The Role of Biophysical Mechanisms on Apoptosis and Cancer Pathogenesis

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Received December 22, 2023
Accepted April 01, 2024
Electronic access April 15, 2024

A multitude of crucial biological and physical processes play key roles in the onset of apoptosis and cancer pathogenesis. Apoptosis plays a pivotal role in the balance of tissue homeostasis by mediating the existence of cells, with caspase enzymes and apoptotic proteins used to condense cellular membrane and thus dispose of faulty cells. In this paper, we ask: How do the biomechanical and physical processes that govern apoptosis and cancer proliferation function? This question is important given its implications in current advances made in novel cancer treatments involving deliberate initiation of apoptosis. The overall findings of the research go into depth regarding the physical processes of extrinsic and intrinsic signal transduction, mitochondrial permeability, oxidative stress, execution pathway, cellular physics of metastasis, and gene mutations of apoptosis. From this research, it is evaluated that the in-depth review of the processes of VDAC during apoptosis or review of shear stress during metastasis can help better predict the factors that would facilitate such processes and thus prove useful in the development of new cancer treatments that leverage these biophysical processes. As such, the application of biophysics could provide novel perspectives and findings that would greatly benefit the development of future cancer treatments that induce apoptosis and would also allow for findings behind the factors that lead to metastasis.

Keywords: Signal transduction, apoptosis, metastasis, caspases, p53, shear stress, mitochondrial permeability, cancer, biophysics

Introduction

The current forefront of the battle within the medical world is the development of cancer therapeutic technologies and their interplay with the process of apoptosis. Cancer is defined as the overarching term referring to diseases characterized by uncontrolled growth of abnormal cells with the capacity to destroy healthy body tissue[1]. As reported by the World Health Organization, cancer claims the lives of approximately 10 million individuals annually[2], with over 1.8 million new cancer cases found per year in the United States[3]. Due to the absence of a definitive cure to the disease and the precarious nature of the illness, it emphasizes why the disease is the principal focus in research and development around the globe. On the other hand, in relation with cancer is a phenomenon known as apoptosis, colloquially known as "programmed cell death", can be defined as the genetically predetermined and safe form of cell suicide[4]. This mechanism plays a crucial role in essential physiological processes such as embryogenesis and adult tissue homeostasis, while simultaneously acting as a mechanism for tumor surpression[5]. Apoptosis is crucial for the well-being of cells and the human tissue, as a dysfunction of this process can cause damaged or worn-out cells to replicate and take over healthy cells and tissue, forming a tumor that can potentially be cancerous[6].

Biophysics is a multidisciplinary subject that involves combining the two disciplines of biology and physics with the goal of deciphering biological processes and systems using physics and scientific principles[7]. The core similarities between the two subjects involves the implementation of the scientific method, and the varying theoretical explanations of phenomenon allow the two subjects to complement one another to explain real-world systems. Biophysics, in particular, applies a unique approach to investigating biological systems by examining interactions between cells and their constituent particles[8]. It is through the fusion of theoretical physics with empirical biology that we gain valuable insight into living organisms and the intricate mechanisms that underly their existence.

Within this paper, current findings of literature were utilized to compare the implications of apoptosis and its relationship with cancer. This was accomplished by employing biophysical concepts and mechanisms to assist the explanation of the biological processes, such as apoptosis and cancer[9]. The objective was to investigate the interactions between cells and their surroundings, with a particular emphasis on understanding the molecular dynamics, mechanical behaviors, and signaling pathways that impact cell fate and contribute to cancer formation[10]. In addition, the employment of mathematical models and formulae through biophysical investigations were seen in order to identify

the principles that govern these complex processes.

Methods

The primary tools utilized to conduct this research paper were Google Scholar and Elsevier, which involved searching up peer-reviewed research papers by utilizing an array of keywords. The criteria employed when filtering relevant papers were: i) the paper should have been originally published in English, ii) the paper should be authored by one or more scientists, iii) the paper should be published in mid-to-high impact journals, iv) the title of the paper must contain at least one of the key words underlined in Table 1, v) the paper should demonstrate a high level of impact evidenced from high citation rates and downloads, vi) each paper should provide novel insight and additional contribution to existing knowledge. To mitigate potential biases, the cross-review of various papers had been done to include similar information and all perspectives delineated below are accompanied with citations. Additionally, the quality of such papers was analyzed by their extent of employing professional formatting and proofreading, coupled with presence of reputable academic positions attained by authors.

