Resurrection biology: Melatonin as a modulator of anastasis (Review)

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Abstract. Although apoptosis is regarded as an irreversible and terminal process, recent research has identified anastasis as a cellular mechanism that enables cell recovery even after the activation of executioner caspases. While important in supporting tissue homeostasis following mild or transient injury, anastasis presents significant challenges in oncology, as cancer cells may exploit this phenomenon to evade chemotherapy, subsequently acquiring aggressive traits such as genomic instability, stem-like properties, and increased metastatic capacity. N-acetyl-5-methoxytryptamine (melatonin), recognized for its antioxidant activity and role as a mitochondrial regulator, has been associated with several biological processes that overlap with pathways involved in anastasis, including mitochondrial bioenergetics, redox homeostasis, and DNA repair mechanisms. However, direct evidence supporting a role for melatonin in regulating anastasis remains limited. The present review consolidated current insights into the molecular regulation of anastasis, examining its biphasic transcriptional profile and oncogenic consequences, while exploring the mechanistic links between melatonin biology and pathways relevant to apoptotic recovery and evaluating the therapeutic prospects of melatonin in targeting anastasis as a strategy to mitigate tumor recurrence and improve clinical outcomes.

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1. Introduction

Programmed cell death (PCD) is an essential, tightly regulated process with critical roles in the development and the maintenance of cellular and tissue homeostasis. More than 20 distinct forms of PCD have been identified, with apoptosis being the most investigated (1,2). Apoptosis is a caspase-mediated process that plays a vital role in normal cell turnover, immune regulation, development and tissue atrophy. Aberrations in the apoptotic process are implicated in numerous pathologies, including cancer, neurodegenerative diseases, ischemic injury, and autoimmune conditions (3).

The term 'apoptosis' was initially introduced by Kerr, Wyllie and Currie in 1972 (4), who described it as a process of regulated cell deletion that serves a complementary role, yet opposite, to mitosis in the regulation of animal cell population balance. Over the past 50 years, research has greatly enhanced our understanding of the molecular mechanisms underlying apoptosis. Nonetheless, the morphological criteria originally described by Kerr, Wyllie, and Currie, including nuclear condensation, membrane blebbing, cellular fragmentation into apoptotic bodies and their subsequent engulfment by phagocytic cells, are still accepted as the basic cellular events associated with apoptotic death (5).

Historically, apoptosis was regarded as an irreversible, one-way process which invariably led to cellular death. However, recent discoveries have dismantled this binary view of cellular life and death. It is now evident that cells undergoing the early stages of apoptosis can reverse the death process and recover their function upon the removal of the stress stimulus (6-8). This phenomenon has been termed 'anastasis' (Greek for 'rising to life') (9). In the Christian tradition, 'Anastasis' specifically refers to the Resurrection of Jesus Christ. By adopting this potent terminology, this scientific definition underscores a reversal of destiny; just as the biblical

Anastasis represents a miraculous return from mortality, cellular anastasis describes the unexpected ability of cells to halt the 'falling' trajectory of programmed death and 'rise' back to functional survival.

The molecular events underlying this death-cheating phenomenon are yet to be fully elucidated. This process becomes highly relevant in the case of cancer cells. While anastasis serves as a vital safeguard for tissue preservation following transient injury of otherwise normal cells, the molecular machinery of anastasis can be manipulated by cancer cells to enhance their survival after chemotherapy, contributing to disease relapse and progression. Consequently, elucidating the precise molecular orchestration of anastasis and translating this knowledge into the clinical practice for the therapeutic benefit of cancer patients has garnered significant scientific attention.

N-acetyl-5-methoxytryptamine (melatonin) has emerged as a promising candidate for the pharmacological modulation of anastasis (10). While best known for regulating circadian rhythms, melatonin is also a potent antioxidant and mitochondrial guardian with profound cytoprotective properties (11). However, the extent to which melatonin directly influences anastasis remains uncertain. The current review provides a comprehensive evaluation of the molecular evidence implicating anastasis in oncogenesis, highlighting its capacity to drive cancer cell survival and promote a more aggressive cellular phenotype. In addition, it examines whether the pleiotropic actions of melatonin may influence pathways relevant to apoptotic recovery and its role as a potential pharmacological modulator capable of intercepting the process of anastasis.

2. Discussions on comparison of apoptosis and anastasis

The molecular basis of apoptosis and the 'point of no return'. Apoptosis is induced by a variety of stimuli and mechanisms, which are generally classified into two principal routes: The extrinsic and intrinsic pathways. These distinct signaling cascades ultimately converge on the activation of shared executioner molecules that mediate programmed cell death (1,2). The molecular events characterizing apoptosis are divided into three consecutive temporal phases: The initiation phase, where an extrinsic or an intrinsic stress signal is received, activating the proximal components of the cell death machinery; the effector phase, characterized by the irreversible activation of executioner molecules; and the degradation phase, during which classical morphological hallmarks become evident (12).

Investigators have often aimed to determine the exact 'point of no return' in apoptosis, representing the specific molecular transition at which a cell becomes irreversibly committed to its demise (13,14). This critical juncture is widely associated with mitochondrial outer membrane permeabilization (MOMP), a process controlled by the proapoptotic members of the Bcl-2 protein family (15-17). When apoptotic stimuli are encountered, a subset of proteins translocate to the mitochondria, compromising the integrity of the outer mitochondrial membrane and resulting in the release of apoptosis-inducing factors such as cytochrome *c*. These mitochondrial proteins initiate the activation of downstream effector molecules, predominantly the caspase network (18). The subsequent activation of executioner caspases leads to irreversible proteolysis of various cellular substrates, ultimately resulting in the orderly disassembly of the cell. Additionally, dysfunctional mitochondria and the associated release of cytotoxic proteins into the cytoplasm contribute to the induction of caspase-independent cell death pathways (18,19).

