



Targeting cancer-cell mitochondria and metabolism to improve radiotherapy response

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ABSTRACT

Radiotherapy is a regimen that uses ionising radiation (IR) to treat cancer. Despite the availability of several therapeutic options, cancer remains difficult to treat and only a minor percentage of patients receiving radiotherapy show a complete response to the treatment due to development of resistance to IR (radioresistance). Therefore, radioresistance is a major clinical problem and is defined as an adaptive response of the tumour to radiation-induced damage by altering several cellular processes which sustain tumour growth including DNA damage repair, cell cycle arrest, alterations of oncogenes and tumour suppressor genes, autophagy, tumour metabolism and altered reactive oxygen species. Cellular organelles, in particular mitochondria, are key players in mediating the radiation response in tumour, as they regulate many of the cellular processes involved in radioresistance. In this article has been reviewed the recent findings describing the cellular and molecular mechanism by which cancer rewires the function of the mitochondria and cellular metabolism to enhance radioresistance, and the role that drugs targeting cellular bioenergetics have in enhancing radiation response in cancer patients.

Introduction

Cancer is a multifactorial disease and the choice of treatment options is dependent on many factors. Therapeutic options include surgery, chemotherapy, immunotherapy, targeted and endocrine therapies, and radiation therapy [1,2]. Despite the availability of these options cancer remains difficult to treat, particularly in advanced stages, with treatment resistance contributing to cancer progression and mortality [3]. Radiation therapy represents a method used to treat locally advanced cancer and roughly half of cancer patients are treated with radiotherapy in conjunction with surgery and/or chemotherapy, as primary therapy [4]. Radiotherapy uses high doses of ionizing radiation (IR) to evoke cell death primarily by causing cellular DNA damage [5]. Resistance to radiation also known as radioresistance is a major clinical problem in various cancer types including glioblastoma [6], breast [7] as well as oesophageal adenocarcinoma [8]. Radioresistance can be defined as a process wherein the adaptation of tumour cells to radiotherapy-induced damage leads to developing resistance to IR. Radioresistance is a complex process involving alteration of several cellular mechanisms including DNA damage repair mechanisms, cell cycle arrest, oncogenes and tumour suppressor genes, tumour microenvironment changes, autophagy, cancer stem cells generation, tumour metabolism and altered regulation of reactive oxygen species [2,9]. In addition, cellular organelles are important targets of IR and they play a significant role in medi-

ating radiation cytotoxic effects. It has been shown that radiation can damage the endoplasmic reticulum, induce changes in the ribosome, damage the lysosome, affect the biological properties and the signal transduction of the plasma membrane, and affect mitochondrial function [5]. DNA damage induced by IR can result in a massive alteration in mitochondria function as the mitochondrial DNA is genetically denser compared to the nuclear genome [10]. Mitochondria are double-membraned organelles that play vital roles in physiological cellular processes such as energy production, macromolecule biosynthesis, gene expression, apoptosis, calcium homeostasis and regulation of ROS production [11–13]. Many of these mitochondrial processes are altered in cancer [14] and increasing evidence suggests that altered mitochondria morphology and metabolism are associated with radioresistance [15]. In particular, energy metabolism reprogramming is an emerging hallmark of cancer [16] which plays a critical role in radioresponse [2]. Warburg effect is the best-known example of energy metabolism reprogramming in cancer, where cancer cells preferentially use the less efficient glycolytic pathway even in the presence of oxygen to generate energy and to produce important molecules sustaining cancer progression [17]. In recent years increasing evidence demonstrates that rewiring of mitochondrial function and metabolism plays an important role in tumour progression and response to treatment by modulating the mitochondrial energy production processes [15]. In this article have been reviewed the recent findings, summarised in Fig. 1 and in Table 1, describing the

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Table 1

Summary of the findings describing the mechanisms of radioresistance regulated by mitochondrial dysfunction and altered metabolism in cancer.