Specific terms
Apoptosis and programmed cell death
Apoptotic
Cancer and metastasis
Biophysics and biomechanics
VDAC
Reactive oxygen species
Cell adhesion
Shear stress and epithelial cells
P53 and mutations
Matrix stiffness and fluids
Mitochondria and caspases

Table 1 The specific terms searched in the Google Scholar and Elsevier search engines related to the research question.

Overview of Apoptosis

Signal Transduction Pathways

Apoptosis, also known as programmed cell death, is a highly intricate system of processes crucial for maintaining tissue homeostasis and eliminating unwanted or damaged cells[4]. When encountering external stimuli from the environment or internal stimuli in the form of DNA damage, apoptosis undergoes two signaling pathways: the extrinsic and the intrinsic pathway[12,13]. Certain proteins such as pro-apoptotic Bcl-2 proteins initiate the release of cytochrome-c into the cytoplasm during the intrinsic pathway and cause in the activation of caspase enzymes, which are enzymes responsible for cleaving various cellular substrates initiating morphological changes[14]. However, in the extrinsic pathway, it can be seen in figure 1A that death domain proteins are more directly involved in caspase autocatalytic activation[11]. After caspase cleavage, proteolytic events cause the breakdown of various cellular components and the condensation of cellular contents lead to the formation apoptotic bodies, which are subsequently engulfed and cleared by phagocytes in order to prevent inflammation[15].

Within the extrinsic pathway, apoptosis is initiated in response to external stimuli such as toxins, hormones, cytokines or growth factors detected in the extracellular landscape. These stimuli can cause cellular damage or malfunction, triggering extracellular signals throughout the immune system to start the production of apoptotic death receptors[16]. These death receptors include Fas receptors, death receptors 4/5 (DR4/DR5), tumor necrosis factor receptors (TNF-R), and TNF-related apoptosis-inducing ligand receptors (TRAIL-R[11,12]. Upon the interactions at the cell surfaces, the death receptors interact with their respective ligands, which are molecules designed to bind with certain receptors, to recruit cytoplasmic adaptor proteins such as Fas-associated Death Domain protein (FADD) or tumor necrosis factor type 1 associated death domain protein (TRADD)[17]. The role of these adaptor proteins is to collaborate with the death receptors to form death domains that activate specific apoptotic enzymes known as caspases (cysteine-dependent aspartate-directed proteases) through signaling complexes such as the death-inducing signaling complex (DISC) for FADDs or complex I for TRADDs[18,19]. These signal complexes induce the autocatalysis of the inactive initiator pro-caspase-8 to the active caspase-8 as seen in figure 1A, with the pro-caspase interacting with the signaling complex to undergo activation[11]. Active initiator caspases such as caspase-8 and caspase-10 acts as a catalyst that initiates the activation of various other executioner caspases such as caspase-3, 6 or 7 that are involved in the execution process of apoptosis[11,18].

In comparison, the intrinsic pathway refers to the intracellular signaling transmitted due to the detection of positive or negative stimuli[13]. Negative signals result from the absence of certain growth factors, hormones, and cytokines, triggering apoptosis by failing to suppress death programs[20]. On the other hand, positive signals, such as radiation, toxins, hypoxia, hyperthermia, viral infections, and free radicals, actively induce apoptosis within the cell[20]. Upon detection of the positive or negative signals causing changes in the permeabilization of the mitochondrial membrane of a cell, pro-apoptotic Bcl-2 family proteins such as Bax and Bak which are present in the mitochondrial membrane of the cell release cytochrome c (Cyt-c) proteins into the cytoplasm upon their activation[21]. Usually, anti-apoptotic Bcl-2 family proteins such as Bcl-2 and Bcl-xl act to preserve mitochondrial integrity by blocking the efflux of Cyt-c to prevent cell death of healthy cells[22]. However, in the case of an imbalance of pro-