Re-evaluating the irreversibility of apoptosis. For decades, initiation of apoptosis was regarded as an irreversible event culminating in cellular death. There is evidence, however, suggesting that cells can retain viability even following MOMP or activation of executioner caspases (8,20). Tang *et al* (6) demonstrated that cancer cells subjected to cytotoxic agents and exhibiting both morphological and biochemical markers of apoptosis, unexpectedly survived and subsequently resumed proliferation following the removal of the toxic inducer. These observations were confirmed across multiple cell lines and with various cytotoxic stimuli, supporting the existence of a previously unknown mechanism that allows cancer cells to escape the apoptotic pathway, provided that the cytotoxic stimulus is withdrawn (7). Notably, >90% of primary liver cells and embryonic fibroblast (NIH 3T3) cells demonstrate the capacity to reverse all apoptotic markers after removal of the apoptosis-inducing stimulus, even following DNA damage. However, these cells retained persistent genetic alterations, including an increased frequency of micronuclei, a biological indicator of substantial chromosomal rearrangements, aberrant micronuclei formation during early post-apoptosis cell division and a marked rise in karyotypic abnormalities such as chromosomal aneuploidy and radial configurations. These findings suggest that the persistence of genetic alteration following apoptotic reversal may confer a transformed phenotype with potential carcinogenic consequences (7). The phenomenon of cellular evasion from apoptosis has also been observed by other investigators. Roux *et al* (21), for example, analyzed the concept of 'fractional cell killing', which describes the incomplete elimination of cells via the extrinsic pathway of apoptosis.

The term anastasis, derived from the Greek word meaning 'rising to life', was introduced by Tang *et al* (22) to characterize the reversal of apoptosis (9). This concept challenges the notion that apoptosis represents an irreversible process, suggesting that cells retain the potential for physiological recovery and continued viability even following activation of executioner caspases, provided the lethal stimulus is withdrawn.

3. Molecular signature of anastasis

To elucidate the transcriptional dynamics of anastasis, Tang *et al* (23) utilized a time-course microarray analysis on mouse primary liver cells recovering from ethanol-induced apoptosis. The study compared gene expression in apoptotic cells following treatment with 4.5% ethanol for 5 h, recovering cells (harvested at 3, 6, 24 and 48 h post-washout) and untreated controls. This analysis revealed distinct, time-dependent waves of gene expression. During the early phase of anastasis (at 3 h), a broad upregulation of genes associated with Activator protein-1 (*AP-1*) transcription factors, the transforming growth factor-β (TGF-β) signaling pathway and its related regulators, pro-survival Bcl-2 family members (*Bag3*) and p53 inhibition (*Mdm2*) was observed. This upregulation also extended

to pathways involved in antioxidant responses (*Hmox2*), antiproliferative processes (*Btg1*), DNA damage (*Ddit3*, *Ddit4*), vesicular trafficking (*Vps37b*) and stress-inducible responses (*Dnajb1, Dnajb9, Herpud1, Hspb1, Hspa1b*) was observed. Following this initial response, a different set of pathways was activated at 6 h post-recovery, characterized by significant upregulation of genes governing cell cycle arrest (*Cdkn1a*), autophagy (*Atg12, Sqstm1*), and cell migration (MMPs). Reverse transcription-quantitative PCR validation in the human liver cancer cell line HepG2 confirmed these gene expression patterns, a finding suggesting that the core transcriptional program of anastasis is conserved between primary and malignant cells. Taken together, the upregulation of these genes during anastasis indicates potential regulatory mechanisms that degrade released cytochrome *c*, inhibit activated executioner proteins and reestablish a functional mitochondrial network essential for energy production (9,23).

In a similar study, researchers exposed HeLa cells to ethanol in order to trigger apoptosis (24). RNAseq compared gene expression in untreated, apoptotic and surviving cells at various time points after removing ethanol. Analysis revealed distinct sets of early and late response genes. Early-response genes were primarily related to transcription, chromatin modification and stress regulation, while late-response genes involved noncoding RNA processing, ribosome biogenesis, focal adhesion and actin cytoskeleton regulation, indicating a clear temporal shift in cellular programs and a transition from a proliferative towards a migrative phenotype during the different stages of anastasis. Moreover, this study documented that the transcripts of some early-response genes were already elevated in apoptotic cells compared to untreated ones. This suggested that cells enter a 'poised for recovery' state, which is characterized by the accumulation of specific survival-associated mRNAs. Translation of these mRNAs enables rapid recovery if the stress is removed, otherwise, these mRNAs are degraded and the cell proceeds to death (24).

To facilitate interpretation of the findings of the two previously mentioned studies, some of the reported gene expression alterations observed during anastasis are summarized in Tables I and II. Table I presents representative genes with upregulated expression, whereas Table II summarizes representative genes with downregulated expression. As these studies employed different experimental systems and methodologies, as well as distinct sampling time points, the datasets are not directly comparable. Therefore, the tables are intended solely as descriptive summaries of the reported findings rather than comparative analyses. For organizational purposes, the phases of anastasis are conceptually grouped as Early phase (1-4 h) and Late phase (≥5 h) following recovery initiation.

