Book Chapter

Mitochondrial Dynamics Disturbance: Meeting Different Cancer Traits and Antitumor Immunity

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Abstract

Cancer is amongst the foremost reasons of mortality worldwide, and the number of new cases remains to rise. In spite of new improvements in diagnosis and therapeutic approaches, millions of cancer-related deaths happen, representing the necessity for improved therapies and diagnostic strategies. Mitochondria have been recognized as critical factors in numerous characteristics of

cancer biology, including cancer growth, metastasis, and drug resistance. Though, the modification of mitochondrial dynamics was thought to disturb the regulation of cancer cells. Mitochondria responsibilities in dynamic nets comprise variations in size and distribution of sub-cellular components, and these dynamics are upheld by two chief contrasting processes: fission and fusion. Mitochondrial fusion is facilitated by dynamin-like proteins, including mitofusin 1 (MFN1), mitofusin 2 (MFN2), and optic atrophy 1 protein (OPA1). On the other hand, mitochondrial fission outcomes in a great number of small fragments, which is mediated mainly by dynamin-related protein 1 (DRP1). As disturbed mitochondrial fission or fusion dysregulates the cellular processes that subsidize to tumorigenesis, then understanding how mitochondrial dynamics machinery is involved in cancer would present the basics to manipulate mitochondria-related processes for cancer therapy in the future. Herein, we review current advances linking mitochondrial dynamics to tumor progression at different stages and at meeting different cancer cell traits from uncontrolled proliferation, angiogenesis to invasion and metastasis, as well as on metabolic reprogramming, being a novel cancer cell trait. Additionally, this review will also cover the latest findings on the implication of mitochondrial dynamics on cancer cell extrinsic regulator, in other words the immune system.

Keywords

Cancer; Mitochondrial Dynamics; Mitochondrial Fusion; Mitochondrial Fission; Metabolic Reprogramming

Introduction

Cancer is a group of over thousand diseases characterized by abnormal uncontrolled cell growth [1]. In a healthy body, cells grow, die and are replaced in a highly controlled mechanism [1]. Damage or change in the genetic material of cells by environmental or internal factors sometimes result in cells that do not undergo apoptosis and continue to multiply until a mass of cancer or tumor develop [2]. Most cancer-related deaths are due to metastasis, malignant cells that penetrate into the

circulatory system and establish colonies in other parts of the body [3]. Great advancements have been made, but cancer is still the leading cause of death for people under the age of 85 years. In US, 1 in every 40 people die from cancer [3]. Regardless of the advancements in diagnosing and treatment strategies, millions of cancer-related deaths are still occurring, implying for better therapeutic strategies. Taking into account the essential role played by the mitochondria from cellular energy metabolism, free radical production (ROS, NOS), to apoptosis, it is not surprising that mitochondrial function failings has been assumed to contribute to the development and progression of cancer [4]. Mitochondrial stress has been chatted widely in the context of cancer. Although couple of studies investigated the effect of mitochondrial dynamics disturbance on cancer biology, it has not been reviewed much in the setting of cancer biology meeting different traits and stages of cancer. Mitochondrial dynamics are wisely delimited by dedicated proteins and lipids [5]. Under extracellular stimulations, mitochondria experience constant fission and fusion dynamics to encounter cellular demands [5]. The fact that the molecular players in these mechanisms are known to interact with various factors including tumor suppressors [6], regulators of cell cycle among others [7], allowed us to discuss in this review the role played by disturbed mitochondrial fission and fusion mechanisms on different traits of cancer during its development and progression. We will also cover recent findings on the effect of mitochondrial dynamics on the cancer cell extrinsic regulators, i.e. the immune system.

Insight into the Cancer Field

Cancer is well thought-out as a highly assorted and complex disease caused by the intricate interaction between the individual's genetic makeup predisposition and environmental stressors that drives the advanced transformation of normal cells into malignancy by a transition-state and a stepwise process [2]. Tremendous studies aimed at unravelling the genetic modifications occurring in tumors, but these have limited relevance for the build out of efficient therapies [2]. It is suggested that the development of an effective antitumor therapy will demand targeting of the biological tracks modified in tumor

cells [2]. Indeed, endless proliferative potential, ceaseless angiogenesis, escaping apoptosis, tissue attacks and metastasis are all well-known cancer cell traits [3]. However, quiet lately, the commonly named "metabolic reprogramming" of tumor cells is now documented as a trademark of cancer [8]. This later refers to the competence of tumor cells to modify their own metabolism in order to uphold the increased energy demand due to the ongoing growth, hasty proliferation of such cells, and to rapidly adapt for stress such as hypoxia and limited nutrient conditions [9]. The outcome of accumulated aberrations in a number of supervisory systems within cancer cells allow them to answer differently to these environmental stressors where these changes act as stimulators of cancer cells, introducing signals allowing them to adapt to these changes and survive, thereby, imitating many aspects of cancer cell behavior differentiating them from their normal counterparts [2]. Tumors can either be benign or malignant and are both classified based on the type of cell from which they arise [10]. On the mainstream, there exist three main sets of cancers, carcinomas, sarcomas, and lymphomas [11]. As carcinomas account for more than 90% of human cancers [11], so it will be the one of focus in this review.

