Apoptosis-Induced Compensatory Proliferation in Cancer

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Abstract

Apoptosis is a biological process that allows adequate cellular turnover and the elimination of damaged or infected cells. However, there are compensatory molecular mechanisms that promote cell proliferation after increased apoptotic events. These events are commonly mediated by mitogenic proteins, released by apoptotic cells, and received by neighboring cells, that trigger mechanisms similar to cell repair after an injury or traumatic event. This
effect is known as "apoptosis-induced proliferation". This chapter addresses the process of apoptosis-induced proliferation, the regulatory mechanisms, and its importance in cancer development, progression, and therapy development.

**Key words**: apoptosis-induced proliferation; cancer proliferation; extrinsic pathway of apoptosis; intrinsic pathway of apoptosis; JNK signaling pathway

**Running title**: Apoptosis-Induced Proliferation in Cancer

**INTRODUCTION**

Apoptosis, commonly referred to as "programmed cell death", is a natural or induced process by which senescent or damaged cells are eliminated via a self-destructive but orderly mechanism. This mechanism causes the destruction of proteins involved in cell survival, growth, and membrane integrity, finally leading to DNA breakdown without inflammation (1). Apoptosis is orchestrated by several signaling pathways, among which the cystein-aspartic proteases (caspases) stand out as proteolytic regulators of multiple proteins involved in this process (2). Apoptosis, on one hand, has been a therapeutic target for cancer because of its ability to control the proliferation of transformed cells. On the other hand, there are compensatory mechanisms after the increased induction of apoptosis that promote cell proliferation, either from dying or neighboring cells (1,2). In cancer therapy, this process is of great importance because it can generate resistance or insensitivity to treatments. Interestingly, many of the compensatory mechanisms of cell proliferation are mediated by caspases, which have been observed to have a role beyond cell death by regulating signaling pathways related to proliferation, survival, repair, and cellular inflammation, triggering the apoptosis-induced proliferation process (AiP).

**WHAT IS APOPTOSIS-INDUCED PROLIFERATION?**

AiP is a compensatory proliferation process that has been observed to be active during programmed cell death and is associated with cell turnover during the development of an organism or tissue damage (3). The first findings of this process were observed in 1977 in *Drosophila melanogaster* (*D. melanogaster*) wings, and later studies demonstrated the
implication of caspases in this process (4). It is believed that, in epithelial cells, this process allows cell turnover in an orderly manner, allowing a balance between dying and nascent cells. This occurs through the release of mitotic signals from the apoptotic cell to the microenvironment, activating neighboring cells in a process similar to that has been observed in wound repair (5). It has been shown that dying or apoptotic cells trigger mitotic signals that lead to the activation of stem cells in which caspase-3 and caspase-7, considered effectors of cell death, actively participate thus becoming promoters of tissue regeneration. The activation of phospholipase A (PLA) is a repeatedly observed mechanism, which promotes increased synthesis of prostaglandin E2 (PGE2) (6) by cyclooxygenase-2 (COX 2), and whose increased activity is associated with tumor growth and resistance of tumor cells to chemo and radiotherapy (7).

The expression levels of effector caspases are important to carry out cell death; caspases are known to cleave around 1000 protein substrates, so the number of active caspases is related to their biological activity (6). It has been observed that TGF-β (tumor growth factor beta) and Wnt pathways are commonly mediated by caspases as well as the signaling pathways mediated by Notch (neurogenic locus notch homolog protein 1) and JAK-STAT (Janus kinases/signal transducer and activator of transcription proteins); however, the triggering mechanisms and the intermediate molecules involved in these pathways are not entirely clear (8). Studies in D. melanogaster showed that, although the two existing isoforms of the p53 protein (Dp53 and DΔNp53, N-terminally truncated isoform) are capable of inducing apoptosis, only the DΔNp53 isoform promotes AiP. This process inhibits the D. melanogaster proapoptotic protein 1 (DIAP1) and induces the Wg protein (Wnt homologous) more efficiently than the “complete” form of the p53 protein (9).

On the other hand, Myo1D, a myosin involved in the left/right development of the visceral organs of D. melanogaster, is an important mediator of AiP; Myo1D translocates Dronc (Drosophila Nedd2-like caspase) to the basal side of the membrane of disc epithelial cells and salivary gland cells, leading to increased ROS production and the involvement of Myo1D in the process of cell growth and migration, promoting the process of AiP and tumorigenesis. Therefore, it was proposed that the basal side of epithelial cells is associated with a non-
apoptotic compartment of caspases. The location of Dronc-caspase in the plasma membrane was observed to also stabilize it in undead cells, promoting the activation of Dronc-caspase and the degradation of proteins (10). Furthermore, the outer mitochondrial membrane has been shown to provide a non-apoptotic scaffold for the activation of Dronc-caspase, which occurs during sperm maturation (11). Membranes can provide a microenvironment for non-apoptotic caspases, and their activation resulting from incomplete permeabilization of the outer mitochondrial membrane (MOMP) can induce DNA damage, genomic instability, and promote tumorigenesis (12).