Altered cellular process	Authors	Cancer type	Mechanism of radioresistance	Ref
Redox balance	Lynam-Lennon, N. et al.	Oesophageal adenocarcinoma	Higher basal level of ROS	[15]
	Wei, Y. et al.	Non-small cell lung carcinoma	Lower radiation-induced ROS level	[19]
	Lynam-Lennon, N. et al.	Oesophageal adenocarcinoma	Maintenance of glutathione levels stable post irradiation	[21]
	Hanot, M. et al.	Tongue squamous cell carcinoma	Altered glutathione levels	[22]
	Chen, X. et al.	Oesophageal squamous cell carcinoma	Increased IDH2 expression	[24]
	Sun, J. et al.	CHO cells	MnSOD overexpression	[20]
	Hirose, K. et al.	Melanoma		[25]
	Kalen, A.L. et al.	Head-and-neck cancers		[26]
	Fisher, C.J. et al.	Pancreatic		[27]
	Lynam-Lennon, N. et al.	Oesophageal adenocarcinoma	Increased repair of radiation-induced DNA damage	[21]
DNA repair	Hyun, J. W. et al.	Leukaemia	Low OGG1 activity	[42]
	Ramdzan, Z.M. et al.	Breast, Lung, Glioblastoma, Colorectal	CUX1 overexpression	[46]
	Wang, Y. et al.	Non-small cell lung carcinoma	Downregulation of SSBP1	[54]
	Roy, K. et al.	Glioma	Methylation of the ATM promoter	[56]
	Squatrito, M. et al.	Glioblastoma	Loss of components in the ATM/Chk2/p53 pathway	[57]
	You, W.C. et al.	Glioblastoma	ATAD3A-mediated attenuation of DSB repairs	[58]
	He, Q. et al.	Oesophageal squamous cell carcinoma	High LKB1 expression	[66]
	Wang, Z. et al.	Mouse embryonic fibroblasts	MKP1 inhibition of JNK-mediated apoptosis	[68]
	Candas, D. et al.	HER2-positive breast cancer	MKP1 overexpression	[148]
	Wei, Y. et al.	Non-small cell lung carcinoma	Prolonged G2 arrest	[19]
Apoptosis	Cloos, C. R. et al.	Pancreatic	Suppressed G2 activation increased cyclin B1 and CDK1	[77]
	Muschel, R. J., et al.	Cervical cancer	Altered Cyclin B expression	[78]
	Liu, R. et al.	Colon, Glioblastoma, Breast	Increased SIRT3 activity	[80]
	Wei, Y. et al.	Non-small cell lung carcinoma	NF- κ B/ PI3K/AKT2/mTOR activation	[19]
	Cloos, C. R. et al.	Pancreatic cancer	Mitochondrial DNA depletion	[77]
	Dong, Q. et al.	Oesophageal carcinoma	Modulation of BMI-1 expression	[84]
	Li, Y.L. et al.	Head and neck cancers	Increased GDF15 expression	[85]
	Huang, L. et al.	Glioma	Overexpression of mtK _{ATP} channel	[86]
	Arif, T. et al.	Breast, lung Glioblastoma	VDAC1 overexpression	[14]
	Pitroda, S.P. et al.	Tongue squamous cell carcinoma	STAT1 regulation of energy metabolism	[91]
Cell cycle checkpoints	De Schutter, H. et al.	Head and neck cancers	GLUT1 overexpression	[95]
	Kunkel, M. et al.	Oral cavity squamous carcinoma		[96]
	Blatt, S. et al.	Head and neck cancers	High levels of lactate	[97]
	Sandulache, V.C. et al.			[98]
	Hao, J. et al.	Prostate	Increased LDHA	[99]
	Li, D. et al.	Pancreatic	Non-canonical glutamine metabolism pathway	[107]
	Xiang, L. et al.	Cervical	Increased GLS2 expression	[105]
	Lynam-Lennon et al.	Oesophageal adenocarcinoma	Increased ATP5B expression	[15]
	Le Bleu, V.S. et al.	Breast	Increased PGC1 α	[110]
	Viale, A. et al.	Pancreatic	Increased expression of OXPHOS genes	[112]
Grasso, D. et al.	Head and neck cancer	Increased OXPHOS metabolism	[113]	