The foremost step in the process of cancer is tumor initiation, this step is believed to be a result of genetic changes or alterations in indispensable genes regulating cell cycle such as proto-oncogenes and tumor suppressor genes (TSGs) leading to atypical proliferation of a single cell, forming clonally-derived tumor cells [11]. The formed proliferative cell population is benign and alone it's not adequate for them to attack the surrounding tissue and thus they form a benign adenoma (Epithelial-derived cancer) [11]. Then clonal selection promotes further growth of such adenomas giving rise to malignant carcinomas capable of invading the surrounding tissue through basal lamina into the underlying connective tissue, they also spread into other parts of the body through the circulatory and lymphatic vessels (metastasis) [11]. As cancer cell rapidly grow, they require more nutrients and oxygen supply to meet their elevated demands, hence, this is reached when cancer cells release growth factors allowing new blood vessel formation (angiogenesis) which is needed for cancer to grow [12].

Additionally, epithelial mesenchymal transition (EMT), invasion and metastasis are all well-known properties of cancer cells that affect their interaction with the tissue components and influence the progression of cancer [13]. Such hallmarks are shown in Figure 1.

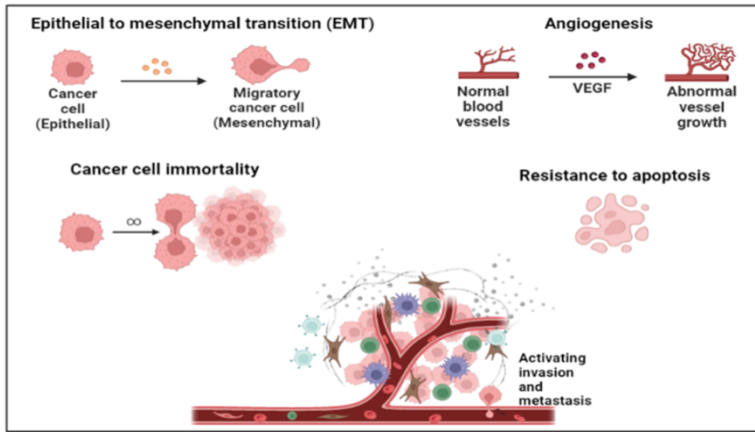

Figure 1: Cancer cell hallmarks. The Hallmarks of Cancer were planned as a set of functional competences developed by human cells as they make their way from normalcy to abnormal growth states, more precisely competences that are critical for their aptitude to form malignant tumors. These hallmarks comprise resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis (EMT). [3].

Mechanism of Tumor-Induced Angiogenesis

Angiogenesis, growth of vascular network from existing vasculature, is necessary to supply nutrients, oxygen and to upkeep the growth of the proliferating tumor [12]. Such blood vessels are made in response to growth factors (GFs) secreted by tumor cells, which in turn pushes the proliferation of endothelial cells in the walls of capillaries in the immediate tissue, resulting in the extension of new capillaries into the tumor [12]. This process doesn't merely support tumor's amplified demand to nutrients and oxygen, but also support cancer metastasis [12]. Over the past decade, our understanding of the molecular mechanism of angiogenesis has augmented and lead to the agreement of anti-angiogenic drugs for cancer [12]. But

inadequate efficacy and resistance remain an issue to be fixed. Tumors release and persuade angiognic and antiangiogenic factors which play fundamental roles in regulating endothelial cell (ECs) proliferation, migration, apoptosis, cell-cell or cell-matrix interaction and adhesion through diverse intracellular signaling, which are assumed to be critical mechanisms during this process [12]. Well, the steps of angiogenesis are acknowledged which comprise: degradation of the basement membrane by proteases, migration of ECs, lumen formation and formation of a new basement membrane among other completing steps of the process [12]. The epithelial progenitor cells (EPCs) are thought to be the ones in charge for angiogenesis [14]. The furthermost frequently found angiogenic factors are vascular endothelial growth factors (VEGF) and Basic fibroblast growth factor (bFGF), which when meeting ECs, they bind to the Tyrosine kinase receptors (TKRs) on EC membranes, causing the activation of numerous signaling proteins comprising src, PI3-Kinase, signal transducers and activators of transcriptions (STAT), which in turn initiates pathways provoking the cell cycle machinery [15]. VEGF triggers ECs to yield urokinase-like plasminogen activator (uPA), proteolytic enzymes and interstitial collagenase [15]. Plasminogen activators activate plasminogen to plasmin which can break down extracellular matrix (ECM) components [15]. Tang et al have demonstrated that Urokinase-type Plasminogen Activator Receptor (uPAR) occupancy on ECs results in phosphorylation of focal adhesion proteins and the activation of MAP kinase through thus influencing EC migration and proliferation [16]. Actually, liberal growth of tumors generates continuing hypoxia, which upregulates numerous proangiogenic factors comprising VEGF, bFGF and TGF-β among others [15].