As well as transcriptional changes associated with recovery, evidence suggests that cells surviving apoptosis may also acquire functional phenotypic alterations. A transcriptional analysis of melanoma cells that have undergone failed apoptosis identified a gene expression profile enriched for pathways associated with cell motility, including focal adhesion and cell adhesion molecules, transendothelial migration and actin cytoskeleton regulation. Subsequent *in vitro* and live imaging studies demonstrated that these cells exhibited superior matrix adhesion, larger focal adhesions, enhanced non-directional migration ability, and greater invasive and migratory capacities compared to the control cells. These findings imply that failed apoptosis may enhance the migratory and invasive potential of melanoma cells (25).

Collectively, these findings delineate the molecular signature of anastasis as a highly conserved, biphasic process, governed by a strictly orchestrated transcriptional program. The early phase functions as an emergency survival response, characterized by the upregulation of stress-inducible pathways, such as AP-1 and TGF-β signaling. These modifications arrest cell cycle progression, promote DNA repair and neutralize apoptotic executioners. On the other hand, the late phase marks a transition toward structural recovery and phenotypic plasticity, prioritizing cytoskeleton reorganization, ribosomal biogenesis and motility over proliferation. This temporal shift implies that anastasis is not merely the cessation of apoptosis, but a distinct, biologically conserved, adaptive mechanism that restores mitochondrial integrity while potentially driving surviving cancer cells toward a more migratory, and perhaps metastatic, phenotype.

4. The oncogenic role of anastasis

The capacity of anastasis to rescue dying cancer cells raises critical concerns regarding its role in oncogenesis. DNA damage is a hallmark of apoptosis, resulting from the combined action of apoptosis-related DNases and the caspase-3 induced cleavage and inactivation of DNA repair enzymes such as PARP-1 (26,27). The genomic damage observed during apoptosis constitutes an aspect of cellular disassembly and does not carry biological significance, as the cell is undergoing PCD. However, halting the destruction process, such as in the case of anastasis, leads to numerous mutations due to DNA damage, which results in the accumulation of genetic alterations and chromosomal rearrangements with unpredictable biological outcomes and a potential association with carcinogenesis (20,28,29).

Wang *et al* (30) used human liver cancer cells HepG2 to investigate the consequences of apoptosis reversal following ethanol treatment. Clones that recovered from apoptosis exhibited a significantly higher inhibitory concentration (IC_{50}) for ethanol compared to controls (19.7±4.0 g/l vs. 14.8±1.7 g/l; $P<0.001$). Subsequent *in vitro* studies demonstrated increased motility and invasive capacity of the recovered cells, suggesting the development of a more aggressive cancer cell phenotype following apoptosis survival. A separate study exposed breast cancer cells to the toxic drugs, staurosporine and paclitaxel, to induce PCD. Following the removal of these cytotoxic agents, a proportion of cells managed to reverse apoptosis and demonstrated enhanced tumorigenic and stem cell-like traits. These reversed cells formed mammospheres more readily *in vitro*, which led to the formation of tumors of larger size *in vivo*, faster and at lower counts compared to controls (31). In addition, the findings documented an increased presence of $CD44^+/CD24^-$ cells in populations recovering from apoptosis, a phenotype characteristic of breast cancer stem cells (32). This corresponded with increased CD44 mRNA and decreased CD24 mRNA levels. This change was attributed to an epigenetic modification, specifically an altered methylation status of the promoter of these genes, induced during the apoptosis reversal process.

Table I. Representative genes with upregulated expression during anastasis.

First author/s, year	Phase of anastasis	Gene	Biological role	(Refs.)
Tang *et al*, 2017; Sun *et al*, 2017	Early	AP-1 family (e.g.,Atf3, Fos, Fosb, Jun, Junb)	Transcription factors	(23,24)
Tang *et al*, 2017; Sun *et al*, 2017	Early	TGF-β signal pathway and its regulators (Inhba, Snai1, Tgif1, Sox4, Sox9, Klf4, Klf6, Klf9)	TGF-β regulation/EMT/Migration	(23,24)
Tang *et al*, 2017	Early	Bag3	Anti-apoptotic Bcl-2 protein	(23)
Tang *et al*, 2017	Early	Mdm2	Inhibitor of p53	(23)
Tang *et al*, 2017	Early	Hmox1	Anti-oxidation	(23)
Tang *et al*, 2017; Sun *et al*, 2017	Early	Btg1	Anti-proliferation	(23,24)
Tang *et al*, 2017; Sun *et al*, 2017	Early OR Late	Ddit3 and Ddit4	Stress responsive genes	(23,24)
Tang *et al*, 2017; Sun *et al*, 2017	Early	Vps37b	Vesicular trafficking	(23,24)
Tang *et al*, 2017; Sun *et al*, 2017	Early	VEGFA	Angiogenesis	(23,24)
Tang *et al*, 2017	Early	Hist1h2ae	Histone	(23)
Tang *et al*, 2017; Sun *et al*, 2017	Early OR Late	Cdkn1a	Cell cycle arrest	(23,24)
Tang *et al*, 2017	Late	Trp53inp1	Cell cycle arrest	(23)
Tang *et al*, 2017	Late	Atg12	Autophagy	(23)
Tang *et al*, 2017	Late	Sqstm1	Autophagy	(23)
Tang *et al*, 2017; Sun *et al*, 2017	Late	H2af	Histone	(23,24)
Tang *et al*, 2017	Throughout	Rnu6	RNA splicing	(23)
Tang *et al*, 2017	Early	Gadd45g	Growth arrest and DNA repair	(23)
Sun *et al*, 2017	Early	SNAI1, SNAI2	Transcription factors/EMT	(24)
Sun *et al*, 2017	Throughout	PGF	Angiogenesis	(24)
Sun *et al*, 2017	Throughout	EPHA2, EPHB2, EPHB4	Angiogenesis	(24)
Sun *et al*, 2017	Throughout	EFNB1, EFNB2	Angiogenesis	(24)
Sun *et al*, 2017	Throughout	SPRY2	Angiogenesis	(24)