demonstrated in a number of mammalian models [37–39]. Enzymes important in BER repair such as DNA glycosylases, abasic-endonucleases (APE), DNA polymerase, and DNA ligase have been found to be either localised to the mitochondria or actively transported to the mitochondria [40]. Oxoguanine glycosylase (OGG1) is a major DNA glycosylase enzyme involved in repair of 8-hydroxy-2'-deoxyguanosine mutation, and it has been shown to have an important role in mtDNA damage repair, a key mechanism regulating radiation response [37,41]. Hyun et al. showed that a loss of OGG1 was associated with enhanced radiosensitivity in acute lymphocytic leukaemia, thereby highlighting an important role of OGG1 in radioprotection [42]. In addition, the enzymatic activity of OGG1 is directly stimulated by both CUX1 [43,44] and CUX2 [45], haploinsufficient tumour suppressor genes which play an important role in radioresistance [46]. Interestingly, CUX1 gene copy number is increased in over 70% of human cancers, and its expression inversely correlates with patient survival [47,48]. CUX1 knockdown was lethal to cancer cells following ionizing radiation [46]. Several drugs that inhibit BER enzymes, such as PARP1 and APE1, are tested in the clinic with different treatment modalities (<https://clinicaltrials.gov/>) to treat cancer. However, BER enzymes exert essential functions in human tissues since over 30,000 base alterations/day are produced in healthy cells [49], thus its inhibition is associated with side effects. In contrast, CUX1 only functions as an auxiliary factor that accelerates repair of ox-

idative damage [44,50], therefore it is not essential in normal human cells [51] suggesting that CUX1 might represent an ideal therapeutic target for cancer treatment.

Mitochondrial Single Stranded DNA Binding Protein 1 (SSBP1) is part of the single-stranded DNA binding protein family which are guardians of genome stability controlling DNA damage response in the cell [52]. In an *in vitro* model of osteoblastoma it was shown that SSBP1 expression was linked to cancer progression, suggesting its use as a prognostic biomarker [53]. Downregulation of SSBP1 has been associated to increased radiosensitivity in lung cancer by decreasing the mtDNA copy number and mitochondrial morphology and function [54].

IR produces a wide variety of DNA damages. Double-strand breaks (DSBs) are considered to be the major effectors for IR-induced cell death [55]. Once DSBs occur, numerous sensor proteins, including ataxia-telangiectasia, Rad3-related, DNA-dependant protein kinase and ataxia-telangiectasia mutated, are recruited to the site of the damage (ATM) [4]. It has been shown that ATM plays an important role in glioblastoma response to IR, as cells lacking the ATM protein were highly sensitive to ionizing radiation and [56]. Another study showed that loss of components in the ATM/Chk2/p53 pathway was associated with radioresistance in a glioma mouse model, and it was demonstrated that Chk2 is required for glioma response to IR [57]. In addition, *in vitro* models of glioblastoma showed that mitochondrial enzyme ATAD3A plays a role

in ATM function as silencing of ATAD3A was associated with attenuation of DSB repairs and enhanced radiosensitivity [58,59].

Mitochondria, apoptosis and radioresistance

One of the hallmarks of cancer is the ability of cancer cells to avoid apoptosis [60]. Evasion of apoptosis in cancer is associated with treatment resistance to IR. IR primarily triggers the mitochondrial dependent pathway of apoptosis and therefore mitochondria dysfunction in cancer plays a crucial role in regulating treatment resistance and evasion of apoptosis [61].

Human tumour suppressor LKB1 is a primary upstream kinase of adenosine monophosphate-activated protein kinase (AMPK) pathway, a necessary element in cell metabolism that is required for maintaining energy homeostasis, metabolism, polarity, growth and autophagy [62–64]. Saigusa et al. showed that in locally advanced rectal cancer treated with neoadjuvant chemo-radiation therapy the expression of LKB1 was higher in patients with tumour recurrence and poor pathological response, demonstrating that LKB1 may play a role in treatment resistance [65]. In addition, it was demonstrated that overexpression of LKB1 induced radioresistance by inhibiting apoptosis and by activating autophagy, suggesting that LKB1 might be a novel therapeutic target to maximise radiation response in oesophageal cancer [66].

