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Apoptosis and Cancer Progression: Balancing Tumor Suppression and Disease Advancement

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Abstract

Background:
Apoptosis is a tightly regulated form of programmed cell death that is essential for tissue homeostasis, normal development, and tumour suppression. Although defective apoptotic signalling is a hallmark of cancer, accumulating evidence indicates that apoptosis may also paradoxically promote tumour progression through its effects on the tumour microenvironment (TME), giving rise to the concept of the "apoptosis paradox."

Objectives:
To critically review the dual role of apoptosis in cancer progression, with particular emphasis on its immunomodulatory, regenerative, and pro-tumorigenic functions within the TME, and to discuss the therapeutic implications of targeting apoptosis-associated pathways.

Methods:
A comprehensive narrative review of the contemporary literature was conducted using peer-reviewed studies addressing the molecular mechanisms of apoptosis, apoptosis-mediated remodelling of the TME, immune regulation, autophagy, angiogenesis, metastasis, therapeutic resistance, and emerging apoptosis-targeted cancer therapies.

Results:
Current evidence demonstrates that, beyond eliminating damaged or transformed cells, apoptotic tumour cells actively influence the

TME by releasing bioactive mediators that regulate immune responses, promote pro-tumorigenic macrophage polarization, stimulate angiogenesis and tissue regeneration, and facilitate tumour growth, metastatic dissemination, and resistance to therapy. Furthermore, the intricate interplay between apoptosis, autophagy, and immune signalling highlights the context-dependent nature of programmed cell death in cancer biology, challenging the traditional view of apoptosis as solely tumour suppressive.

Conclusions:
Apoptosis exhibits a dualistic role in cancer, functioning as both a tumour-suppressive and tumour-promoting process depending on the biological context. A deeper understanding of apoptosis-mediated interactions within the TME may uncover novel therapeutic targets and support the development of precision-based strategies that improve treatment efficacy and clinical outcomes in patients with cancer.

Keywords: Apoptosis, Cancer progression, Programmed cell death, Metastasis, Chemoresistance, Targeted therapy

Introduction

Apoptosis vividly represented as ‘programmed cell death’ in a synchronized manner which maintains regular cell equanimity through enacting usual physiologic processes like tissue homeostasis, embryogenesis. Apart from this apoptosis is also well known for its tumour suppressor action. As a consequence of many hazardous stimuli, infections, irreparable cellular injury, cytotoxic drug therapy, radiotherapy, apoptosis is the typical cell death reaction. The precise apoptotic mechanism demands the distinct initiation of caspase cascade through intrinsic or extrinsic pathway. The intrinsic pathway is triggered via mitochondrial outer membrane permeabilization (MOMP) and the extrinsic pathway is initiated at the cell surface by death receptor activation. The similarity lies in between these two pathways is, they both converge on caspases activation. The apoptosis contributing genes are been classified into two broad category, anti-apoptotic gene (Bcl-2, Bcl-XL) and pro-apoptotic genes (p53, BAX, Bad and CASPASE family members) [1]. Evasion of apoptosis is a principal hallmark of cancer. Dysregulated cell proliferation with parrying apoptosis builds the cancer lesion more tough to treat. Therefore, the prognosis of cancer treatment depends on the cancer cell damage as well as the cellular potential to reactivate the apoptosis process. In latest studies cancer therapy has chiefly concentrated its aim on minimizing tumour size via maximum tumour specific cell death makes it less hostile. Clinical investigations are also made to appreciate the molecular process of eluding apoptosis. But on a contrary note, it has been monitored in varied cases, high grade cancers with poor prognosis often reveal presence of frequent apoptotic cells. Thereafter it can be suggested that, these dying cells can regulate the overall tumour proliferation, expansion and durability rate. Hence this contentious notion about the conflict between live and dead cell in cancer may arise advance outlook and modalities of research work. Tumour microenvironment (TME) and its adjacent zone are very much altered by the whole cellular disharmony which need revised cancer treatment. This review article deliberately explains the opinion regarding the apoptosis paradox in TME.