Genes listed in the table exhibit increased expression during anastasis as reported in transcriptomic analyses by Tang *et al* (23) and Sun *et al* (24). Notably, some genes (Ddit3, Ddit4 and Cdkn1a) were reported to be dysregulated during different phases of anastasis across the two studies. For organizational purposes, the phases are conceptually grouped as Early (1-4 h) and Late (≥5 h) following recovery initiation. Owing to differences in experimental systems, methodologies and sampling time points, the studies are not directly comparable; therefore, the table is intended as a descriptive summary of the reported findings rather than a comparative analysis. AP-1, activator protein-1; TGF-β, transforming growth factor-β; Bag3, Bcl-2-associated athanogene 3; Mdm2, mouse double minute 2; Hmox1, heme oxygenase 1; Btg1, B-cell translocation gene 1; Ddit, DNA damage inducible transcript; Vps37b, Vacuolar protein sorting 37B; VEGFA, vascular endothelial growth factor A; Hist1h2ae, histone cluster 1, H2ae; Cdkn1a, cyclin-dependent kinase inhibitor 1A; Trp53inp1, transformation related protein 53 inducible nuclear protein 1; Atg12, autophagy-related 12; Sqstm1, sequestosome 1; H2af, H2A histone family, member J; Rnu6, U6 small nuclear RNA; Gadd45g, growth arrest and DNA-damage-inducible 45 gamma; SNAI, Snail family genes; PGF, placenta growth factor; EPH, ephrin receptors; EFN, ephrins; SPRY2, spouty 2.

Reversal of apoptosis might be associated with the development of cancer clones with higher tumorigenic capacities and stem-like features (31).

Vasileva *et al* (33) investigated the capacity of seemingly apoptotic metastatic melanoma cells to proliferate under conditions of anchorage independence. The study observed that a

Table II. Representative genes with downregulated expression during anastasis.

First author/s, year	Phase of anastasis	Gene	Biological Role	(Refs.)
Tang *et al*, 2017	Late	Hist1h2ak	Histone	(23)
Tang *et al*, 2017	Late	Hist1h2ag	Histone	(23)
Tang *et al*, 2017	Late	Fzd2	Transmembrane receptor	(23)
Tang *et al*, 2017	Late	Sdpr	Cell stress adaptation	(23)
Tang *et al*, 2017	Late	Bmp4	TGF-β regulation	(23)
Tang *et al*, 2017	Late	Gadd45g	Growth arrest and DNA repair	(23)
Sun *et al*, 2017	Throughout	SLFN5	Transcriptional repressor	(24)

Genes listed in the table exhibit decreased expression during anastasis as reported in transcriptomic analyses by Tang *et al* (23) and Sun *et al* (24). For organizational purposes, the phases are conceptually grouped as Early (1-4 h) and Late (≥5 h) following recovery initiation. Owing to differences in experimental systems, methodologies and sampling time points, the studies are not directly comparable; therefore, the table is intended as a descriptive summary of the reported findings rather than a comparative analysis. Hist1h2ak, histone cluster 1, H2ak; Hist1h2ag, histone cluster 1, H2ag; Fzd2, frizzled homolog 2; Sdpr, serum deprivation response; Bmp4, bone morphogenetic protein 4; Gadd45g, growth arrest and DNA-damage-inducible 45 gamma; SLFN5, Schlafen family member 5.

non-adherent, FSClowSSChigh melanoma cell subpopulation, typically considered as non-viable in melanoma cell cultures, demonstrated a preferential enrichment of cell surface CD24 expression, a marker which in the case of melanoma is associated with stem-like features and acquired resistance to targeted therapies (34-37). Although this cellular fraction displayed apoptotic features, it nonetheless retained metabolic activity and exhibited proliferative capacity. These findings indicated that CD24 expression may function as a potential surface marker for anastasis in melanoma cells, highlighting the need for more aggressive management (33).

Human colorectal cancer cell lines have also been used to investigate the characteristics acquired by cells that survive chemotherapy-induced apoptosis (38). Consistent with previous findings, these surviving cells demonstrated enhanced migratory and metastatic capacities, both *in vitro* and *in vivo*. RNA sequencing of this cell population indicated an upregulation of *BIRC3*, a gene that encodes the cellular Inhibitor of Apoptosis-2 (cIAP2), a member of the IAP protein family which has been associated with regulating cellular migration (39,40). Subsequent investigation revealed that cIAP2 facilitates the migration of anastatic cells by activating NF-κB signaling. These two molecules were found to establish a positive feedback loop, which reciprocally enhances their expression and promotes the migratory activity of anastatic cells. Finally, the anastatic cells acquired resistance to chemotherapeutic drugs, including 5-FU, oxaliplatin and irinotecan. This resistance was mechanistically linked to the upregulation of cIAP2 since knocking down the *BIRC3* gene markedly reduced the difference in chemoresistance between cell populations (38).

Combined mathematical modeling and experimental validation were used to demonstrate that interfering with the regulatory interconnection between initiator and effector caspases can induce a 'third state' of partial substrate cleavage (41). This condition, existing between cell survival and death, poses significant risks, as cells may persist with extensive DNA damage, thereby promoting genomic instability, a core characteristic of cancer. This finding offers a new potential pathogenic role for oncogenes such as Bcl-2; these molecules might not only inhibit cell death but also promote the accumulation of genetic alterations by maintaining cells in this dysfunctional state. Supporting this observation, at sub-lethal concentrations TNF-related apoptosis-inducing ligand promotes mutagenesis in surviving cells, through a caspase 8-dependent manner (42).