Mitogen-activated protein kinase (MAPK) phosphatase (MKP)-1 is the major member of MKPs that dephosphorylates and inactivates MAPK, a major signaling transduction molecules in apoptosis [67]. In a study was demonstrated that IR-induced MKP-1 played an anti-apoptotic function *via* inhibition of JNK-mediated proapoptotic pathway, and siRNA-mediated inhibition of MKP-1 significantly enhanced apoptotic response in irradiated cells [68].

Mitochondria dysfunction and the cell cycle checkpoints in cancer cell radioresistance

Cell cycle checkpoints are often violated in cancer due to increased expression of growth factors and evading growth suppressors which lead to dysregulation of cell progression control mechanisms [16]. After exposure to IR, eukaryotic cells undergo a division delay which is reflected by increased time spent in the G2 portion of the cell cycle. The cell cycle checkpoints are regulated by cyclin-cyclin dependent kinases (CDK) complexes, and the G2/M checkpoint which controls progression to mitosis is primarily controlled by Cyclin B1-CDK1 complex activity [69]. Cyclin B1 has been found overexpressed in various cancers including oesophageal squamous cell carcinoma [70], non-small cell lung cancer [71], oral carcinoma [72], prostate adenocarcinoma [73], breast cancer [74], astrocytomas [75] and *Helicobacter pylori*-associated gastric MALT and MALT lymphoma [76]. It was shown that IR-induced G2 activation was suppressed by mtDNA depletion in human pancreas cancer cell and was accompanied by increased levels of Cyclin B1 and CDK1. The pancreatic cells with mtDNA depletion were more resistant to IR compared to cells with functional mitochondria [77]. Similarly, mtDNA depletion in lung cancer cells showed prolonged G2 arrest accompanied by a more radioresistant phenotype [19]. It has been shown that a cell division delay was induced when HeLa cells were irradiated in G2 phase which coincided with a lower level of cyclin B protein, identifying cyclin B as a key molecule in the cellular response to ionizing radiation [78].

SIRT3, a member of the sirtuin family of NAD(+)-dependent protein deacetylases in the mitochondria, regulates mitochondrial processes by promoting metabolic homeostasis through regulation of mitochondrial protein deacetylation [79]. It has been demonstrated that SIRT3 expression was induced in a number of radiation-treated human cancer cells and xenografts, and it was showed that enhanced SIRT3 transcription and posttranslational modifications contributed to adaptive radioresistance in tumour [80].

MtDNA depletion and radioresistance

Mitochondria-to-nucleus retrograde signalling (RTG) allows crosstalk between the mitochondria and nucleus influencing changes in a variety of cancer cellular phenotypes including survival, metastasis, drug resistance, stemness and metabolism [81]. RTG can be influenced by alterations in the copy number and mutations in mtDNA, respiratory chain component defects in the mitochondria, and loss of mitochondrial membrane potential [82]. Wei et al. showed that mtDNA depletion in lung cancer may induce radioresistance through activation of the RTG signalling pathway of NF- κ B/PI3K/AKT2/mTOR [19]. This requires further study to determine if mtDNA alteration could be used as a predictor of response to radiation therapy and whether NF- κ B/PI3K/AKT2/mTOR pathway might represents a potential therapeutic target to enhance radiosensitivity.