Review

It is well rooted in malignant diseases that depletion of cells via considerable cellular death happens in basic manner. Where cellular loss is primarily calibrated, the tumour cell multiplication rate is potentially in slower pace [2]. In aggressive malignancy there is unrestricted cell death, that is typically apoptosis. Although evasion of apoptosis being a dominant hallmark of cancer, those malignant tumour cells are incapable of arresting apoptosis in a variety of malignancy. Apoptosis is also vital cellular feedback to cancer therapy; in fact, the major focus of many non-surgical cancer therapies is to eliminate all cancer affected cells through cell death [3].

On the basis of Paget’s seed and soil theory [4], the primary cancer growth and its metastasis is based on the basis of tumour ‘niche’, the TME. Clinical evidences are found that genetic alterations and extracellular matrix molecular changes are responsible for approximately all cancer hallmarks which become eminent as tumorigenesis progresses [5]. The heterogenous components of the TME tangles the cancer scaffold more, in addition encircling different cell lineage at many levels of differentiation can command the extent of its function in reparatory activity. List of cells includes neoplastic cells, infiltrating immune cells, endothelial cells, fibroblasts, mutant cells. Intricate interactions between cellular and non-cellular composition of TME coordinate the whole process from tumour establishment to tumour invasion.

The tumour microenvironment (TME) controls or enhances tumour survival and function. Cancer cells can develop an invasive phenotype through the interaction of TME structural elements with cells, which results in a complicated and multi-step metastatic cascade that spreads to distant places from the initial site [6]. The interplay between TME cellular and structural elements promotes the aggressiveness and distant metastatic dissemination of cancer cells. A growing body of research suggests that when present in the tumour microenvironment (TME), innate immune cells (such as macrophages, neutrophils, innate lymphocytes, myeloid inhibitory cells, and NK cells) and

adaptive immune cells (such as T cells and B cells) aid in the growth of tumours (Figure-1) [7,8].

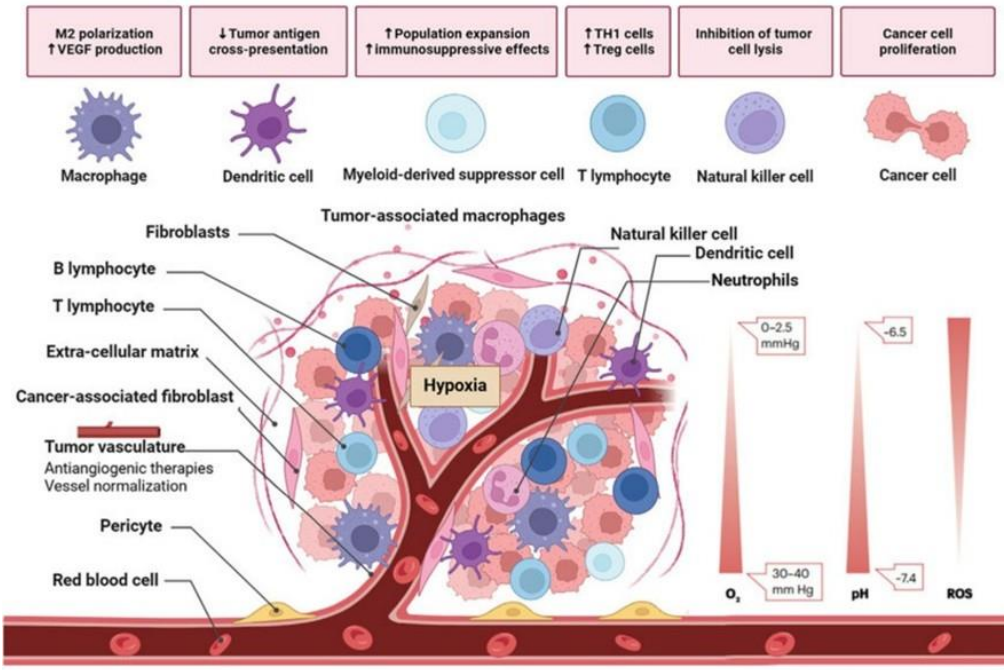

Figure-1: The photograph showing TME, tumour's surrounding complex of cellular and non-cellular elements

Apoptosis is a regular characteristic of TME. It has been also studied that more aggressive tumours are linked to higher apoptosis rate. But the striking fact is that apoptosis also plays tumour suppressive role. Overall, in tumour mass the partial apoptosis is helpful in TME equilibrium. It may hypothesize tumour oncogenesis in malignant transformation even in metastasis.