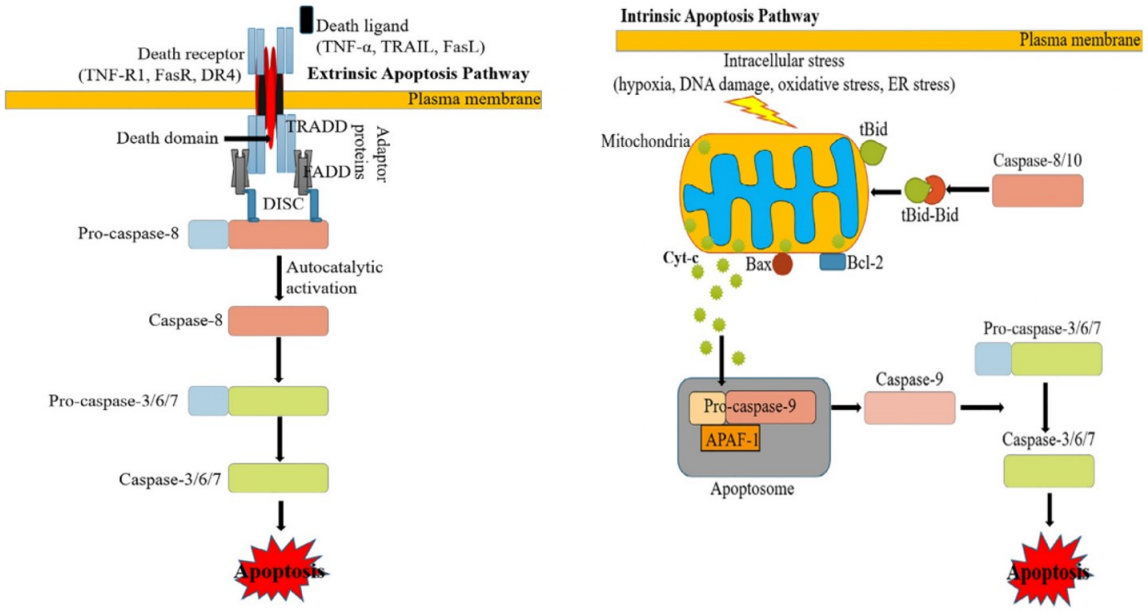

Fig. 1 An overview of the two main pathways in apoptosis: the extrinsic pathway (Figure 1A) and the intrinsic pathway (Figure 1B).[11]

apoptotic and anti-apoptotic proteins and an under expression of anti-apoptotic proteins can cause excessive apoptosis and thereby lead to autoimmune disorders that kill off healthy cells. Conversely, the under expression of pro-apoptotic proteins can lead to unhealthy and faulty cells to remain and proliferate into a malignant tumor[23].

As seen in figure 1B, activation of pro-apoptotic proteins occurs through the conversion of a protein called Bid to tBid by initiator caspases-8 or -10 activated from the extrinsic pathway, showing how the two pathways interact together[11]. Another form of activation is through activation of p53 induced by stressors, which leads to the activation of BH3 initiator proteins like PUMA and Noxa thus activating the respective pro-apoptotic proteins[24]. After the interactions between the various pro-apoptotic and anti-apoptotic proteins on the mitochondrial membrane, the permeability is comprised thus allowing for Cyt-c to get released into the cytosol to interact with a cytosolic molecule called apoptosis factor-1 (Apaf-1)[25]. These two components interact with the inactive enzyme of procaspase-9 to form a protein structure known as an apoptosome which plays a role in mediating the activation of initiator caspases by transforming the procaspase-9 to the active caspase-9. This caspase helps initiate the inactive procaspase-3,6, and 7 in order to be activated into their respective executioner caspases playing the important role of breaking the cell apart to be disposed[26].

Mitochondrial Permeability

The mitochondrial outer membrane's permeability is a crucial element in the intrinsic pathway, dictating the release of pro-apoptotic substances from mitochondria. The Bak and Bax proteins function by oligomerizing at the mitochondrial outer membrane with other surface mitochondrial proteins to induce pore formation, facilitating the release of cyt-c[27]. There are several biophysical theories that explain the various mechanisms that cause pro-apoptotic proteins to increase mitochondrial permeability. The first theory simplifies the process of mitochondrial penetration to be a physical process that involves the insertion of these Bak and Bax proteins into the mitochondrial outer layer to directly form a channel for Cyt-c to pass easily[28]. Another theory that is brought up is the involvement of voltage-dependent anion channels (VDAC) through the interactions with the mitochondrial membrane proteins to form large pores. This works by regulating the influx of bodies such as ions, nucleotides, metabolites in order to mediate the transportation and interactions between the cytosol and the intermembrane space of mitochondria[29]. The application of voltage is seen through the emission of electrical signals causing the flow of charged bodies, with the electric potential of 30 mV and higher seen to be in its closed position while any lower causes the VDAC protein to transition to its open state[30]. Due to the size of VDACs being too small for proteins to pass, this particular theory assumes that the pro-apoptotic Bak and Bax proteins undergo conformational changes when interacting with the surface of the mitochondria[23,25,31]. When the matrix experiences an exces-