Tumor Cell Migration and EMT: The Road for Metastasis

Cancer cells are less strictly controlled than normal cells by cell-cell and cell-matrix interactions. Generally, cancer cells are less adhesive than normal cells, often as a result of reduced expression of cell surface adhesion molecules (CAMs) [17]. E-cadherin, is encoded by CDH1 gene, it is localized within the

adherens junctions at the baso-lateral membrane, it is a principle adhesion molecule of ECs, and it is important in the development of carcinomas [18]. Reduced expression of CAMs in cancer cells permit them to be unrestrained by the cell-cell and cell-matrix interactions, in that way, contributing to their aptitude to invade and metastasize [17]. Moreover, the reduced adhesiveness of cancer cells to the other cells or to their matrix, also outcomes in changes in their cytoskeletal protein arrangements, giving such cells a mesenchymal cell shape, being a stage in epithelial mesenchymal transition (EMT) [19]. EMT, a significant biological process over which epithelium-derived malignant tumor cells obtain the skill to migrate and invade, acts as a crucial role in cancer development and metastasis [20]. Several oncogenic pathways act to induce EMT and this include TGF-β, Wnt, and Notch pathways [20]. These pathways have been revealed to trigger transcription factors such as snail and slug which in turn act as transcription repressors of E-cadherin expression [20]. During EMT, ECs loose tight and adhesion junction proteins such as E-cadherin and α-catenin and up-regulate the mesenchymal cell specific marker proteins, N-cadherin, Vimentin, and Fibronectin [20]. Afterwards, ECs lose cell-cell adhesion structures and polarity, they then attain the motility and invasive features allowing them to enter the blood or lymphatic vessels and colonize distant tissues [20].

Metabolic Reprogramming of Cancer Cells: A Novel Cancer Cell Trait

"Metabolic reprogramming" refers to the talent of cancer cells to adjust their metabolism in order to support the augmented energy demand owing to continuous growth, rapid proliferation among others [21]. It encompasses some vital changes in bioenergetics and thus involves the mitochondria in this actual setting [21]. Uncontrolled proliferation is one of the most relevant characteristic of cancer cells, and not only does this feature lead to the de-regulated control of cell proliferation, but also corresponds to the adjustment of energy metabolism to meet the increase in cellular energy demands [22]. That's to say that cancer cells get used to this condition by skewing its metabolism towards aerobic glycolysis, glutaminolysis, and mitochondrial

biogenesis and activities, all of which are prominent in the majority of cancers [22]. Inhibition of glycolysis has been shown to hinder cancer growth in vivo and in vitro [23]. Under normoxic circumstances (i.e. aerobic conditions), the metabolic activity of cells predominantly relies on the mitochondrial oxidative phosphorylation (OXPHOS) to generate ATP [24]. Whereas cancer cells become desirous for glucose as they favorably undergo glycolysis even under aerobic conditions [24]. As aerobic glycolysis produces only 2 ATP/ glucose molecule, amplified uptake of glucose is encountered by cancer cells via the up-regulation of glucose transporter expression [24]. Cancer cells does this so by regulating the equilibrium between oncogenes and TSGs, MYC and HIFA, being oncogenes have been revealed to induce cancer glycolysis, however, P53, being a TSGs that is down-regulated in many cancer cells, has been shown to impede cancer glycolysis via downregulating glucose transporters [24]. This shift of cellular metabolism from OXPHOS to aerobic glycolysis even under totally functional mitochondria is designated the "Warburg effect" [24]. The purpose of the Warburg effect for tumor growth remains mysterious. Nevertheless, hypothetical calculations by means of evolutionary game model support that cells at an advanced rate, but lesser yield of ATP might gain a discerning benefit when challenging for shared and inadequate energy incomes [25]. In reality, the tumor microenvironment have restricted availability of glucose and accordingly tumor cells must contest with stromal and immune cells for the glucose [26]. Additionally, it has been suggested that the Warburg effect may represent an advantage for the cell growth in the tumor microenvironment. The aerobic glycolysis of cancer cells creates lactic acid which gets secreted to the extracellular space, in this manner, creating an acidic microenvironment [24]. It is suggested that elevated H^+ ions within the tumor surroundings modifies the tumor-stroma border, allowing for heightened invasiveness [27]. Backing up this suggestion, it has been thought that the higher rates of glycolysis within the tumor cells limit the accessibility of glucose required by infiltrating tumor lymphocytes to sustain their effector function [28], thereby, supporting pro-tumor immunity.

Mitochondrial Dynamics: Insight into Fission and Fusion Processes

The mitochondria are highly dynamic organelles experiencing fission and fusion in a highly controlled manner. Thus, they can divide, combine, and traffic along the cytoskeleton in order to meet cell metabolic needs, where the morphology of the mitochondria is linked to its functions, including the production of ATP through OXPHOS, apoptosis, and regulation of oxidative stress [29]. The role of mitochondrial dynamics is to control the morphology, quantity, and quality of the mitochondria [29]. Besides, mitochondrial dynamics is involved in mitochondrial biogenesis, cell cycle, immunity, and apoptosis [29]. Mutations in the main apparatus constituents and flaws in mitochondrial dynamics have been linked with frequent human diseases [29]. Mitochondrial fission is a multistep procedure permitting the partition of one mitochondrion into two daughter mitochondria, whilst mitochondrial fusion is the union of two mitochondria resulting in one mitochondrion [29]. The chief proteins constituting the basic machinery are large GTPase proteins fitting to the Dynamin family (Figure 1) [30]. These factors can oligomerize and modify conformation to cause membrane remodeling, contraction, scission and/or fusion [30]. Mitochondrial fission is delimited by the recruitment of the GTPase Dynamin-related protein 1 (Drp1), a cytosolic protein, to mediate mitochondrial constriction and Dynamin2 (Dnm2) which carriers out mitochondrial scission [30]. However, mitochondrial fusion is guaranteed by mitofusins 1 and 2 (Mfn1 and Mfn2) and optic atrophy 1 (OPA1), which arbitrate outer mitochondrial membrane and inner mitochondrial membrane fusion, correspondingly [30]. Mitochondrial dynamics proteins are not merely focused in the process of fusion and fission; though they cooperate with other proteins either to accomplish their functions or to participate in other cellular processes [30]. For instance, both mitochondrial fusion and fission proteins are implicated in mitophagy, a selective mitochondrial autophagy. In contrast, mitochondrial fusion proteins are implicated in other processes like cell apoptosis, endoplasmic reticulum/mitochondrial tethering, and ensuring the alignment of the respiratory chain complexes [30].