Connection between malignancy and the quantity of cellular apoptosis is still under research. On the other side, increased expression of pro-apoptotic factors may not be related with less aggressiveness of tumour and vice versa. As an example, pro-apoptotic Bax expression [9] or caspase cascade activation [10] is corelated with aggressive tumour proliferation, and anti-apoptotic Bcl-2 is associated with low grade aggressive tumour [11]. Besides, genomic instability and tumour niche formation may be stimulated by death of tumour cells which encourage the regrowth of tumour, by more invasive tumour cell clones. Furthermore, cell death may promote genomic instability and niche formation, which, in the setting of nascent and developing tumours, could result in repopulation by tumour cell clones with more aggressive features [12].

Evidence suggests that the apoptotic program can give pro-oncogenic signals at the cell population level, contributing to the imbalance between cell birth and cell death that causes cancer (Figure-2) [13]. Cancer exploits innate regenerative responses to apoptosis to promote and maintain net tumour growth and progression. Of particular importance in this regard is the well-established fact that apoptotic cells attract and polarize macrophages to M2-like reparatory and regenerative activation states, with the ability to promote cancer growth and spread through various pathways [14].

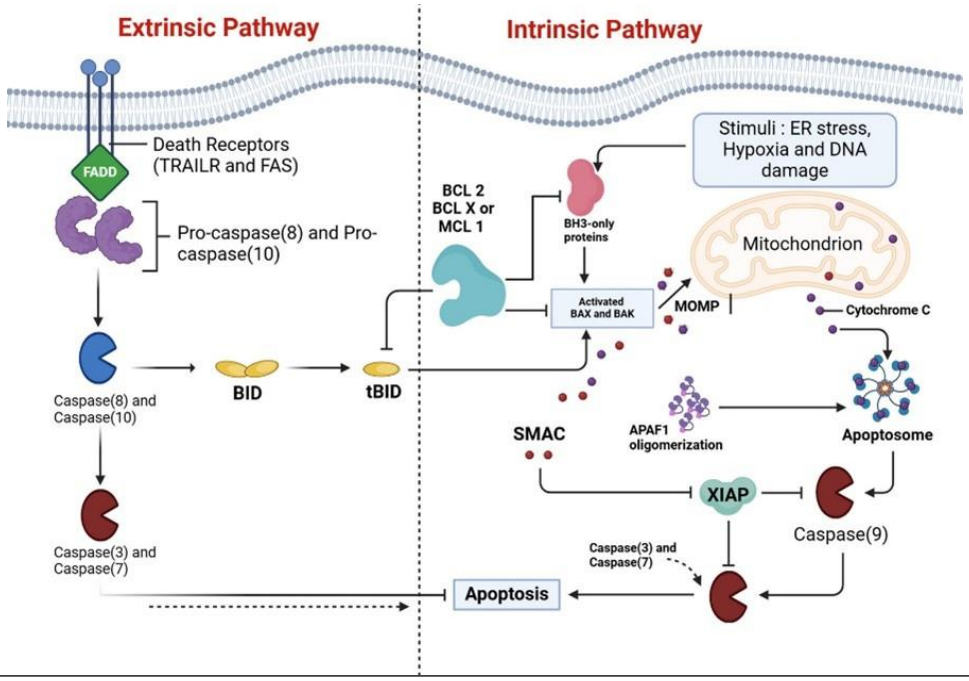

Figure-2: The photograph showing Common intrinsic and extrinsic apoptotic signaling pathways

Tumour cell apoptosis in the TME of an aggressively growing lesion can be caused by nutrient and oxygen deficiency due to tumour cell proliferation outpacing angiogenesis [15], and clonal 'cancer hallmark insufficiency', which refers to premalignant or malignant clones that have acquired genetic mutation, whereas 'Apoptosis-induced Apoptosis' (AiA) are additional factors that trigger apoptosis [16].