MECHANISMS OF APOPTOSIS-INDUCED PROLIFERATION
AiP involves multiple processes such as apoptosis, the induction of proliferation mediated by caspases, and changes in the mechanisms that involve the JNK (c-Jun N-terminal kinase) signaling pathway. Apoptosis can be achieved by the extrinsic pathway, caused primarily by cytotoxic T cells of the immune system and the intrinsic pathway, initiated by DNA damage or loss of mitochondrial membrane potential.

Extrinsic pathway of apoptosis
The extrinsic pathway is triggered by external signals that are transmitted mainly by innate immune natural killer (NK) cells, and by adaptive CD8⁺-positive cytotoxic T lymphocytes (CTL). Both cell types can detect and induce death of infected cells or mutated cells (13). This pathway begins with the interaction of the tumor necrosis factor receptor (TNFR) with its ligand (TNF), which can be found in soluble form or bound to CTL membrane, which has a death domain that functions as a coupler of a large group of proteins that form a death complex. This process allows caspase-8 activation (14), which in turn promotes caspase-3 activity, considered the great effector of apoptosis. Caspase-3 blocks DNase inhibitors preventing gene transcription and the division of genetic content, which promotes the breakdown of actin sheets, thus interfering with the process of cell division (15,16).

Intrinsic pathway of apoptosis
On the other hand, intrinsic apoptosis is associated with the loss of permeability of the mitochondrial membrane, which allows the increase of pro-apoptotic proteins such as
cytochrome c. This process is regulated by proteins of the Bcl-2 family, such as Bax, and Bcl-2 itself. The entry of Bax through the transition pore of mitochondrial permeability and the exit of Bcl-2, promotes the release of cytochrome c to the cytosol, which forms a protein complex with the apoptotic peptidase activating factor 1 (APAF1). This complex is known as apoptosome, which promotes caspase-9 activity, and in turn, the activation of caspase-3 (17).

**Role of caspases in cell proliferation and survival**

Mammalian caspases can be broadly divided into apoptotic (caspases -2, -3, -6, -7, -8, -9 and -10) and inflammatory (caspases -1, -4, -5, -11 and -12) (18). Non-apoptotic activity of caspases has recently been observed through the proteolytic effect on cytokines, kinases, transcription factors and polymerases, as well as non-proteolytic interactions with FLICE (cellular caspase-8 inhibitory protein), human caspase-12, coat complex protein (COP), inhibitory caspase-associated recruitment domains (INCA) and ICEBERG (inhibitor of generation of IL-1beta by interacting with caspase-1), which actively participate in cell survival, proliferation, differentiation, and inflammation (19).

In immune system cells, it has been observed that the activation of caspase-8 by the T cell receptor (TcR) and its association with the protein FADD (Fas-associated Death Domain), promotes the activation of NF-κB, resulting in the production of cytokines and chemokines, which in turn promote inflammation, immune response, survival, and cell proliferation (20). It has also been observed that caspase-8 deficiency in patients leads to serious immunodeficiencies, mainly by bacterial infections, which can result in patient death due to the lack of activation of T lymphocytes, B lymphocytes, and NK cells (21).

On the other hand, caspase-3 activity is widely related to cell growth and tumor progression. In cells deficient in caspase-3 (caspase-3KO), fewer tumor cells were observed based on their proliferative and invasive capacity. Cells that are caspase-3KO show greater sensitivity to mitomycin C and radiation, demonstrating the importance of this enzyme in cancer progression, especially in invasion mechanisms (21). In the same way, caspase-3 is also necessary for the production of VEGF-A (vascular epithelial growth factor A) during
angiogenesis, which keeps tumor cells alive, especially during the development of metastasis. Caspase-7 has been known to be involved in the activation of IPLA2 (intracellular phospholipase 2), but its role has recently evidenced in the activation of protein kinase C delta (PKCδ), which induces Akt phosphorylation (also called protein kinase B), p38 and JNK1/2, activating mitogens to repopulate tumors after radiation (22).