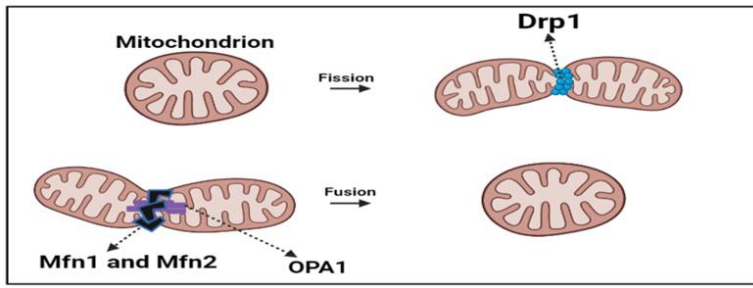

Figure 2: Mitochondrial dynamics main machinery. Mitochondrial fission is a multistep procedure permitting the partition of one mitochondrion into two daughter mitochondria. This process is mediated by Drp1. whilst mitochondrial fusion is the union of two mitochondria resulting in one mitochondrion. This process occurs due to the action of OPA1 and the mitofusins Mfn1/2. [30].

Mitochondrial Dynamics Disturbance: at Crossroads with Cancer

Mitochondrial dysfunction is a trademark of several diseases. Mitochondria and metabolic alterations have been documented as significant for cancer evolution [31]. However, a more detailed understanding of how to operate mitochondria-related procedures for cancer therapy remains to be recognized. Mitochondria are extremely dynamic organelles which constantly fuse and divide in response to miscellaneous stimuli [30]. Contribution in the above-mentioned procedures requires an accurate regulation at many points that permits the cell to connect mitochondrial activity to nutrient availability, biosynthetic demands, proliferation rates, and external incentives [32]. The altered fission/ fusion ratio is thought to correlate with different types of cancers [33]. Current studies demonstrate that augmented mitochondrial fission is a pro-tumorigenic phenotype [33]. Although much more studies point towards a link between increased fission and cancer progression, some studies demonstrated increased fusion processes during cancer evolution. Multiple factors could influence mitochondrial dynamics and this include severe stress (hypoxia, high glucose etc.) [34]. Tumor hypoxia progresses owing to irrepressible cell proliferation, altered metabolism, and irregular tumor blood vessels causing reduced transport of oxygen and nutrients [35].

Hypoxia is one of the chief characteristic of solid tumors and was revealed to associate with poor prognosis of cancer patients [35]. It has been shown to elevate the expression of some oncogenes including HIF1-α [35]. Many cancer cells showed elevated expression of HIF1-α including human prostate cancer cell lines, thyroid carcinomas, breast cancers, and liver cancers [36]. HIF1-α has been shown to promote mitochondrial fission via a process involving cyclin B1/ CDK1-dependant phosphorylation of Drp1 at s-616, allowing its translocation to the mitochondria to induce fission [37]. The expression level of Drp1 was found raised in hepatocellular carcinoma (HCC) tissues [38], glioblastoma U251 cells [39], oncocytic thyroid tumors [40], and in lung adenocarcinoma cell lines among others [41]. In human pancreatic cancer, the expression of oncogenic Ras or activation of MAP kinase pathway was associated with erk2-mediated phosphorylation of Drp1 at S-616 leading to Drp1 mitochondrial translocation and thus increased mitochondrial fission (Fragmentation) [42]. Interestingly, inhibition of this phosphorylation has been revealed as sufficient to chunk tumor growth [42]. This phosphorylation was also observed as increased in some lung cancers [43]. In contrast, a study by li et al discovered that raised mitochondrial fusion supports liver cancer and fuels tumor cell growth via shifting their metabolism [44]. Different studies have stated that the knockdown of the fusion machinery factors, chiefly OPA1 and Mfn1/2 lead to the blocking of the mitochondrial fusion process and was linked with the inhibition of cell growth in vitro and tumor creation in vivo [44].