The TME plays a crucial role in the formation, evolution, and spread of tumours by regulating cell birth/cell death ratios. Dynamic modification of the tumour microenvironment (TME) is necessary to favour this ratio during tumour genesis and growth. Recent evidence suggests that TME responses to apoptosis play a crucial role in this process (Figure-3) [2].

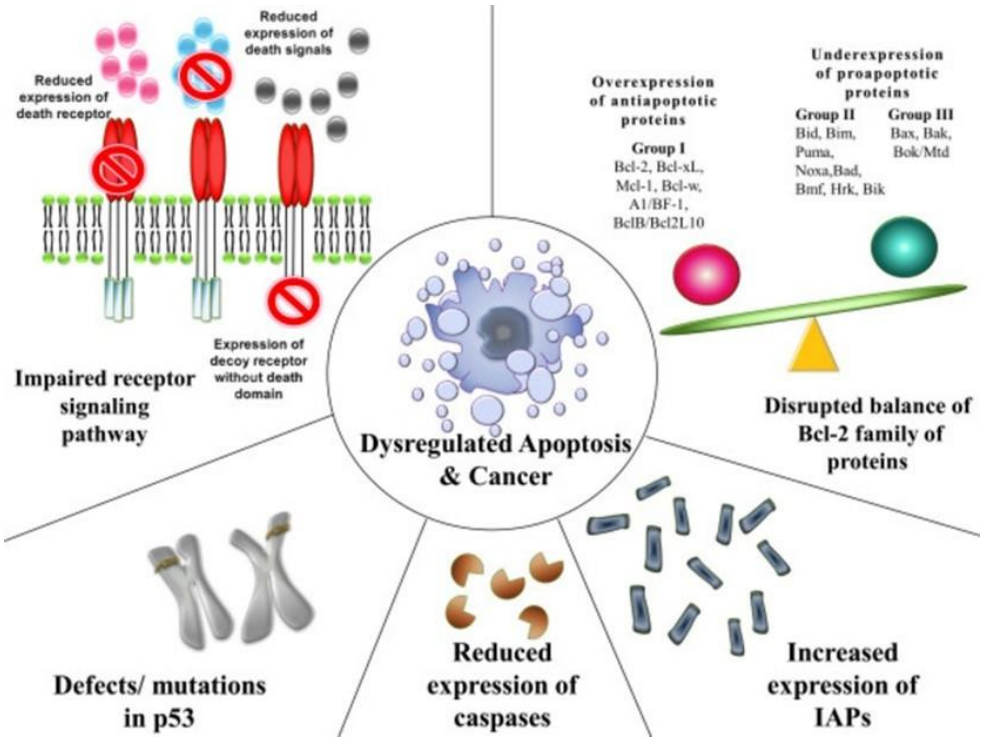

Figure-3: The photograph showing Mechanisms contributing to evasion of apoptosis and carcinogenesis