Likewise, caspase-2 is active when there is DNA damage due to oxidative stress, and its absence promotes high proliferation and faster immortalization in mouse fibroblasts. Several studies have shown the interaction of caspase-2 with cyclins and cyclin-dependent kinases, and its deficiency is associated with aneuploidy and tumor development. Active caspase-2 has been shown to stabilize p53 after DNA damage (23). In the same way, caspase-9 has been related to cell survival processes. Thus, in experiments with the anti-inflammatory FR122047 in MCF-7 breast cancer cells, cell death increased after caspase-9 inhibition, which indicated that caspase-9 was involved in the resistance to this mechanism (24).

Therefore, functions other than apoptosis have been reported for caspases, including inflammation, immunity, differentiation, cell remodeling, and AiP (25,26). Some studies have shown a paracrine regulation of AiP in apoptotic cells through the secretion of mitogenic signals (27).

**The JNK signaling pathway**

The JNK protein plays a preponderant role in AiP. The JNK pathway is one of the three protein signaling pathways known as mitogen-activated kinases (MAPK) and whose molecular, metabolic, and physiological effects are well known. It is currently known that JNK can act dually, both in survival and in the induction of cell death. Three genes are known to code for JNK 1, 2 and 3 proteins, and 12 isoforms have been reported. It is known that several members of the mitogen activated protein (MAP) kinase kinase kinase (MAPKKK) can interact and activate JNK. JNK activation occurs from the signaling of cytokines such as TNF, IL-6, TGF-β, Toll-like receptors (TLR-3, 4 and 9) and antigen receptors of T cells and B cells. These promote the MAP3K activity that activates MAP2K, MKK4 and MKK7, which contribute to the activation of JNK, which in turn activates activator protein-1 (AP-1),
a transcription factor of genes related to proliferation, survival, and cell growth (28). JNK can activate c-Jun, a component of the AP-1 complex, through three known mechanisms: (i) interaction with its NH2-terminal or phosphorylations at serines 63 and 73; (ii) c-Jun also functions as an activating factor for JNK, allowing feedback loops of the signaling pathway; and (iii) as a substrate for different transcription factors such as ATF-2 (activating transcription factor 2), Elk-1 (ETS like-1), p53, DPC4 (deleted in pancreatic carcinoma locus 4), Sap-1a (SRF accessory protein 1) and NFAT4 (activated T-lymphocyte nuclear factor 4), which in turn are activators of c-Jun protein that combines with c-Fos protein leading to the activation of genes of the AP-1 family which triggers cell proliferation (Figure 1) (29,30).

Although JNK is generally associated with cell proliferation and survival, it is now reported that JNK1 is the one that is related to this process; JNK2 has been found to be involved with apoptotic cell death in most cells and tissues, and JNK3 has shown different functions mainly in the brain and, to a lesser extent, in the heart and testicles (31,32). The affinity of JNK2 for c-Jun is much higher than that of JNK1, therefore it has been considered as the main kinase of c-Jun, although JNK1 isoforms with greater activity have recently been found. In mouse fibroblasts stimulated for survival, high JNK1 activity was observed, while JNK2 was found to be more active in non-stimulated cells (33,34).

The JNK signaling pathway has been associated with DNA fragmentation after gamma ray stimulation. JNK knock-out mouse fibroblasts showed resistance to apoptosis after exposure to UV rays, methyl-methanesulfate, and anisomycin, which raises the hypothesis that the acute and transient activation of JNK is related with survival and cell growth whereas sustained activation with apoptosis (35).

Studies carried out in three glioma cell lines (U251, U87-MG and C6) and an animal model (xenografted BALB/c-Jun mice) showed that extract from the bark of Tripterygium wilfordii (celastrol) induced cell cycle arrest and apoptosis, both related to a notable ROS production and increased JNK activity (36, 37). Similarly, in rat renal pheochromocytoma PC-12 cells, it was observed that treatment with colistin promotes an increase in JNK activity, having its maximum peak at 12 h, which in turn promotes apoptosis mediated by ROS production (36).
On the other hand, it has been observed that in undead cells of *D. melanogaster*, Dronc is capable of promoting the activation of JNK signaling, which acts as the main inducer of AiP (22). It has also been observed that once Dronc is active, it can promote the generation of extracellular ROS, which activate JNK signaling in the disc tissue of the undead eye. JNK can promote a positive feedback loop by transcriptionally activating the apoptosis inhibitory proteins (IAPs) Hid and Reaper which in turn allows to amplify the AiP process. In undead cells, downstream JNK pathway can produce and secrete mitogens such as Wg (Wingless) from the WNT-beta family (37), Spi (Spitz) that is an EGF homolog (38), and Upd (unpaired interleukin-6 homolog), in addition to the BMP/TGF-β DPP (decapentaplegic homolog) (39). These mitogens send their signals to neighboring cells and in this way, proliferation begins. Along with JNK signaling, p38 and JAK/STAT signaling are necessary for AiP (40). Studies show an important participation of JNK which is highly related to the intracellular production of ROS, but also to the time of exposure to the triggering agents of JNK activation (Figure 1B), which strengthens the theory that prolonged times of this signaling pathway leads to apoptotic processes.

