotal checkpoint within the fate of a cell after a death stimulus. The proapoptotic molecules BID, BAD, and BAX undergo modification and intracellular translocation on receipt of a death stimulus, connecting distinct upstream signal transduction pathways with the common, core apoptotic pathway. The distribution of inactive conformers of the BH3-only members suggests that they will function as sentinels for recognizing cellular damage. BIM would monitor microtubule function, BID would amplify minimal caspase 8 activation, and BAD would patrol for metabolic stress after loss of critical survival factors. This model would explain how seemingly diverse cellular injuries converge on a final common pathway of necrobiosis.

The cellular pathway to apoptosis appears to communicate with the pathway for cell proliferation. As a result, activation of cell proliferation by oncogenes also ends up in sensitization to apoptosis. Reciprocally, the expression of antiapoptotic molecules often retards cell-cycle progression. This interconnection provides a means for limiting the threatening expansion of cells with a lesion in either pathway. These observations fit the evidence that defects are required in both proliferation and cell death pathways, as single defects tend to be self-correcting in their net effect on cell number. The molecules mediating apoptotic pathways provide an exciting opportunity for rational design of recent therapeutic agents to specifically promote apoptosis of cancer cells.

Infammation

Infammation and immune system are activated to eliminate pathogens and non-self molecules or, at least, to manage their dissemination or systemic colonization of the organism [8]. At the same time these physiological responses induce repair mechanisms to recover tissue function and integrity. When transformed cells (expressing non-self molecules) aren't killed by the immune response and also the tumor starts to grow in an organism, tumor mass isn't an extraneous parasitic body but a complex organized tissue formed by both transformed and normal stromal cells in an exceedingly symbiotic relationship that sustains the expansion of the tumor and eventually favors its dissemination to distant tissues. this can be reminiscent of an organism's relationship with infectious pathogens that, within the case of chronic infections, establish a near-symbiotic relationship with the reactive surrounding tissues, often reorganized in specifc anatomical structures like the granulomas.

Only 15% of tumors may be attributed to a carcinogenic infection. Some pathogens infecting humans that directly induce cell transformation are human papilloma virus (HPV), epstein-barr virus (EBV), or human T-lymphotropic virus-I (HTLV-I). Other viruses (e.g., hepatitis viruses) or bacteria like Helicobacter pylori favor carcinogenesis by inducing chronic infammation within the infected tissues. In fact, most human tumors originate from tissues with sterile chronic infammation (and a tumor-promoting effect of infammation is now suspected also for transforming viruses).

Chronic infammation affects all phases of carcinogenesis. Infammation favors the initial genetic mutation, functional protein modifcations, or epigenetic mechanisms that drive cell transformation and cancer initiation. For instance, ROS and reactive nitrogen species (RNS) can induce DNA strand breaks, single-base or more complex DNA mutations, and epigenetic modifcations in proto-oncogenes, tumorsuppressor genes, and other genes encoding proteins that control apoptosis, survival, DNA repair, and cell-cycle checkpoints, predominantly in stem cells that become cancer stem cells (CSCs). additionally, these tissue-dependent infammatory responses recruit hematopoietic infammatory cells. The leukocyte population present on a developing cancer is quite diverse and includes neutrophils, dendritic cells, macrophages, and lymphocytes, all of them capable of secreting a series of cytokines, ROS, membrane-perforating agents, or IFNs, molecules that contribute to the infammatory milieu present in a very developing tumor, participating in its growth and within the dissemination of transformed cells. as an example, although tumor-associated macrophages contribute to the elimination of transformed cells once activated by cytokines, they also produce potent angiogenic and growth factors like VEGF-C and -D that potentiates neoplastic progression.

Conclusion

Apoptosis is a process of programmed cell death that can occur in multicellular organisms. Biochemical processes lead to changes in cell characteristics and death. These changes include cell metering and shrinkage, nuclear fragmentation, condensation and fragmentation of chromatin and chromosomal DNA. Unlike necrosis, which is a form of traumatic cell death resulting from acute cell injury, apoptosis generally benefits the body throughout its life cycle. Apoptosis also produces cell fragments called apoptosis bodies that phagocytic cells can quickly swallow and remove before the cell contents can spill onto surrounding cells and cause damage.

References

1. Aigner, K. R., & Stephens, F. O. (2009). Basics of Oncology. Springer-Verlag Berlin Heidelberg.
2. Sylvester B, Olopade, O. I, Offermann, M. K., (2012). The Biology of Cancer and Its Relationship to Disparities in Cancer Occurrence and Outcomes" in Elk, R.; Landrine, H. (eds): Cancer Disparities - Causes and Evidence-Based Solutions", American Cancer Society, Springer Publishing Company, LLC, New York, USA, pp. 18. - 19.
3. Balducci, L., & Extermann, M. (Eds.). (2005). Biological basis of geriatric oncology (Vol. 124). Springer Science & Business Media.
4. Miller, R. R. (2013). Ethanol-induced lipid peroxidation and apoptosis in embryopathy. In Alcohol, Nutrition, and Health Consequences (pp. 35-62). Humana Press, Totowa, NJ.
5. Pourmohammadali, H.; Kohandel, M.; Sivaloganathan, S. (2018). Biomechanics of Cancer in Al-Mayah, A. (ed), Biomechanics of Soft Tissues - Principles and Applications, CRC Press, Taylor & Francis Group, Boca Raton, USA, pp. 96. - 97.
6. Tang, M., Yu, X., Jiang, Y., Shi, Y., Liu, X., Li, W., & Cao, Y. (2014). Common Methods Used for the Discovery of Natural Anticancer Compounds. In Cancer Prevention (pp. 33-52). Humana Press, New York, NY.
7. Korsmeyer, S. J., & Zinkel, S. S. (2001). Molecular biology of cancer: apoptosis. Cancer Principes & Practice of Oncology, 6.
8. Cordero, O. J., Varela-Calviño, R., & Graña-Suárez, B. (2020). Immunology and Immunotherapy of Colorectal Cancer. In Cancer Immunology (pp. 261-289). Springer, Cham.