In summary, the aforementioned studies provided evidence confirming that the rescue of dying cells through anastasis serves as a significant factor in tumor evolution and therapeutic resistance. This process allows for the preservation of a subpopulation of cells exhibiting considerable genomic instability and epigenetic modifications. The resulting 'anastatic' phenotype is distinguished by increased chemoresistance, as well as the development of stem-like properties and greater metastatic capacity. Accordingly, anastasis appears to act as a mechanism of clonal selection, indicating that sub-lethal therapeutic stress may unintentionally promote the emergence of more aggressive, relapse-prone cancer variants rather than achieving complete tumor eradication (43). Fig. 1 provides a schematic overview of the principal events associated with anastasis, which ultimately contribute to the development of a more aggressive cancer cell phenotype.

5. Melatonin: A multipotent modulator of cellular recovery

Biosynthesis and physiological pleiotropy. Melatonin is an indoleamine initially discovered by Lerner *et al* (44,45), following its isolation from the bovine pineal gland. The indoleamine is synthesized within pinealocytes from tryptophan, a process primarily driven by the nocturnal upregulation of serotonin-N-acetyltransferase (46,47). Notably, melatonin's nocturnal peak production is invariably associated with the daily dark phase regardless of the

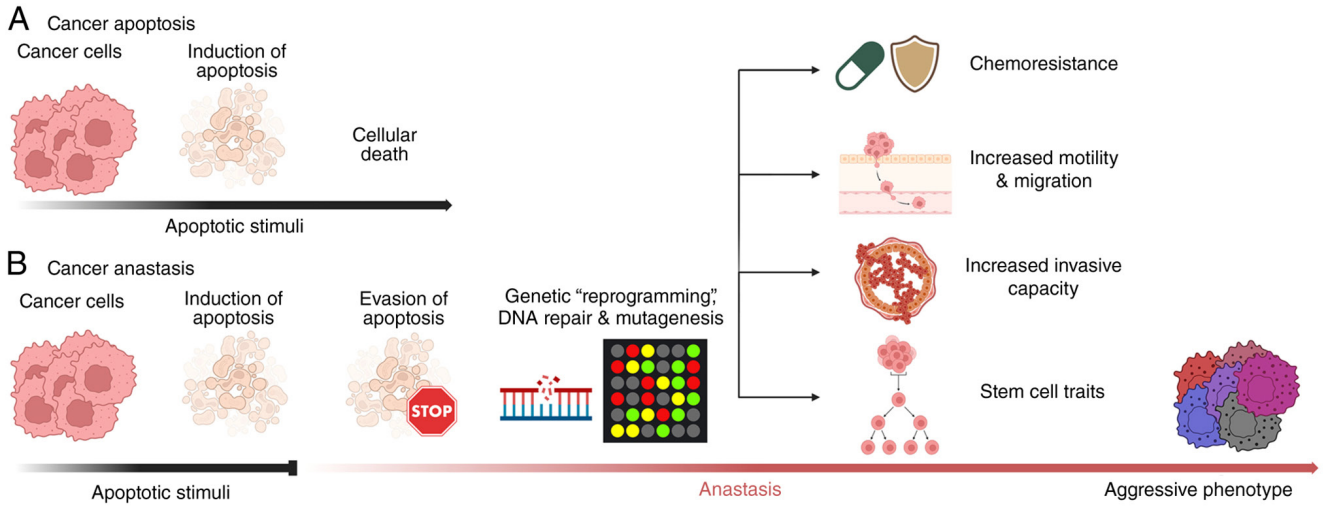

Figure 1. Schematic overview of the principal oncogenic outcomes associated with anastasis. (A) Although apoptotic stimuli ordinarily induce cellular death, (B) the process of anastasis enables cells to reverse this trajectory. This recovery promotes a form of genetic reprogramming and mutagenesis, which may contribute to the emergence of aggressive cancer cell phenotypes exhibiting increased chemoresistance, increased motility and invasiveness and stem cell-like properties. Created in BioRender. Georgiou, A. (2026) https://BioRender.com/eppw4go

activity pattern of the species, that is, diurnal, nocturnal, or crepuscular. In addition to the daily variation, pineal melatonin production appears to be directly related to the length of the night and, by extension, exhibits temporal variation throughout the year (48).

Melatonin synthesis also occurs in multiple extrapineal tissues and may, in fact, be ubiquitous in all somatic cells (49-51). Moreover, the identification of melatonin in the mitochondria of neural cells and hepatocytes, even in pinealectomized animals, and the identification of its synthetic enzymes in neurons has unequivocally confirmed the existence of extrapineal sources in melatonin production (52-55). Although the pineal gland is the primary source of circulating circadian melatonin, it accounts for <5% of total production (56). It is now apparent that most melatonin is synthesized within the mitochondria of non-pineal cells (57-59). This mitochondrial synthesis depends on acetyl coenzyme A (acetyl-CoA) derived from pyruvate via the action of pyruvate dehydrogenase (60). Under conditions of aerobic glycolysis or hypoxia, decreased mitochondrial pyruvate results in acetyl-CoA deficiency, thereby inhibiting melatonin production. Notably, supplementation with melatonin can restore normal function by promoting pyruvate transport into mitochondria, reestablishing acetyl-CoA synthesis and supporting a healthy cellular physiology (59).