Mitochondrial Dynamics and Tumor Cell Proliferation

In normal cells, hundreds of genes complicatedly regulate the procedure of cell division [2]. Normal growth necessitates an equilibrium between the action of those genes that encourage cell proliferation and those that suppress it [2]. Cells come to be cancerous after mutations accumulate in the numerous genes that regulate cell proliferation [2]. However, it is not surprising that defects in the expression of genes inhibiting or activating cell cycle inducers and suppressors also play an action in the process

[2]. Additionally, a normal equilibrium in fission/fusion of mitochondria is important in cell cycle progression [45]. Mitochondrial fission is an extremely controlled process that, when disturbed, can modify metabolism, proliferation and apoptosis. Interestingly, the role of Drp1 that controls mitochondrial fission has been gaining lately an interest as it has been increasingly associated with tumorigenesis via its interaction with cell cycle proteins and TSGs [46]. Theory determined study on epithelial ovarian cancer (EOC) exposed that Drp1 co-expresses exactly with the cell-cycle module accountable for mitotic evolution [46]. Shinya et al. examined cell proliferation and cell cycle utilizing the cutaneous SCC A431 and DJM1 cells that were actually transfected with shRNA vectors targeting Drp1 [47]. The study revealed that the MAP kinase signaling trail is involved in the process where MEK inhibitor PD325901 repressed cell proliferation, plus inhibited the phosphorylation of ERK1/2 and Drp1Ser616 [47]. Indicating that MEK which is activated in many cell cancers acts upstream of drp1 promoting cancer cell proliferation possibly via phosphorylation of Drp1 at serine 616. Noting that Drp1 S616 phosphorylation is essential for mitochondrial fission and even though cancer cells can survive without the energy from the mitochondria [48], they simply can't grow without mitochondria as they need it to form new strands of DNA, which we know well that it plays a key role in the process [48]. This could explain the association between increase mitochondrial fission and cancer enhanced proliferation. In addition to that, Qichao Huang et al conclusions proved that augmented mitochondrial fission plays a serious role in the regulation of HCC cell survival [49]. Where the treatment by mitochondrial division inhibitor-1 meaningfully repressed tumor development in an in vivo xenograft nude mice model [49]. Though, mitochondrial fusion has been shown to protect against cell proliferation [50]. The mitofusin Mfn2 has been presented to inhibit the ERK/MAPK signaling trail [50]. Additionally, Drp1/Mfn expression inequity has also been shown to cause additional mitochondrial fission and reduced mitochondrial fusion in human lung cancer cell lines, which is a significant process for cell cycle [51].

Mitochondrial Dynamics Implication in Apoptosis during and Outdoor of Cancer

Mitochondria play crucial roles in triggering apoptosis in mammalian cells [52]. In healthy cells, mitochondria constantly split and fuse to form an active intersecting network [53]. This network breaks during apoptosis at the time of cytochrome C release and preceding to caspase activation, producing abundant and smaller mitochondria [53]. New work shows that proteins tangled in mitochondrial fission and fusion also vigorously meet and contribute in apoptosis pathways. It remains controversial whether fission is absolutely for the progression of apoptosis. On majority, most of the studies mentioned in the literature points for the implication of mitochondrial fission in the process of apoptosis. The study by J Estaquire et al. demonstrated that Drp1-mediated mitochondrial fission inhibition prevents apoptosis via hindering the release of cytochrome C during the process of apoptosis [54]. Numerous models elucidating the mechanisms of cytochrome release have been recommended. One recommends that it rests on the activation of Drp1-mediated mitochondrial fission [55]. It is noteworthy that elevated mitochondrial fission generate more ROS which activates CD95L which further activates CD95 and mediate T cell apoptosis [56]. It has also been witnessed that the apoptotic executioner protein BAX and Drp1 has been revealed to actually interact and that this interaction is improved during apoptosis [57]. It has been noticed that upon BAX activation, Drp1 firmly associates with the mitochondrial outer membrane (MOM) through BAX/ Bak-dependent SUMO alteration of Drp1 [58]. The augmented mitochondrial fission ties up with the release of cytochrome C, where fission inhibition via RNAi targeting Drp1 slows down the release of cyto-C [54]. Martirou and colleagues lately confirmed that Drp1 encourages the formation of a nonbilayer hemifussion intermediate wherein the triggered and oligomerized BAX makes a hole, leading to MOMP [59]. Though, the procedure of fission can happen even helplessly of apoptosis processes. Consequently, in what way Drp1 contributes to apoptosis is a significant concern for upcoming studies. Not much studies for now investigating mitochondrial fusion in cancer apoptosis yet, but more fresh indication

designates that inhibiting mitochondrial fusion encourages apoptosis [60]. Qichao Huang and coworker's experiment of MFN1 knockdown was associated with the encouragement the of HCC cells survival both in vitro and in vivo largely via enabling autophagy and hindering mitochondria-dependent apoptosis [49]. The overexpression of the mitochondrial fusion machinery Mfn1/2 outcomes in slowed Bax activation, cyto-C release, and apoptosis, signifying a role for Mfn1/2 in cell death [61]. A mutant form of mfn2, which has an alteration in one of the 3 preserved residues exposed to the IMS, was incapable to protect cells from undergoing apoptosis induced by the treatment with staurosporine [62]. Moreover, since Mfn2 is recognized to inhibit ERK1/2 activation [63], and since ERK activation has been shown to encourage apoptosis [64], then Mfn2 may defend cells against apoptosis. OPA1, another fusion machinery protein, has also been revealed to be obligatory as a guard of cells from apoptosis. Olichon et al. discovered that OPA1 loss persuades unprompted apoptosis of cells. OPA1i-mediated cell death has been shown to be overcome via overexpression of bcl2 (anti-apoptotic), pointing for the likely action of mitochondrial fusion in cell death upstream of MOMP [65]. In fact, OPA1 is known to regulate normal cristae structure [65]. The majority of cyto-C is known to localize within the cristae in healthy cells, for this it has been suggested that the complete release of cyto-C from mitochondria could be a result of cristae remodeling [66]. As it appears that OPA1 oligomers seems to hold cristae at junctions together. Interestingly, the overexpression of OPA1 prevented tBid-induced cyto-C release to the IMS, which further supports mitochondrial fusion protects cells against apoptosis [67]. A recent study by Sheng-Teng Huang et al evaluated the mechanism by which Tanshinone IIA (Tan IIA) induces apoptosis in osteosarcoma cells [68]. They demonstrated that Tan IIA treatment and administration caused a noteworthy reduction in the mitochondrial fusion proteins, Mfn1/2 and Opa1, along with an elevation in the fission protein Drp1 [68]. Which further support that mitochondrial dynamic change is involved in apoptosis and that Tan IIA could represent a possible candidate to inhibit tumor progression. Hence, further studies investigating the implication of fusion blocking on apoptosis during cancer progression as a possible therapy are needed, as