**APOPTOSIS-INDUCED PROLIFERATION IN CANCER**

Some of the features of cancer include increased sensitivity to growth signals, decreased perception of growth arrest signals, unlimited replication, promotion of angiogenesis, activation of invasion-related mechanisms, metastasis, and resistance to apoptosis (41,42). These signals start on the cell surface by the interaction of IGF (insulin growth factor) with its receptor (IGFR), which keeps programmed cell death inhibited, promoting cellular proliferation. Also, in transformed cells, there is a decrease in the number of FAS death receptors and cell death signals, and increased survival pathways, thus avoiding apoptosis (43,44). The release of growth signals from dying tumor cells in tumors showed that caspase-3 upregulates a series of growth factors (44).

ROS, especially H$_2$O$_2$, can randomly damage DNA and lead to tumorigenesis through genomic instability (45). While oncogenes such Ras can promote ROS production (46), tumor suppressor genes such as p53 can restore ROS levels and decrease the oxidative status of tumor cells through the regulation of antioxidant enzymes such as GPx1 (glutathione
peroxidase 1) and SOD2 (superoxide dismutase 2) (47,48). It is known that the expression and concentration of the NOX enzyme (NADPH oxidase) is increased in many tumor types because the NOX enzyme is involved in the overproduction of ROS that mediate DNA damage and tumorigenesis through the activation of redox-sensitive pathways (49). NOX enzymes are known to regulate MAPK/ERK and PI3K/Akt/mTOR signaling pathways through H$_2$O$_2$-mediated oxidation of phosphatases (50). Many tumors have mutations in ETC (electron transport chain) proteins, encoded by mitochondrial DNA, which have been shown to be responsible for the production of mitochondrial ROS (51). Mitochondrial ROS are responsible for activating HIF (hypoxia inducing factor) in tumor cells that have decreased oxygen levels, allowing them to adapt to a hypoxic microenvironment in order to survive. When oxygen is decreased, superoxide is formed by mitochondrial ETC, stabilizing the HIF-1alpha and HIF-2 alpha subunits (52).

An increase in ROS can contribute to AiP. In D. melanogaster, increase in exogenous ROS in hemocytes (blood cells of insects) triggers JNK activity in epithelial cells through the release of TNF and the interaction with its receptor. Drun protein, homologue of Caspase-9 in this model, has an isoform that can induce JNK-mediated AiP in dying cells (53). An increase in ROS in injured intestines enhances intestinal stem cell proliferation mediated by increase in calcium uptake which in turn is mediated by TRPA1 receptors (transient receptor potential cation channel), and RyR (ryanodine receptor) (54). On the other hand, in a study in Danio rerio zebrafish larvae, it was observed that a high hydrogen peroxide gradient is required to carry out the repair and healing process (55).

Another mechanism related to AiP is autophagy, which is a highly regulated process with very important homeostatic functions, such as the maintenance of the cell in moments of lack of nutrients, the reduction of ROS, and the destruction of damaged and harmful structures within the cell. Prolonged activation of autophagy has been observed to trigger cell death, in the same way the process is canonically related to cell survival (56,57). Autophagic process also induces AiP, where the homolog of ULK (autophagy triggering complex) in D. melanogaster, called dAtg1, has an important role and is regulated by JNK. Likewise, dAtg1
also transcriptionally controls the Wg mitogen, whose role in AiP has been shown to be highly relevant (56).

**THERAPEUTIC IMPORTANCE OF APOPTOSIS-INDUCED PROLIFERATION**

Targeted therapies have undoubtedly been a great advance in the treatment of various types of cancer; however, adaptive or resistance responses to these therapies have been observed. While a multitude of mechanisms for therapy resistance have been identified, from the therapeutic point of view, inhibition of one signaling pathway leads to the activation of compensatory pathways allowing the continued progression of cancer. For example, when the AKT signaling pathway was inhibited with the pro-apoptotic compound LBH589 in colorectal cells, a compensatory cellular response through an increase in the activity of the STAT3 pathway was observed (58). Similarly, the compensatory activation of STAT3 was observed in lung cells in which the PI3K/AKT signaling pathway was chemically and genetically inhibited. The activation of STAT3 was observed to be induced by the MET proto-oncogene, and a better response was observed when the inhibition was carried out for both the PI3K/AKT and STAT3 pathways (59). Thus, a therapeutic approach using inhibitors of multiple signaling pathways may be required.