Melatonin is now recognized as a functionally pleiotropic molecule. Its roles extend well beyond the regulation of circadian and seasonal biorhythms, encompassing functions in retinal physiology, immune modulation, tumor suppression, broad-spectrum antioxidant activity, and significant cardioprotective effects (61,62). Melatonin exerts its physiological effects through a dual mechanism of action: Receptor-mediated and receptor-independent pathways. Several receptor subtypes have been identified, most notably MT1 and MT2, members of the transmembrane G-protein-coupled receptor superfamily (63). The receptor-independent actions of melatonin primarily involve its capacity to directly scavenge free radicals, thereby protecting cells from oxidative damage (64).

Melatonin as a mitochondrial guardian. The direct cytoprotective efficacy of melatonin against oxidative stress is most pronounced in mitochondria, the principal source of cellular reactive oxygen species (ROS). Martín *et al* (65) indicated that melatonin accumulates in mitochondria at concentrations up to 100-fold greater than those found in plasma, where it provides protection as an endogenous antioxidant, supporting critical glutathione redox homeostasis. Consistent with its high intramitochondrial concentrations, melatonin enhances the activity of respiratory chain complexes, thereby minimizing electron leakage and free-radical generation, a protective process referred to as 'radical avoidance' (66).

The significant accumulation of melatonin within mitochondria positions it at the molecular epicenter of anastasis, where it regulates mitochondrial function and exerts essential protective mechanisms (67-69). Using multiphoton laser scanning microscopy, Jou *et al* (70) managed to elucidate the protective role of melatonin in cells harboring the mitochondrial DNA 'Common Deletion', a defect characterized by respiratory chain dysfunction and elevated mitochondrial ROS (mROS). The authors demonstrated that melatonin markedly reduced the augmented mROS formation by preventing the depolarization of the mitochondrial membrane potential, thereby inhibiting the subsequent opening of the mitochondrial permeability transition pore and the release of cytochrome *c*.

Another important mechanism of protection is melatonin's ability to preserve cardiolipin structure and functionality. Cardiolipin is a phospholipid integral to the inner mitochondrial membrane and it is essential for regulating bioenergetics and oxidative phosphorylation. However, its high unsaturated fatty acid content and proximity to sites of high ROS production render it highly susceptible to peroxidation (71,72). As a critical molecule in mitochondrial bioenergetics, any alterations to cardiolipin, such as decreased content due to reduced synthetase activity or changes in acyl chain composition resulting from altered remodeling or peroxidation under oxidative stress, can impair mitochondrial function and result in cell death through mitophagy and apoptosis (73). Cardiolipin

deficiency results in mitochondrial enlargement and loss or disruption of cristae structures, both of which are critical for the progression of apoptosis. By maintaining cardiolipin integrity and supporting mitochondrial bioenergetics, melatonin directly contributes to the energy-intensive repair processes that underlie successful anastasis (43).

Context-dependent modulation of DNA repair: Cytoprotection vs. tumor sensitization. In addition to its prominent protective function within mitochondria, melatonin serves as a critical line of defense against oxidative DNA damage, a principal adverse effect that occurs during anastasis. This genoprotective effect of melatonin appears to be context-dependent, exhibiting distinctions between normal and cancerous cells. Generally, melatonin supports genomic integrity through its comprehensive antioxidant capacity, functioning directly by scavenging free radicals and indirectly via its active metabolites, stimulation of antioxidative enzymes, and modulation of DNA repair pathways (74,75). Liu *et al* (76) employed the alkaline DNA comet assay in breast (MCF-7) and colon cancer (HCT-15) cell lines to demonstrate that melatonin pretreatment markedly increases repair capacity following methyl methanesulfonate exposure. Genome-wide gene expression analyses have suggested that this enhancement is mediated by the upregulation of critical DNA integrity-maintenance proteins, including centrosomal protein of 152 kDa and NEDD4-binding protein 2-like 2.

By contrast, a recent investigation on non-small cell lung cancer identified a distinct mechanism by which melatonin modulates genomic stability by operating as an inhibitor rather than a facilitator of DNA repair (77). A specific subset of malignant cells exhibiting aberrant germ cell gene expression demonstrate a notably aggressive phenotype, characterized by accelerated DNA double-strand break repair, rapid cellular proliferation and enhanced resistance to radiotherapy. This aggressive behavior is predominantly driven by the thyroid hormone receptor interactor 13 (TRIP13) (78). The study revealed that melatonin effectively suppresses TRIP13 expression, consequently inhibiting the critical DNA repair proteins DNA repair protein RAD51 homolog 1 and DNA repair protein Ku80. As a result, the capability of these cancer cells to conduct DNA repair is markedly diminished, thereby increasing the sensitivity to genotoxic anti-cancer interventions (77). These findings underscore the multifaceted and context-dependent role of melatonin: While it facilitates DNA repair and preserves genomic integrity in healthy or stressed cells, it can selectively impair DNA repair processes in malignant cells, thereby restricting their proliferation, increasing their sensitivity to treatment and functioning as a selective physiological regulator.

Tunneling nanotube (TNT) formation. Another important aspect in melatonin's role in promoting anastasis is the development of tunneling nanotubes (TNTs), a form of highly sensitive nanotubular structures formed *de novo* between cells to establish intricate functional networks. Originally described by Rustom *et al* (79), TNTs enable the selective transfer of membrane vesicles, cellular organelles and small molecules between cells (80,81). Mitochondria are among the key elements transported via TNTs, allowing recipient cells to incorporate exogenous mitochondria into their existing networks, thereby enhancing their energy reserves and resulting in notable alterations in bioenergetics and overall cellular function (82). Restoring cellular bioenergetics is fundamental to facilitating repair mechanisms in damaged tissue. An *in vitro* study targeting post-ischemic endothelial cells confirmed that healthy mesenchymal stem cells (MSCs) transfer functional mitochondria to cells with dysfunctional organelles via TNTs. This process effectively rescued aerobic respiration and protected the endothelial cells from apoptosis (83). Additionally, in a murine model of lipopolysaccharide-induced acute lung injury, administration of wild-type MSCs resulted in the establishment of gap junctions with alveolar epithelial cells, which allowed mitochondrial transfer and led to a significant elevation of alveolar ATP levels. Restoration of energy metabolism was critical for restoring the physiological function of alveolar cells and limiting mortality (84).