well as investigating the possibility of combing the targeting both fission and fusion processes during cancer.

Mitochondrial Dynamics and Tumor Angiogenesis

Even though ECs function is influenced by mitochondrial metabolism [69], the role of mitochondrial dynamics in angiogenesis is unidentified. As tumors experience unrestrained, extreme proliferation leading to hypoxic microenvironment, such settings encourage angiogenesis to achieve cancer cell's demand for oxygen and nutrients [9]. Yet, as mitochondrial fission has been demonstrated to increase during hypoxia [70], the mechanisms encouraging angiogenesis in the context of mitochondrial fission remains foggy. The role of Drp1 in Epithelial Progenitor Cell (EPC)-mediated angiogenesis has been evaluated by Kim et al, where inhibiting Drp1 either via siRNA or treatment with Mdivi1 (Drp1 inhibitor) lead to intense drop in EPC migration, invasion, and tube formation, highlighting a role of mitochondrial fission arbitrated by Drp1 in tumor angiogenesis [70]. It is noteworthy to add that mitochondrial fission protein Fis1 has also been shown to shape EPCs and influence angiogenesis [71]. Hsueh-Hsiao Wang and colleagues overexpressed Fis1 in senescent EPCs, which lead to augmented proliferation, and restored the angiogenic potential [71].

In addition, a recent study by Stéphanie et al showed that the IMM mitochondrial fusion protein OPA1 is obligatory for tumor angiogenesis [72]. They discovered that in response to angiogenic stimuli, OPA1 levels quickly rise and that endothelial Opa1 is certainly essential in a nuclear factor kappa-light-chain-enhancer of activated B cell (NFκB)-dependent pathway crucial for tumor angiogenesis [72]. As the exact signaling involving both drp1 and opa1 in tumor angiogenesis remains unexplained, further studies into such topic is needed to unveil possible targets in the context of cancer therapy.

Mitochondrial Dynamics Meeting EMT during Cancer

Other features to be well-thought-out are cross-links with mitochondrial dysfunction and elevation of tumor cells metastasis. Epithelial–mesenchymal transition (EMT) allows

cancer cells to acquire the migration skills to traffic out of the primary tumor and translocate to new target organs. EMT coverts the EC to mesenchymal phenotypes in many epithelial tumor cells that are influenced by mitochondrial dysfunction [73]. Based on the literature, it turns out that mitochondrial dysfunction initiates EMT via EMT signaling pathways. TGF-β is recognized as a main growth factor regulates EMT development through TGF-β/SMAD/SNAIL, phosphatidylinositol-3-kinase (PI3K)/AKT signaling pathways. TGF-β phosphorylates TGF-β receptor-regulated Smad2 and Smad3, then elevate the expression of their downstream gene, Snail-1, being a positive regulator of EMT and metastasis [74]. Activated PI3K/AKT signaling can also elevate the expression of Snail, thus persuading the EMT [74]. In the tumor microenvironment, the hypoxia-induced accumulation of HIF-1 α triggers the expression of TWIST which eventually persuades EMT [75]. Additional connection with mitochondria in cancer cell metastasis is epidermal growth factor receptor (EGFR). EGFR was found highly expressed in the mitochondria of highly invasive non-small cell lung cancer (NSCLC) cells [76]. EGF is a growth factor that initiates the EMT by activating the RAS/RAF/MEK/ERK MAPK signaling cascade [76]. The activated ERK1/2-MAPK induces EMT, promoting the regulation of cell motility and invasion [76]. EGF turns on the mitochondrial translocation of EGFR, mitochondrial fission, and enhances cancer cell motility in vitro and in vivo [77]. Likewise, EGFR can regulate mitochondrial dynamics by disturbing Mfn1 polymerization, consequently, overexpression of Mfn1 opposes the phenotypes consequential from EGFR mitochondrial translocation to induce mitochondrial fission [77]. These observations indicate a possible implication of mitochondrial fusion machinery against EMT. Though encouraging mitochondrial fusion, MFN1 hinders cell proliferation, invasion and migration capability in vitro and in vivo [78]. However, mitochondrial fission has been shown to correlate with EMT during cancer progression. In breast cancer, augmented mitochondrial fragmentation or fission strengthens the capabilities of breast cancer cells to metastasize by triggering Drp1 or silencing Mfn [79]. Which indicates that elevated fission/ fusion ratio possibly associates with tumor metastasis.