sive influx of Ca2+ cations, the transportation of Ca2+ through VDAC1 across the outer mitochondrial membrane, along with the activity of the mitochondrial Ca2+ uniporter (MCU) in the inner mitochondrial membrane (IMM), results in the loss of membrane potential[31]. Lastly, the third theory that aims to explain the change in mitochondrial permeability is a proposal that states the pro-apoptotic Bax and Bak proteins play a role in modifying the mitochondrial proteins to assist the formation of a permeability transition pore and the release of Cyt-c[25].

Redox Regulation of Cell Death

Within cellular processes involving apoptosis, the biophysics concept of reactive oxygen species are pivotal as essential regulators in terms of cellular signaling. Reactive oxygen species (ROS) are an 'umbrella' term for an array of highly reactive molecules that are derivatives of molecular oxygen (O_2), with notable ones including hydroxyl radical (•OH), hydrogen peroxide (H_2O_2), and superoxide anion (O_2^-)[32]. These ROS are generated in moderate amounts as a result of standard cellular physiological processes, which specifically include the oxidative phosphorylation during mitochondrial respiration[33]. However, oxidative stress can occur as a result of excessive ROS production from other potential lifestyle or environmental factors such as ionizing radiation, smoking, or alcohol, which can cause impaired cellular function and thus stimulate intrinsic pathway apoptosis[34]. Under controlled amounts, ROS also play a role as chemical messengers, with important roles such as being involved in receptor-mediated signaling pathways and transcriptional activation to initiate processes such as the intrinsic apoptotic caspase cascade that involve in the cyclical activation of caspases. However, in excessive amounts, ROS molecules may cause DNA damage to occur through redox reactions to forcibly initiate apoptosis[32]. With ROS' multiple functions, some ROS activate sphingomyelinase generating ceramide, a key player in mediating intracellular apoptosis in granulocytes which are a type of white blood cell containing secretory vesicles known as granules to release proteins[35].

Execution Pathway

The execution pathway refers to the actual process of cells being destroyed, caused by the activity of executioner caspases after undergoing the extrinsic or intrinsic signaling pathway. This is considered to be the last phase of apoptosis, involving executioner caspases such as caspase-6, caspase-7 and caspase-3 to cleave various substrates such as cytokeratin and cytoskeleton protein α-fodrin. Executioner caspases work by producing cytoplasmic endonuclease, enzymes that are responsible for cleaving with a phosphodiester bond in order to break down nuclear material[37]. Additionally, they release various proteases which are responsible for breaking down nuclear and cytoskeletal proteins. Caspase-3 is considered to be one of the most crucial and studied executioner caspases due to its role in activating the endonuclease caspase-3 activated DNase (CAD) through cleaving with its inactive form, DFF 45 (ICAD)[38]. This activated CAD makes its way to the nucleus in order to degrade chromosomal DNA within the nuclei, as seen in figure 2 within the nucleus, and causes DNA fragmentation, which refers to the process in which DNA molecules are broken into smaller fragments by the cleaving of CAD at the internucleosomal linker sites in between nucleosomes[39]. In parallel, chromatin condensation takes place within the nucleus, wherein chromatin undergoes a phase change from heterogenous, genetically active networks to an unreactive condensed state that fragmented and disposed of into apoptotic bodies[40].

Another component that defines the execution pathway is the cytoskeletal reorganization and membrane blebbing of the cell surface of the apoptotic cell. During apoptosis, an almost universal component is cell shrinkage causing the loss of contact and detachment from neighboring cells or the extracellular matrix. Upon release from the extracellular matrix, focal adhesions are calibrated, and the cell adopts a rounded shape. After this, a protein known as actin that helps form short, polar filaments to increase tensile strength encounters a loss of its stress fibers and thereby cause the reorganization of this actin into a peripheral ring within the cell[41]. Then, another protein known as myosin II is stimulated via phosphorylation causing the contraction of the cortical actin ring and creation of dynamic membrane protrusions (blebs), as illustrated in figure 2 on the cell membrane. These blebs form due to the pressure gradient between the exterior and interior of the cell and occur at specific locations where the strength of the cytoskeleton is weakened[42].