Mitochondrial membrane and radioresistance

The mitochondrial membrane potential ($\Delta\Psi$) generated by proton pumps (Complexes I, III and IV) is an essential component in the process of energy storage during oxidative phosphorylation [83]. A study showed that histone deacetylase inhibitors (HDAC inhibitor), an emerging anti-cancer therapy, reverse the acquired radioresistance in an *in vitro* oesophageal cancer by modulating polycomb complex protein BMI-1 expression leading to enhanced G2/M arrest, decreased $\Delta\Psi$, increased production of ROS, and enhanced radiation induced apoptosis [84]. Growth differentiation factor 15 (GDF15) is a member of the TGF- β super-family that alters the $\Delta\Psi$ inducing ROS suppression. It has been shown than GDF15 promoted cancer stemness, and inhibition of GDF15 sensitised cells to IR [85].

Mitochondrial ion channels are present on both the inner and outer mitochondrial membrane and play important roles in protein transport, ATP production and Ca²⁺ uptake. Mitochondrial ATP-sensitive potassium channel (mtK_{ATP}) channel has been shown to have a key role in glioma radioresistance by regulating the ROS activation of EKR pathway. High expression of mtK_{ATP} in glioma tissue correlated to shorter survival time and a high malignancy grade, suggesting that use of mtK_{ATP} channel blockers in glioma treatment may improve patient outcomes [86]. Voltage-dependent anion channel 1 (VDAC1) is a class of membrane channel acting as a gatekeeper at the outer mitochondrial membrane. VDAC1 is involved in various mitochondrial processes and serves as a link between glycolysis and OXPHOS due to its interaction with hexokinase [87]. It has been shown that depletion of VDAC1 led to inhibition of tumour development and growth of cancer cells in both *in vitro* and *in vivo* models of breast, lung and glioblastoma, as well as and induction of metabolic rewiring reversing the oncogenic properties of cancer cells [14].

Role of metabolism in radioresistance

The alteration of the cellular metabolic pathways in tumour cells, also known as metabolic reprogramming, is considered one of the hallmarks of cancer [88]. Altered activation of oncogenes, inactivation of tumour suppressor genes and changes in cellular signaling pathways are crucial factors regulating metabolic change in tumour [89,90]. Increasing number of evidences suggest that metabolic reprogramming in cancer is one of the major factors contributing to radioresistance to IR [91]. Mitochondria play a key role in this process. Mitochondria can rapidly adapt to the increasing energy requirements of the tumour by changing energy production processes in the cells, and radioresistance has been associated with changes in the mitochondrial energy metabolism profile, mitochondrial size, morphology and functions [15]. Carbohydrates are the preferred source of cellular energy in the cells participating in the process of the metabolism of glucose by glycolysis and OXPHOS [92]. Alterations in the glycolytic metabolism in cancer has been shown to contribute to radioresistance development [91]. A class of transporter

proteins, GLUT family, is required by the cell for glucose metabolism in the cell [93]. Increasing evidence suggests that high glucose transporter-1 (GLUT-1) expression is associated with radioresistance in cancer. Abnormal GLUT-1 expression in cancer is regulated by various factors including hypoxia and altered MAPK and PI3K/AKT signalling pathways [94]. Overexpression of GLUT1 was linked to radioresistance in both head and neck squamous cell carcinoma [95] and oral cavity squamous cell carcinoma [96] making it an attractive target for enhancing radiosensitivity. A study showed that GLUT1 inhibitors led to sensitization of radioresistant breast cancer cells to IR, suggesting a potential role of GLUT1 inhibitors as anti-cancer agents [94]. Lactic acid/lactate is a product of glycolysis and high levels of lactate was associated with increased tumour recurrence and poor survival in head and neck cancer patients, suggesting that lactate may have a value as a predictive biomarker of patients survival [97]. Lactate levels have been associated with hypoxia-induced radioresistance. A study showed that acute perturbations in tumour lactate levels acted as a surrogate marker of radiation response, suggesting that lactate might be a quantitative biomarker of acute genotoxic stress that could inform clinical decision making [98]. Lactate dehydrogenase (LDHA) is the main metabolic enzyme for lactate generation, a terminal product from glycolysis. It has been demonstrated that knockdown of LDHA could sensitize radioresistant prostate cancer cells to radiotherapy, and proteomic analysis revealed potential protein markers of radioresistance, concluding that targeting LDHA combined with radiotherapy could increase radiosensitivity in radioresistant prostate cancer [99].