The study by Jing Guoet al revealed that Drp1 elevated expression owing to high glucose resulted in augmented EMT, migration and invasion in the endometrial cancer context [80]. Where all these changes produced by high glucose could be somewhat lessened by Drp1 knockdown. Additionally, Seung-Wook Ryu et al established that TGF-β action caused in elongation of mitochondria escorted by the instruction of N-cadherin, vimentin, and F-actin in retinal pigment epithelial cells [81]. They similarly presented that Drp1 reduction augmented cell length and persuaded reorganization of F-actin [81]. In this study the authors also showed that the exhaustion of Mfn1 blocked the upsurge in cell length throughout TGF-β-mediated EMT. The results of their study together validate the participation of mitochondrial dynamics in TGF-β-induced EMT.

Mitochondrial Dynamics and Cancer Metabolic Reprograming

Metabolic reprogramming generally occurs in cancer. Mitochondrial dynamics plays a significant part in tumor evolution [31]. Though, how these dynamics mix tumor metabolism in cancer progression is quiet foggy. A study involving HCC showed that MFN1 controls metastasis through metabolic switch from aerobic glycolysis to OXPHOS [82]. Where the treatment by glycolytic inhibitor 2-Deoxy-D-glucose meaningfully suppressed the possessions persuaded by reduction of MFN1. Tian Gao et al revealed that Salt-inducible kinase 2 (SIK2), which belongs to the AMP-activated protein kinase family, encourages reprogramming of glucose metabolism via PI3K/AKT/HIF-1α pathway and Drp1-mediated mitochondrial fission in ovarian cancer [83]. As improved mitochondrial fission is established to be positively controlled through certain triggering oncogenic mutations; such as B- rapidly accelerated fibrosarcoma (BRAF), thus improving tumor progression, Rayees Ahmad et al revealed that BRAF-**V600E** induced colorectal cancers shows fragmented mitochondria which deliberates glycolytic phenotype and growth benefit to these tumors as their findings demonstrate that BRAF-**V600E** Colorectal cancer cells have higher protein levels of pDRP1-**S616** leading to a further fragmented mitochondrial state as

compared to those having a wild type BRAF [84]. Moreover, Androgen-induced expression of DRP1 has been shown to control mitochondrial metabolic reprogramming in prostate cancer [85]. Carmela Guido et al showed that mitochondrial fission encourages glycolytic reprogramming in cancer-associated myofibroblasts, inducing stromal lactate construction, and tumor growth in early stages. Where the recombinant over-expression of MFF (mitochondrial fission factor) lead to metabolic re-programming towards glycolytic metabolism [86]. As the metabolic reprogramming underlying the DRP1 inhibition is quiet undecided in cancer cells, Wenting Dai et al found that cancer cells treated with Drp1 inhibitor shows less enrichment in TCA cycle intermediates indicating less oxidative metabolism leading to reduced cell proliferation [87]. Additionally, the knockdown of the fusion regulator genes, OPA1 or MFN1, repressed the fusion process in HCC cell lines and CCA tumors [88]. This was accompanied by an inhibition in cell growth in vitro and tumor creation in vivo as well as lessened oxygen ingesting and cellular ATP manufacture of tumor cells [88]. As metabolic reprogramming represents a good way for cancer to progress, further understanding of mitochondrial dynamics in this process is warranted.

Mitochondrial Dynamics Machinery Disturbance on Anti-Tumor Immunity: A Possible Target in Immunotherapy

The innate and adaptive immune responses evoked against tumors to control them is termed “antitumor immunity” [89]. Though, the immune system has a hard time eliminating cancer cells [89]. This is due to the fact that cancer twitches when normal cells develop aberrations and begin to grow irrepressibly. Perhaps that’s why the immune system doesn’t continuously identify them as foreign [89]. For this, immunotherapy, utilizing the immune system to drive away cancer, has been planned as one of the main innovations in cancer biology [89]. This includes vaccines, cytokines, CAR T cell therapy, and monoclonal antibodies among others [89]. However, regardless of these intense advances, the effectiveness of such methods is not common and difficulties remains for the field of cancer immunotherapy. In the current years, numerous investigators

have acknowledged the possibly serious roles of mitochondrial dynamics in both innate and adaptive immunity [90]. Well, mitochondrial dynamics has been shown to influence the differentiation, activation, and cytokine construction of immune cells [91]. Immune cells, especially T cells, play a key role in immunotherapy [92]. The regulation of mitochondrial dynamics could influence T cells at different stages from clonal expansion, migration, and differentiation, thereby, affecting their effector function [93]. As it has been detected experimentally that Drp1 knockout is linked with abridged number of mature T cells, and decreased T cell proliferation even after antigen encountering [93]. Interestingly, this reduction in clonal expansion rate could be reversed by the overexpression of the phosphorylated form of Drp1 at serine 616 (Drp1-S616) [93]. Throughout the differentiation of naïve T cells into effector T cells, the metabolic manner goes from OXPHOS and fatty acid oxidation to glycolysis [94]. This procedure rest on the exact adjustment of the calcium current at immune synapses by Drp1, which encourages the transcription of genes involved in glycolysis by maintaining the activation of mTOR/cMyc [95]. It has been observed fragmented mitochondria were mostly detected in effector T cells, and this phenotype be determined by the phosphorylation of Drp1 at Ser616 to facilitate mitochondrial fission [96]. Either inhibiting glycolysis or knocking out drp1, encourages the change of T cells to a memory-like phenotype owing to the powerlessness of mitochondria to split [95]. Additionally, due to the absence of T cells or the existence of nonfunctional T cells in the tumor microenvironment, a substantial number of patients display no answer to immunotherapy [97]. As the tumor microenvironment is characterized by hypoxia and nutrient deficiency where cells compete and tumor cells mainly win, T cells experience constant TCR stimulation and grieve from nutritional shortage and hypoxia, leading to T cell exhaustion [98]. Exhausted T cells are described by reduced proliferation and functional position with co-inhibitory molecules expression [99]. Fascinatingly, exhausted T cells presented impaired mitochondria and irregular ROS production paralleled with normal T cells [100]. These observations points that mitochondrial dynamics are altered