After this process, the last component of apoptosis is seen through phagocytic consumption of apoptotic bodies and fragment. After undergoing the blebbing stage, an apoptotic cell enters a condensation stage that involves the formation of sealed membrane vesicles known as apoptotic bodies that contain intracellular material are formed due to the cytoskeletal instability during the execution pathway[42]. In parallel, the externalization of the phosphatidylserine takes place due to the loss of amino phospholipid translocase activity, however, research indicates the role of caspases such as caspase-3 and caspase-7 in mediating this mechanism. This occurs when phosphatidylserine, normally located in the inner leaflet of the plasma membrane, become exposed on the outer leaflet due to the redistribution of membrane lipids as mentioned previously. The importance of this process is in its role of acting as an 'eat me' signal so that a variety of engulfment receptors can recognize these signals to initiate phagocytosis. During phagocytosis, rapid removal of these apoptotic bodies by macrophages or phagocytes takes place, with the process being notable for preventing leakage of potentially toxic or immunogenic cellular material leading to inflammation[43].

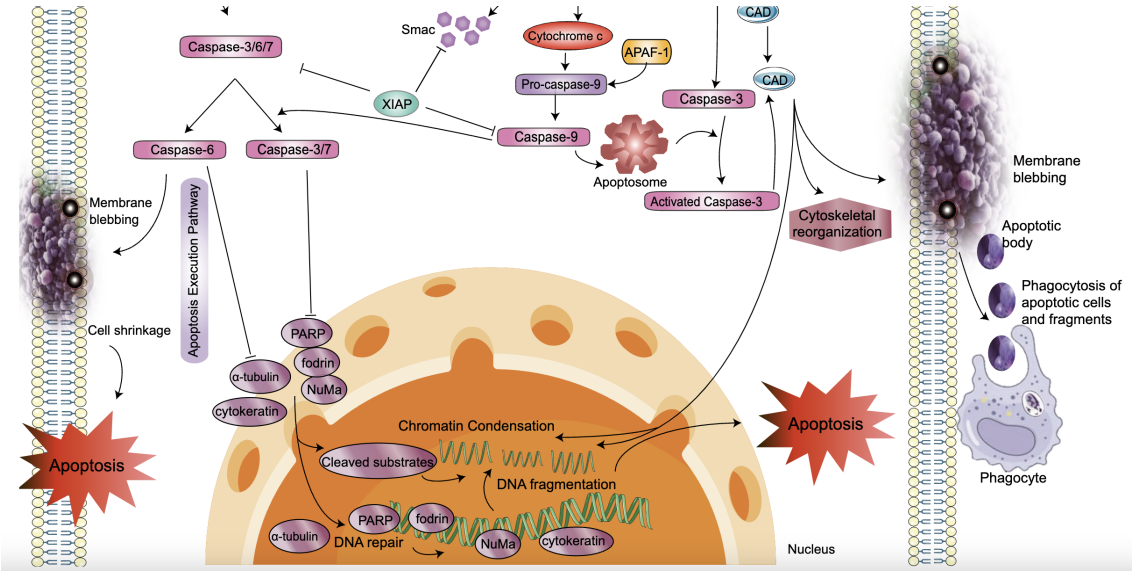

Fig. 2 The network pathways leading to the execution pathway in apoptosis. Processes involve the executioner caspases activated via either the intrinsic or extrinsic pathway to enter the nucleus in order to undergo chromatin condensation and DNA fragmentation. Additionally, cytoskeletal reorganization and membrane blebbing is seen to take place, with these features causing the cell to break down into individual apoptotic bodies. These fragments and apoptotic bodies end up undergoing phagocytosis, with the phagocyte ingesting and eliminating the apoptotic bodies to ensure safety.[36]