The role of melatonin in ferroptosis. Recent advances in molecular biology have elucidated novel forms of PCD, including ferroptosis, which appears to hold a critical regulatory role in cancer progression. Ferroptosis is a morphologically distinct form of PCD characterized by specific mitochondrial alterations including increased membrane density, reduced volume, loss of cristae and rupture of the outer membrane (85).

In contrast to the reversal of apoptosis, eliminating ferroptosis inducers (such as erastin or glutamate) is insufficient to arrest cell death. Instead, the survival and recovery of ferroptotic cells require the concurrent removal of the inducer and supplementation with reduced glutathione or the radical-trapping antioxidant ferrostatin-1 (86). As a mitochondria-mediated form of cell death, it is plausible that ferroptosis is markedly modulated by melatonin. By orchestrating iron chelation and antioxidant defense within the organelle, melatonin holds significant promise as a therapeutic intervention in the ferroptosis cascade (10,87). In the context of cancer therapy, unravelling the interplay between anastasis and ferroptosis is crucial for understanding chemoresistance. Targeting the molecular mechanisms underlying anastasis may potentiate the efficacy of ferroptosis-inducing agents, offering a synergistic strategy to overcome drug resistance (88).

In summary, melatonin transcends its classical role as a circadian transducer to function as a fundamental driver of cellular resilience. Its pleiotropic capacity is defined by a precise context-dependence: acting as a mitochondrial guardian and genomic protector in healthy tissue, while conversely sensitizing malignant cells to therapeutic intervention. By orchestrating these diverse mechanisms, melatonin secures the physiological stability required for successful anastasis and tissue regeneration. Fig. 2 provides a schematic overview of some of the pleiotropic effects of melatonin.

6. Conclusion

The identification of anastasis has fundamentally challenged the long-standing dogma of apoptotic irreversibility, revealing a conserved survival mechanism that preserves tissue integrity under transient stress but may also serve as a potent driver of tumor evolution and therapeutic