A variety of bioactive components are actively exposed and released by apoptotic cells, causing a range of reactions in their immediate vicinity [17-21]. The secretomes of dying cells produced after cancer treatment do, in fact, have significant functional consequences that aid in the development and metastasis of tumours [22]. One of the most well-known features of an apoptotic cell is its capacity to trigger its own phagocytosis by nearby tissue cells of different lineages, such as dendritic cells, fibroblasts, myocytes, endothelial cells, sertoli cells, paneth cells, and primarily macrophages, which are the most commonly observed and researched phagocytes of apoptotic cells. Indeed, unbound apoptotic cells are rarely seen in situ due to the rapidity of the apoptotic-cell engulfment process. Phagocytes clear apoptotic cells through efferocytosis, which involves translation of 'find-me' and 'eat-me' signals from dying cells [20,23]. All of these distinct chemoattractant classes bind to particular G protein-coupled receptors to initiate the chemotaxis of mononuclear phagocytes. It is noteworthy that phagocyte responses to these factors can involve more than just migration; they can also involve the promotion of lymph angiogenesis and metastasis in murine tumour models (activation of S1PR1 by S1P [24,25]), the polarization of macrophages from pro-inflammatory to anti-inflammatory states, and stimulation of engulfment mechanisms, such as through MFG-E8 induction by fractalkine [26]. By preventing granulocyte migration, leukocyte chemotactic control, which involves the release of soluble substances from apoptotic cells, might also favour the concentration of mononuclear phagocytes. This is demonstrated by lactoferrin (LTF), which is released during apoptosis and limits neutrophil and eosinophil migration [27,28]. It has not been studied how this affects the cellularity of the TME, despite the fact that it might be a significant component of the anti-inflammatory action of apoptosis. Phosphatidylserine (PS), an anionic phospholipid that is aggressively externalized in the plasma membrane leaflet during apoptosis, is the most well-known "eat-me" signal. The coordinated caspase-dependent inhibition of flippase activity (P4-ATPase ATP11C), which otherwise keeps PS localized to the inner aspect of the plasma membrane leaflet in viable cells, and activation of scramblase activity (Xkr family member Xkr8), which speeds up PS redistribution across the membrane bilayer, are how this is accomplished [14,29].

A variety of phagocyte receptors involved in efferocytosis can interact with PS exposed on apoptotic cells directly (BAI1, TIM4, Stab2, TLT, and RAGE) or indirectly (MERTK, $\alpha_v\beta_{3/5}$, LRP1). Through PS-binding bridging receptors, such as Gas6 in the case of MERTK, MFG-E8 for the integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$, and C1q to LRP1, indirect connection with PS is accomplished. Apoptotic cells are recognized by other receptors using PS-independent pathways, including the scavenger receptors CD36 and SR-A and the PRRs CD14 and MBL [14,18,20,21]. In a variety of cancers,

tumour-associated macrophages (TAMs) make up a sizable fraction of the TME's cellular compartment. In many of these cases, they are obviously involved in the removal of apoptotic cells. At least in some types of cancer, tumour development and angiogenesis are intimately related to TAM accumulation and pro-oncogenic activation. However, little is currently understood about the relative roles played by the several eat-me, find-me, and anti-inflammatory signaling molecules and pathways mentioned above in TAMs' pro-oncogenic reactions to apoptotic tumour cells. The protein tyrosine kinase MERTK, an indirect PS receptor, is noteworthy for its ability to communicate anti-inflammatory and immunosuppressive responses in addition to the phagocytosis of apoptotic cells; its inhibition can prevent the progression of cancer [30]. Whether PS is involved or not, it appears plausible that phagocyte receptors would coordinate context-dependent immune responses to apoptotic tumour cells [31].

According to recent research, apoptotic stress in cells might trigger survival responses in other cells in the population. For instance, FGF can temporarily upregulate the apoptosis suppressor Bcl-2 [32]. These pleiotropic responses to apoptosis by various cell types in the TME, including immune cells, fibroblasts, endothelial cells, healthy tumour cells, and others, whether phagocytic or not, serve as the foundation for a complex network of programs that assist in identifying whether a tumour is benign, malignant, regressing, or relapsing [33]. It has been effectively documented recently that apoptotic cells are functionally active in secreting bioactive chemicals while their membranes are intact, regardless of their absorption by phagocytes. Consequently, it was shown that apoptotic leukocytes produce particular arrays of metabolites by maintaining particular metabolic pathways and by releasing metabolites through the opening of caspase-activated pannexin I channels. AMP, ATP, GMP, creatine, and glycerol-3-phosphate were among the common metabolites generated by macrophages and lymphocytes in response to various apoptotic triggers. Crucially, the "metabolite secretome" brought on by apoptosis was able to trigger anti-inflammatory signaling, proliferative responses, and reparatory responses in nearby healthy cells [34].