Biophysical Aspects of Cancer

Cellular Physics in Metastasis

One of the foremost attributes associated with malignant tumors is their aptitude for metastasis, wherein secondary tumors are established at anatomically distinct sites from the primary lesion. This characteristic divide Stage III and Stage IV cancers, the latter denoting the ability to sustain primary and secondary tumor[45]. Metastasis occurs through the process of intravasation and transport, involving a series of mechanistic adaptations within malignant cells, allowing for transportation across blood vessels of the host followed by the exit and the beginning of growth of a secondary tumor. To permit for entry and exit through the vascular system, tumor cells go through elastic changes as a result of cytoskeletal reorganization to enable penetration between endothelial cell junctions, with the intravasation section in figure 3 illustrating this feature[44]. Additionally, in consideration of the tumultuous conditions that would be faced within blood vessels, factors such as the viscosity and elasticity of a cell is crucial in withstanding fluid dynamics of blood along with ability to migrate through cellular matrices. Cellular characteristics such as the cytoplasm dictate these features, with the elasticity of a cell being dependent on the ability of the cytoplasm to rebound after experiencing a force, whereas viscosity refers to the ability of the cytoplasm to undergo flow in external shear[46]. Due to the necessity of these adaptations, evidence has shown that cancerous cells are softer than normal cells, and the extent of this feature correlates with increased metastatic potential[47]. However, there is a certain limit, as if a cell is too stiff or soft, cells will be unable to reconstruct the collagen fibres of the extracellular matrix to voyage efficiently[48].

During the cancerous cells' journey through the circulatory system, they are subject to a variety of stresses, including hemodynamic forces, collisions with other cells, and immunological stress. The circulatory tumor cells (CTCs) that overcome these stressors will be able to voyage far and greatly increase their chances of extravasation. However, a large majority of CTCs die or stay dormant, while a minute percentage survive to induce metastasis[49]. The trajectory that a CTC travels through is governed by several physical forces and mechanical parameters: diameter of blood vessels, fluid velocity and pattern of blood flow. Shear stress (τ) occurs between adjacent layers of fluid, blood, in this case, moving at different velocities[50]. As the velocity is maximum at the center and between adjacent zero at the walls, the relative velocities of adjacent layers of blood in laminar flow is characterized to be the shear rate of the system ($\frac{d\gamma}{dt}$), with γ being the amplitude of deformation and t being the time passed. As a result, shear stress is defined to be the product of the viscosity (μ) and the shear rate, being measured in Newtons per square meters (N m^{-2})[44]. Using these parameters, a calculation for the shear stress experienced by the circulating tumor cell within a blood vessel can be achieved.

$$\tau = \mu \frac{d\gamma}{dt}$$

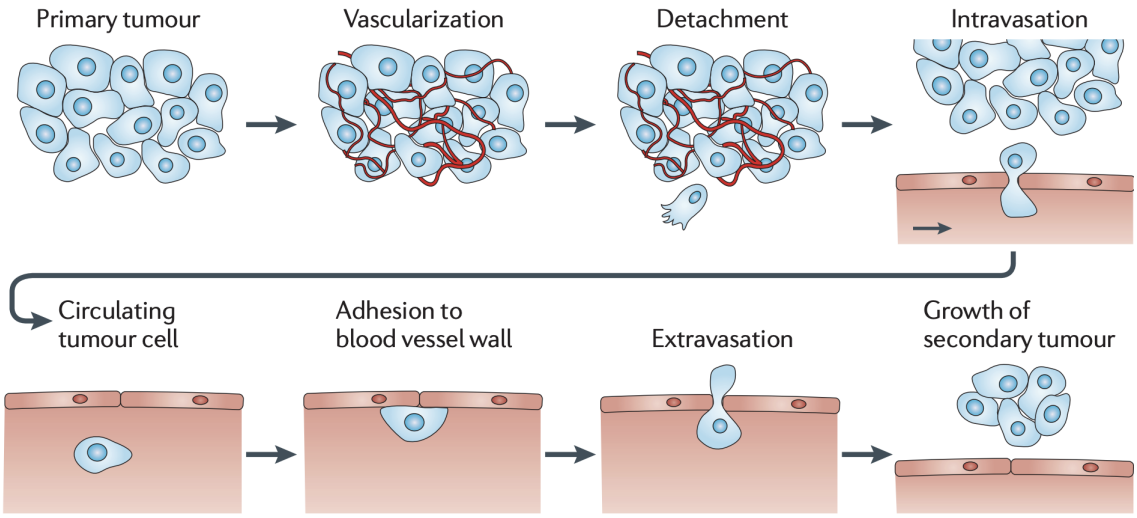

Fig. 3 The methodical process of metastasis, with processes such as detachment of primary tumor and extravasation featured.[44]

As a result of the presence of red blood cells, blood has a viscosity of approximately 4 centipoises (cP), but it is crucial to note that blood viscosity varies to a certain degree due to the fact that it is a non-Newtonian fluid. For example, blood vessels with diameters less than 300 millimeters have lower blood viscosities than vessels with larger diameters[51], causing the shear stress to be impacted through its directly proportional relationship with the viscosity. These parameters influence the orientation and, as a result, the success of a tumor cell arrested by physical obstruction or cell adhesion, with comparatively higher shear stress impeding cell adhesion and extravasation while lower shear stress can facilitate metastasis[51]. Additionally, physical blockage occurs when the diameter of an invading tumor cell exceeds the diameter of the vessel, trapping it and producing extravasation. Cell adhesion occurs when tumor cell receptors connect to the ligands of endothelial cells in a blood artery, creating adhesion forces to induce extravasation[52].