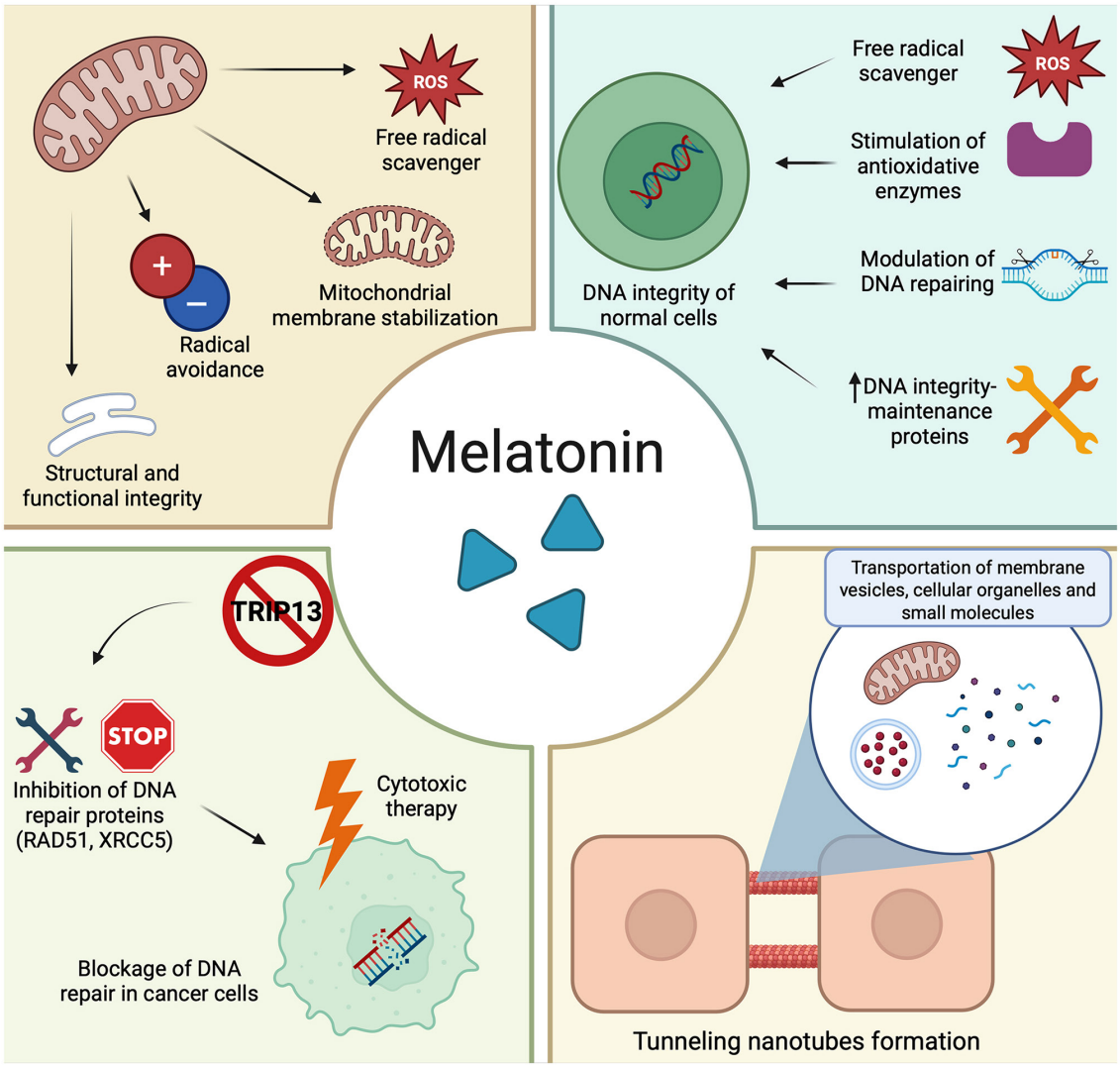

Figure 2. The pleiotropic actions of melatonin associated with cellular anastasis. Melatonin accumulates within mitochondria, serving as a direct free radical scavenger while maintaining their structural and functional integrity through mechanisms such as radical avoidance and mitochondrial membrane stabilization (top left). In non-malignant cells, melatonin supports DNA integrity by stimulating antioxidative enzymes, regulating DNA repair processes, and upregulating proteins responsible for maintaining DNA stability (top right). Conversely, in cancer cells, melatonin exerts context-dependent effects that inhibit DNA repair. For example, by suppressing TRIP13 expression, melatonin reduces the activity of repair proteins RAD51 and XRCC5, thus enhancing cellular sensitivity to cytotoxic therapies (bottom left). Additionally, melatonin promotes the formation of TNTs, which facilitate the intercellular transport of membrane vesicles, small molecules, and functional mitochondria, contributing to the restoration of bioenergetics and supporting anastasis (bottom right). Created in BioRender. Georgiou, A. (2026) https://BioRender.com/0f7njf4. ROS, reactive oxygen species; TRIP13, thyroid hormone receptor interactor 13; RAD51, DNA repair protein RAD51 homolog 1; XRCC5, DNA repair protein Ku80; TNTs, tunneling nanotubes.

resistance. Drug resistance is a principal factor contributing to cancer-related mortality and constitutes a significant challenge that requires urgent attention (89,90). The 'resurrection' of dying cancer cells following sub-lethal cytotoxic stress may facilitate the persistence of more aggressive, genetically unstable clones exhibiting enhanced metastatic potential and stem-like properties.

The anticancer properties of melatonin have been extensively investigated in recent years, with research focusing on both its potential roles in cancer prevention and treatment (91-94). In the context of anastasis, melatonin emerges as a compelling, mechanistically grounded candidate pharmacological modulator whose pleiotropic biology intersects with key molecular determinants of apoptotic recovery. Through its capacity to preserve mitochondrial structural integrity, regulate cellular bioenergetics, and modulate DNA repair pathways in a context-dependent manner, melatonin may exert a dual influence on cell fate. While its cytoprotective and genome-stabilizing properties may support cellular recovery and survival in normal tissues, melatonin has also been shown to exert onco-suppressive and cytotoxic effects in malignant cells by disrupting tumor-promoting processes, including the inhibition of DNA repair, modulation of redox balance, and interference with proliferative signaling pathways (10,95). In addition, melatonin is increasingly recognized as an important regulator of the immune system, capable of modulating both innate and adaptive immune responses, enhancing antitumor immunity, and influencing the tumor microenvironment. These immunomodulatory properties suggest that melatonin may also have potential as an adjuvant in cancer immunotherapy, possibly improving immune-mediated tumor control while protecting normal

tissues from therapy-associated damage (94,96). Taken together, this dual and context-dependent behavior suggests that melatonin may simultaneously protect normal tissues from stress or treatment-induced injury while sensitizing cancer cells to anticancer therapies and supporting antitumor immune responses.

Nevertheless, despite the growing body of evidence supporting the existence of anastasis, several conceptual and methodological challenges remain unresolved. The operational definition of anastasis varies considerably among studies, as differences in experimental systems, apoptotic stimuli, exposure duration and recovery conditions may substantially influence the observed extent of cellular recovery. Furthermore, it remains difficult to ascertain whether cells that survive despite exhibiting apoptotic characteristics truly undergo reversal of the death program or merely constitute a selected population of intrinsically resistant clones. In addition, further investigation is warranted to elucidate the biological effects of melatonin which appear to be highly context-dependent and influenced by factors such as concentration, timing of administration, duration of exposure, and cellular background. Finally, the majority of available evidence has been derived from *in vitro* experimental models and the extent to which these findings accurately reflect the complexity of the tumor microenvironment and their applicability to clinical settings remains uncertain.

The principal objective of the present study was to introduce the concept of anastasis, examine its potential implications for the development of more aggressive cancer phenotypes and therapeutic resistance and, based on mechanistic evidence, propose the possible involvement of melatonin in this process. While the mechanistic rationale linking melatonin to pathways associated with anastasis is biologically plausible, the proposed role of melatonin in modulating pathways associated with anastasis remains largely theoretical and requires further experimental validation. Future progress will depend on the development of robust *in vitro* and *in vivo* models capable of faithfully recapitulating the tumor microenvironment during apoptotic recovery, as well as the identification of reliable biomarkers that can detect and monitor anastasis in clinical settings and evaluate the translational relevance of melatonin in this context.

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Authors' contributions

AG performed the literature review, writing of the manuscript and preparation of the figures and the table. DAS, VZ and RJR contributed to the conceptualization of the study. DAS and VZ supervised the writing process. RJR critically reviewed and polished the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

AG, RJR, VZ and DAS declare that they have no competing interests. DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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