In addition, NOS2, the inducible nitric oxide synthase of iNOS, has been identified as a key molecule upregulated in many aggressive cancer types. Nitric oxide has been demonstrated to act as a modulator of cellular bioenergetic processes and of mitochondrial functions, and therefore has been associated to the alteration of metabolic pathways in cancer [100,101]. Interestingly, iNOS/NOS2-generated nitric oxide has been described as a contributor to radiation resistance in different types of cancer [102,103].

Glutamate metabolism and radioresistance

Glutamate plays key role linking carbohydrate and amino acid metabolism via the tricarboxylic acid (TCA) cycle in the cell [104]. Glutamate is synthesized from glutamine as part of the glutamate–glutamine cycle by the enzyme glutaminase. Xiang et al. showed that a mitochondrial isoform of glutaminase, GLS2, was associated with radioresistance in cervical cancer and its inhibition led to increased radiosensitivity, suggesting that the inhibition of GLS2 may be a potential treatment strategy for radioresistant cervical cancer [105]. A study showed that pancreatic ductal adenocarcinoma tumour growth is facilitated by a KRAS-mediated reprogramming of glutamate metabolism and suggesting that inhibition of glutamine metabolism might potentially synergize with therapies that increase intracellular reactive oxygen species, such as chemotherapy and radiation [106]. It has been shown that pancreatic cancer stem cells relied on the glutamine metabolism pathway and the inhibition of this pathway led to increased radiosensitivity by accumulation of ROS [107].

OXPHOS and radioresistance

Rewiring of energy metabolism in cancer is most commonly associated with a switch from OXPHOS to glycolysis [108]. However increasing evidence demonstrates that cancer cells can use a wide range of energetic profiles, and OXPHOS represents a major source of energy production [109]. It has been previously demonstrated a role for mitochondrial dysfunction and metabolic reprogramming in radioresistance, showing that oesophageal adenocarcinoma radioresistant cells had altered bioenergetics with significantly increased intracellular ATP levels associated to enhanced mitochondrial respiration. Radioresistant cells also demonstrated metabolic plasticity, efficiently switching between

the glycolysis and oxidative phosphorylation energy metabolism pathways, accompanied by enhanced clonogenic survival [15]. ATP5B expression, a marker of oxidative phosphorylation, was significantly increased in patients who had a poor pathological response to neoadjuvant CRT, showing a role for specific mitochondrial alterations and metabolic remodelling in the radioresistance of oesophageal adenocarcinoma [15]. A study showed that circulating cancer cells in a mice model of breast cancer had increased expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1 α). PGC1 α overexpression was associated to a regulation of mitochondrial function by increasing mitochondrial biogenesis and by a preferential use of OXPHOS [110]. It has been also shown that the dependency of pancreatic cancer stem cells on OXPHOS is determined by the balance between PGC1 α and Myc [111]. Viale et al. showed that surviving cells from oncogene ablation in pancreatic cancer were reliant on OXPHOS and responsible for tumour relapse, while inhibition of OXPHOS decreased mitochondrial respiration and the ability of the surviving cells to form spheres affecting their survival [112]. Acquired radioresistance was also associated with a shift from a glycolytic to a more oxidative metabolism and to an increased number of mitochondria with a higher mtDNA content [113].

Cancer rewire the function of the mitochondria and metabolism to enhance resistance to ionising radiation. Radioresistant phenotype has been associated to alteration of ROS generation, antioxidants level, DNA repair mechanisms, apoptosis, cell cycle checkpoints, mitochondria-to-nucleus retrograde signaling (RTG), membrane potential ($\Delta\Psi$), glycolysis, glutamine metabolism and oxidative phosphorylation (OXPHOS). VDAC1, voltage-dependent anion channel 1; TCA, tricarboxylic acid cycle; ETC, electron transport chain; ATP, adenosine triphosphate; GDF15, growth differentiation factor 15; BMI-1, polycomb complex protein BMI-1; ROS, reactive oxygen species; mtK_{ATP}, mitochondrial ATP-sensitive potassium channel; PGC1 α , Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; Cdk1, cyclin-dependent kinase 1; NF-Kb, nuclear Factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphoinositide 3-kinases; AKT2, RAC-beta serine/threonine-protein kinase; mTOR, mammalian target of rapamycin; MKP1, mitogen-activated protein kinase phosphatase 1; LKB1, serine/threonine-protein kinase STK11; JNK, c-Jun N-terminal kinase.