Apoptotic Gene Mutations in Cancer

The interplay of cancer and apoptosis is seen throughout all types of tumors, with the main mechanism that gives promotes cancer cell resistance to remedial treatments is the inhibition of apoptosis. Dysregulation of malignant cells can result from somatic and non-somatic mutations, a reduction in the expression of molecules that promote apoptosis, and an increase in the expression of molecules that prevent apoptosis[54]. One of the most well-researched and prominent mutations that cause the proliferation of cancerous cells are mutations of the p53 protein or a divergence in the signaling pathways to p53[55]. The role of p53 in suppressing cancers is through detection of cellular stressors, such as DNA damage, which leads to a cascade of phosphorylation events and other modifications causing the activation of the p53 protein to undergo cell-cycle arrest, apoptosis or DNA repair[56]. Due to the pivotal responsibility of the p53 protein as a tumor suppressor, almost every tumor formed would have it inactivated, through either mutation of p53 or dysfunction of associated pathways. This is because mutations to the p53 functions cause a cell to be completely devoid of instructions provided from signals and thus would not be able to execute mechanisms to protect cellular homeostasis[57].

The retinoblastoma protein (pRb) plays a crucial role in cancer biology as a tumor suppressor, primarily by controlling cell adhesions dynamics, which is a key mechanism in cancer progression and the onset of metastasis. PRb is activated through the retinoblastoma 1 (RB1) gene which provides instructions for the gene to undergo similar phosphorylation events with cells in order to limit the activation of E2F transcription factors, a family of regulators that promote cell proliferation[58]. Unlike p53, which is an activator in response to signals and is involved in the G1 checkpoint of the cell cycle, pRb is mainly involved in regulating the transition between the G1 and the S phase of cell cycle proliferation[59]. This means that it helps initiate cell cycle arrest if p53 activating factors are detected, and it prevents premature duplication of chromosomes that occurs during the S phase of the cell cycle. In figure 4, when DNA damage or other activating factors occur, p53 is activated and increases the production of p21, a protein that inhibits Cdks thus preventing phosphorylation of pRb. However, the conflict arises when pRb is mutated or dysfunctional. In this case, E2F transcription factors remain active due to the phosphorylation of Cdks with pRb thereby promoting cell proliferation[37]. The difference in scenarios is in that when p53 is functioning, it normally can activate