throughout the course of T cell exhaustion, or perhaps these mitochondrial dynamic alteration causes T cell exhaustion.

Programed cell death-1 (PD-1) upregulation is one of the features of exhausted T cells, which mediates immunosuppression [99]. Simula and coworkers demonstrated that the PD-1 signal hinders the division of mitochondria in T cells by hindering the phosphorylation of Ser616 sites of Drp1, and this inhibition is achieved through the ERK and mTOR pathways [101]. In this study PD-1 inhibitors significantly improved the anti-tumor outcome of wild-type mice. It's noteworthy that reliable with the outcome of Drp1 on T cell migration defined previously, Simula and colleagues established that the density of tumor-infiltrating T cells in wild-type mice was greater than those with Drp1 Knockout, which was linked to Drp1-mediated division and reorganization of the mitochondria situated in the hind part or uropod of T cells [101].

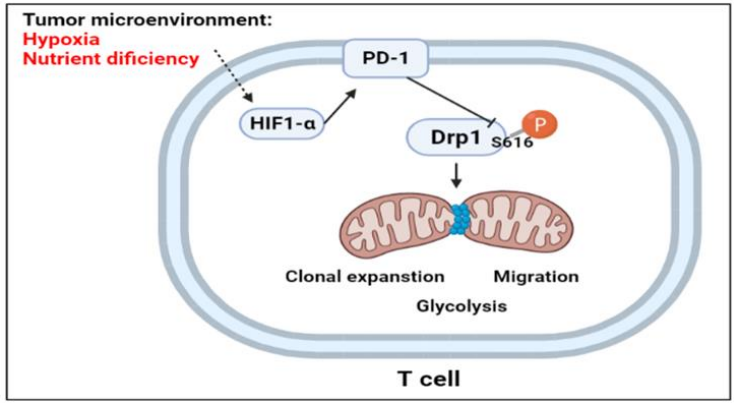

Figure 3: Involvement of mitochondrial fission in T cell activity in the tumor microenvironment. Under hypoxic condition of the tumor environment, HIF1-α becomes activated which in turn activates PD-1. PD-1 enhance T cell exhaustion via inhibiting the phosphorylation of Drp1 at S616, hence preventing mitochondrial fission-mediated processes including clonal expansion, glycolysis encouragement and migration in T cells. [102,103].

Natural killer (NK) cells have vital actions in tumor surveillance [104]. Xiaohu Zheng et al established that tumor-infiltrating NK cells in human liver cancers showed fragmented mitochondria in their cytoplasm, while liver NK cells external to tumors

presented normal large mitochondria [105]. This fragmentation was correlated with NK cell loss, causing tumor avoidance of NK cell-mediated surveillance, which expected poor survival in patients with liver cancer. They also demonstrated that hindering mitochondrial fragmentation was associated with the persistence and the antitumor capacity of NK cells. Hence, mitochondrial fission seems to play an essential role during the antitumor immunity and thus represents a potential target to enhance the antitumor immunity and fight off cancer.

Conclusion

In summary, mitochondrial dynamic disturbance seems to interfere during cancer progression by working for the favor of different cancer traits including tumor growth, angiogenesis, metabolic reprogramming, EMT and invasion (metastasis). Mitochondrial fission/ fusion ratio seems to be higher in the majority of cancers, yet the increased fusion process has been observed in some cancers as well as it leads to the inhibition of apoptosis in tumors. Fission seems to be more involved in proliferation, angiogenesis and EMT but it seems to induce apoptosis, yet increased fission is more likely to induce cancer traits wins over inducing apoptosis. As Drp1 S616 is responsible for mitochondrial fission, regulating its phosphorylation state represents a potential target to fight off tumor itself. However, mitochondrial dynamics also seems to influence the antitumor immunity. But in contrast to the negative effect of increased fission on tumor progression, increased mitochondrial fission or elevated levels of Drp1-S616 has mainly a positive influence on the antitumor immunity.

Future Directions

Further studies investigating the outcomes of combining the inhibition Drp1 phosphorylation at S616 in tumors and the effect of this Drp1 phosphorylation in antitumor immunity on the overall tumor progression in different cancers is warranted. Indicating the need of cell type specific targeting approaches. For this, also approaches aiming at easy screening patient specific cancers for the state of Drp1 phosphorylation will be of interest.

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