Genetic regulation of mitochondria energy metabolism and radioresistance

A set of genes and transcription factors encoded by the nuclear genome regulate mitochondrial biogenesis, functions and transcriptional activity. Alteration of these genes are also associated to radioresistance through modulation of mitochondrial function. For example, PGC1 α is a co-transcriptional regulation factor important in mitochondrial biogenesis, and upregulation of PGC1 α has been linked to chemoresistance and altered energy metabolism in cancer stem cells [111,114]. PGC1 α has been linked to radioresistance due to its role in the activation of many others transcription factors including nuclear respiratory factor 1 (NRF1) and 2 (NRF2) which, in turn, are linked to radiation response in cancer [115]. NRF-1 has been linked to the transcriptional control of genes involved in mitochondrial function and biogenesis and it was demonstrated that NRF1 was a direct target of miR-504 [116]. In an *in vitro* model of nasopharyngeal carcinoma, radioresistance was associated with upregulated expression of miR-504, leading to lower levels of NRF1. Serum from nasopharyngeal carcinoma patients showed that miR-504 was up-regulated during different weeks of radiotherapy and correlated with tumour volume, lymph nodes, and metastasis stages, demonstrating that miR-504 regulated radioresistance by down-regulating the expression of NRF1 [117]. NRF2 is a transcriptional regulator of cytoprotective enzyme encoding genes [116] and several studies have shown that aberrant NRF2 regulation is linked to both radioresistance and chemoresistance in various cancers such as lung [118], prostate [119], breast [120], ovarian [121] and oesophageal [122]. These evidences suggest that NRF2 targeting may be a potential

treatment strategy for overcoming resistance to treatment. NRF-independent mitochondrial gene expression regulation is orchestrated by other factors such as Sp1 [123]. Sp1 is a transcription factor which regulates mitochondrial functions [124,125]. Deng et al. showed that high Sp1 expression levels were correlated to cervical cancer progression, and that knockdown of Sp1 significantly enhanced the cellular response to radiation by inducing G2/M arrest, suggesting that Sp1 might represent a potential therapeutic target in cervical cancer [126]. Tumour hypoxia is an important contributor to radioresistance. Hypoxic microenvironment is associated with modulation of expression of genes regulating tumour survival and growth [127]. Hypoxia-inducible factor-1 (HIF-1) is a protein that activates the transcription of many genes involved in angiogenesis, glucose metabolism, cell proliferation and invasion. HIF-1 α is overexpressed in human cancer as a result of intratumoral hypoxia as well as genetic alterations [128]. For example, a study showed that radioresistance in glioblastoma is sustained by MEK/ERK regulation of HIF-1 α . Signal transduction-based chemotherapy radiosensitised glioblastoma cancer cells by interfering with MEK/ERK pathway preventing HIF-1 α -mediated hypoxic cell survival and radiation escape [129]. Interestingly, increasing evidence demonstrates that the switch from oxidative to glycolytic metabolism is an active response to hypoxia mediated by HIF-1 α . HIF-1 α gene expression alteration in cancer has been associated with altered mitochondrial mass and metabolism, along with increased glucose to pyruvate conversion, and increased cellular influx of glucose, positioning HIF1 as a lead target in radioresistance treatment [130–132]. In addition, a number of studies showed that hypoxia conferred resistance to irradiation through activation of autophagy [133], via c-Jun-mediated Beclin1 expression in lung cancer [134], and by the HIF-1 α /miR-210/Bcl-2 pathway in colon cancer [135].