Recent evidence suggests that apoptosis-driven tissue repair and regenerative responses play a crucial role in generating and supporting TME, similar to how cancers exhibit wounds that do not heal or continue to repair [13,14,19,35-39]. TME refers to the intercellular communication and tissue repair mechanisms activated by apoptosis. These mechanisms promote tumour expansion and invasiveness while suppressing anti-tumour immunity. Sources of both apoptotic and apoptosis-responding cells may include altered cells, as well as other cellular constituents of the TME; communicative pathways include intercellular contact, soluble factors.

Macrophages are important cellular constituents of several tumour classes. While they have demonstrated the ability to eliminate tumour cells in their classically activated state (often referred to as M1), their primary role in cancer is to promote tumour growth through a variety of mechanisms, such as angiogenesis activation, the synthesis of growth and survival factors, invasion and metastasis support, and suppression of anti-tumour immunity. Often called M2 like, this reparatory macrophage phenotype is characteristic of macrophages reacting to apoptotic cells [25,40-43]. In addition to being important in triggering M2-like activation of macrophages, apoptotic cells are also easily ingested by M1 macrophages and significantly reduce M1 anti-tumour activity [44,45].

By triggering autophagic pro-survival mechanisms [46], poorly vascularized tumour cells in cancer can withstand nutrient limitation, hypoxia, and other stressors, including cancer treatments [47-49]. In contrast, autophagy can trigger tumour suppression in response to specific stimuli, as well as for specific cell types and tumour grades, by starting a tightly regulated pathway that leads to cell death [50,51]. In this way, the cell death response serves as a fallback mechanism for maintaining tissue homeostasis [52]. As a result, autophagy may also play dual roles in cancer, either promoting tumour endurance or serving as a self-sacrifice process, preserving tissue integrity (Figure-4) [30,53-55].

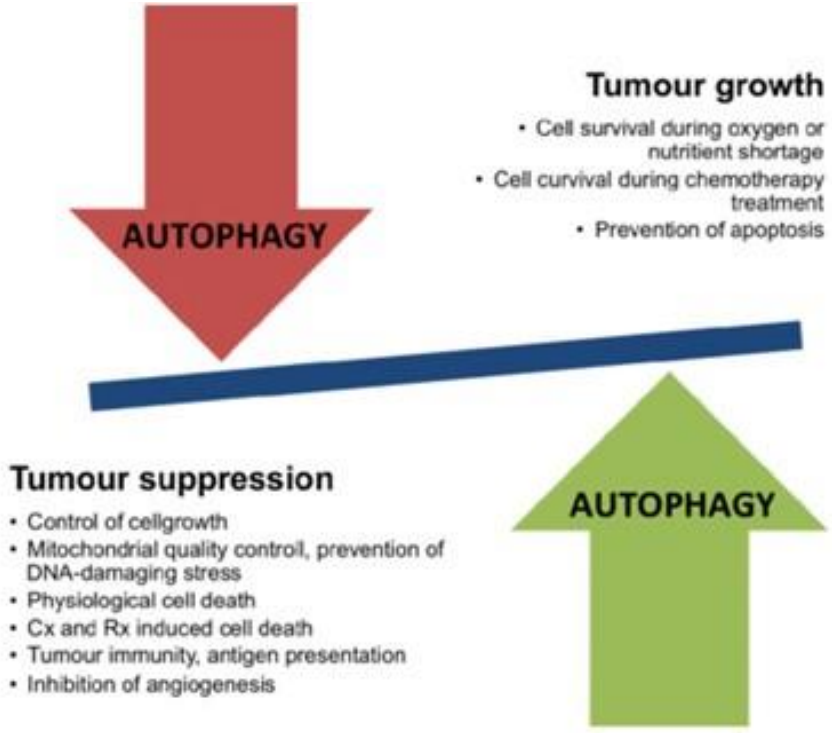

Figure-4: The photograph showing role of autophagy in both cancer development and suppression

Conclusion

There are two roles for cell death in cancer biology, and the complicated picture that emerges goes much beyond the idea that cancer cells are naturally tumour suppressors. The basic elucidation of the molecular and cellular mechanisms governing the control of irreversible cell deletion versus those governing the regenerative cell death that occurs when cells need to be replaced is just one of many approaches that require extensive exploration.

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