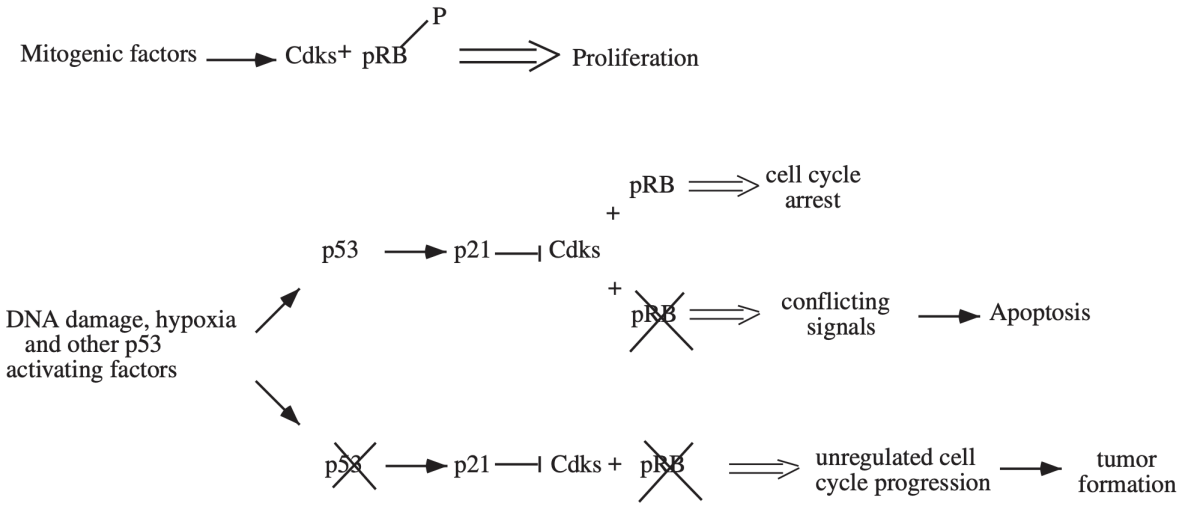

Fig. 4 The methodical process of metastasis, wherein normally pRb binds to and inactivates E2F transcription factors, which prevents cells from entering the S phase of DNA replication. When DNA damage, hypoxia or other factors occur, p53 activation occurs and facilitates p21 production, preventing phosphorylation of pRb. When pRb is dysfunctional, however, E2F remains active and phosphorylates with pRb, promoting cell proliferation.[53]

defense mechanisms such as apoptosis to prevent uncontrolled proliferation. When p53 is also dysfunctional, it can lead to unconstrained cell cycle progression thereby leading to tumor formation[60].

Discussion

The findings of this study sheds light on the interplay between two seemingly disparate disciplines and its importance on the biological processes of apoptosis and its relevance to cancer. The dysregulation of apoptotic pathways in cancer most often involves mutations or other forms of alterations in key biological regulators involved during apoptosis, such as p53 and Bcl-2 family proteins[56]. Such mutations involve structural changes involving radiation and other physical means that cause the structure of chromosomal DNA to be altered. As such, the relation of physics concepts such as electrical signals are seen through the implications of mitochondrial permeability desired for the execution of the intrinsic pathway of apoptosis, involving intricate VDACs to cause electrical imbalances leading to the change in permeability of a cell leading to apoptosis[23,25]. Additionally, this relates to the implications of metastasis in cancer, as this execution process does not take place due to mutations and thus leads to tumor cell travel along the circulatory system. This involves the physics concepts of shear rates and viscosity to best predict the sites of extravasation and explain the cause for proliferation of secondary tumors through cellular adhesion[44].

Until recently, traditional cancer therapies had tend to focus on targeting the principal tumor via invasive or destructive, through treatments such as chemotherapy, radiation and surgery. However, due to the recurring nature of cancer and the risk when undergoing such treatments, these treatments are sometimes inept and are taxing on patients[61]. Some newly proposed therapies aim to initiate inactive apoptosis through the extrinsic pathway via TNF-related apoptosis-inducing ligand (TRAIL) agonists are effective as the TRAIL pathway is independent of p53 and thus can directly activate the caspase cascade. A major advantage of this type of treatment is that it specifically kills tumor cells while leaving normal tissue cells relatively intact, which is a major problem faced by current chemotherapeutic treatments[62]. This is a pivotal step towards cancer treatment and prevention for remission, as the primary drawback facing conventional remedies is the incapacitated immune system that results from the unrestrained 'genocide' of cells causing biological processes to be hampered[62]. However, these treatments are quite novel, and so the physical and biological applications of such apoptosis-inducing remedies need to be researched more extensively in the future.

Conclusion

In the results, it can be seen that apoptosis is a mechanism that involves numerous chain events involving the activation of caspases that initiate membrane blebbing and subsequent apoptotic body consumption by phagocytes. Furthermore, the biophysics behind circulatory tumor cells involving shear rates and viscosity was explored, with the relationship of lower shear stress and higher chance of success for metastasis found out

from the investigation. As such, the analysis of the mechanisms and biophysical features of cancer development and apoptosis from a biophysics standpoint allow for the predictive modelling of biological mechanisms and thereby facilitate targeted therapy development for cancer that selectively induce apoptosis. From this investigation, the hypothesis was seen to be partially met in that various biophysical aspects were looked upon, however, the focus into its relevance directly towards its significance towards treating cancer could have been explained better. Further investigations into the cellular interactions from a structural and mechanical standpoint could be pursued to further explore the combination of physics with cancer and apoptosis. The limitations of this research are that it does not try to conduct a novel investigation that could lead to new discoveries, however, it a literature review that absorbs varying viewpoints of existing research into a compact, informative document. In sum, the field of biophysics has prompted discussions of how little is known of the human body and its afflictions, highlighting the mysteries that the human body holds are similar to that of the universe.

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