Another compensatory mechanism observed is the proliferation stimulated by dying cells. This mechanism was studied in irradiated pancreatic ductal adenocarcinoma cells, PANC1. It was observed that the role of caspase-3, caspase-7, and PKCδ are essential for the proliferation process to take place in neighboring cells of dying cells. Likewise, an increase in the activity of AKT, JNK, and MAPK was observed in non-irradiated neighboring cells. This supports the observations of increased proliferation of pancreatic ductal adenocarcinoma in patients after radiotherapy (22).

On the other hand, in a diethylnitrosamine-induced hepatocarcinoma model, it was observed that IκB kinase β (IKKβ) is important for the regulation of the cell cycle in liver carcinogenesis, since IKKβ knock-out mice showed a marked increase in cell proliferation with an increase in ROS production, a sustained activation of JNK, and an initial increase in hepatocytes death, which resulted in a compensatory proliferation of the surviving cells that
was reduced after administering oral antioxidants (60). A similar process was observed in caspase-3-deficient mice that were treated with diethylnitrosamine and contrary to the expected results for the canonical pathways of programmed cell death, increased p38 activity through activation of the cytokines TNF-α and IL-1α was observed (61). In a similar model of liver carcinogenesis, the importance of the cellular communication network factor 1 (CCN1) protein, commonly involved in cell repair processes in liver lesions, was also shown. In CCN1 knock-in mice, a significant increase in compensatory proliferation was observed whereas in the knock-out model, the compensatory proliferation was effectively inhibited showing accumulation of ROS that in turn promoted the activation of p53 and blocked cell cycle (62). These examples indicate that the mechanisms commonly linked to inflammation and apoptosis are also involved in compensatory proliferation of neighboring cells, promoting drug resistance.

The role of caspases in AiP has been described as “Phoenix Rising” (6). Caspases play a key role in allowing tumors to continue to proliferate after undergoing chemotherapy or radiation cycles (19). In this process, the activation of I PLA2 is necessary, which in turn produces prostaglandin E2 (PGE2) in a calcium-independent way, both induced by the activation of caspases-3 and -7 (7). The production of PGE2 by caspase-3 is necessary for the healing of epithelial wounds in the skin of mice, the regeneration of hepatocytes after a partial hepatectomy, or to repopulate the tumors after cytotoxic therapies (6,63,64). In the same way, during radiotherapy treatment of patients with various types of cancer, it has been observed that dying tumor cells promote the proliferation of neighboring cells as a way to compensate for the induced damage (65). It has been observed that in the normal cells of the salivary glands, which receive a large amount of radiation during the treatment of some head and neck cancers, the functionality is altered, triggering symptoms such as xerostomia and chronic hyposalivation. In these cells, PKCζ, which is partially responsible for cell proliferation and apical polarity, is significantly decreased. Likewise, there is an increase in JNK activity related to compensatory proliferation which, in this case, does not allow cell differentiation, preventing the development of salivary cells. (66). CD24-deficient and CD44-abundant breast cancer cells show resistance to conventional treatment with chemotherapy, likewise,
the importance of HER2 in the proliferation of breast cancer cells was observed, whose mechanism could be compensatory to the decrease in EGFR activity (67).

CONCLUSION
AiP is a compensatory mechanism in response to increased apoptosis. This can occur in different ways including the release of mitogens from apoptotic cells and their interaction with neighboring cells, the activation of compensatory signaling pathways towards blocked signaling pathways in dying cells, and by reversal of autophagy. In cancer therapy, inhibition of one signaling pathway leads to the upregulation of another compensatory pathway enabling the progression of cancer. Therefore, simultaneous inhibition of multiple pathways has been proposed as a potential therapy. AiP is involved in tumorigenesis and resistance of cancers to chemo and radiotherapy. More studies are needed to completely elucidate the signals and mechanisms that trigger AiP.

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CONFLICT OF INTEREST
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Figure 1. Mitogenic effect of apoptotic cells on neighboring cells. A, During the process of cell death by apoptosis, cells release mitogenic proteins such as TNF-alpha. This signal is received by neighboring cell receptors that activate various kinases which promote cell proliferation and survival. B, The effect of the JNK pathway is shown throughout the activation time, having an apoptotic effect in long times and favoring survival in acute activation times.