Targeting mitochondrial energetics for enhanced radiosensitivity

Targeting mitochondrial energetics has emerged as a promising cancer treatment. Studies investigating the role that bioenergetic drugs play in radiation response are increasing [136]. Metformin is a member of the biguanide class of drugs and is widely used as an antidiabetic drug worldwide to treat Type II diabetes [114]. Interestingly, several studies have shown that metformin might have a role as antineoplastic agent, and that metformin is linked to enhanced radiation response in cancer. Storozhuk et al. demonstrated that metformin inhibited lung cancer cell growth and sensitised them to IR through ATM-AMPK signalling modulation [137]. In another study, metformin *in vitro* treatment of oesophageal cancer cells was shown to act as radiosensitiser leading to an increase in apoptosis, G0/G1 arrest and AMPK activation [138]. In addition, metformin was shown to lead to increased radiosensitivity in pancreatic cancer *in vitro*, and these effects were abrogated by AMPK inhibition [139]. Jin et al. showed that metformin treatment in colorectal cancer cells was linked to increased expression of AMPK and enhanced radioresistance, and AMPK inhibition led to increased radiosensitivity in these cells [140]. These evidences suggest that AMPK plays an important role in modulating metformin radiosensitiser effects. It has also been reported that metformin sensitised p53-deficient colorectal cancer cells to IR by reducing DNA repair protein levels, and by increasing the proportion of cells in G2/M phase [141]. In addition, it has been shown that resistance to metformin in cancer was linked to increased glycolysis and reduction in mitochondrial metabolism due to mutations in the electron transport chain or to enhanced hypoxia [111,142]. Benej et al. showed that papaverine, a FDA-approved vasodilator drug, acted as a mitochondria complex I inhibitor, and inhibition of this complex was directly responsible for increased oxygenation and enhanced radiation response in solid tumour. This study suggested that papaverine has the potential to become a clinical radiosensitiser with potentially few side effects as it did not sensitise well-oxygenated normal tissue to IR, thereby increasing the therapeutic index of radiotherapy [143]. In another study, it was demonstrated that inhibition of HIF-1 α with 2-methoxyestradiol (2-MeOE2) significantly enhanced radiosensitivity

in a radioresistant human melanoma cell model through targeting the glycolysis pathway [144]. Another study showed that dichloroacetate, a pyruvate dehydrogenase kinase (PDK) inhibitor currently being used to treat lactic acidosis, was able to alter glioblastoma cell metabolism by activating mitochondrial toward oxidative phosphorylation and by reversing the radiotherapy-induced glycolytic shift, demonstrating that dichloroacetate was able to sensitize glioblastoma cells to radiotherapy by modulating the metabolic activity of the tumour [145]. Finally, Buckley et al. showed that pyrazinib, a pyrazine phenol small molecule drug with anti-angiogenic and anti-metabolic activity, was shown to increase radiosensitivity in a model of radioresistant oesophageal adenocarcinoma by modulating mitochondrial bioenergetics, reducing measures of oxidative phosphorylation and glycolysis, therefore supporting further development of pyrazinib as a novel therapeutic radiosensitiser in oesophageal adenocarcinoma [146].

Discussion

Ionising radiation (IR) is one of the most used therapeutic method for the treatment of many cancers. However, due to development of radioresistance by the tumour, IR remains primarily a conservative cancer treatment. Radioresistance is described as a complex process in which the cancerous tissue adapts to the cellular changes induced by IR and develops resistance by modulating multiple genes, factors, and cellular processes. Such processes include alteration of DNA damage repair mechanism, cell cycle, oncogenes, tumour suppressor genes, autophagy, cellular metabolism, and reactive oxygen species. These altered processes are regulated by mitochondria and implicated in cancer treatment response. Increasing evidence suggests that mitochondria dysfunction and altered metabolism in cancer plays a key role in radioresistance. In fact, radioresistance in cancer has been associated with changes in the mitochondrial energy metabolism profile, mitochondrial size and number, mitochondrial morphology and function accompanied by increased mitochondrial mutation rate, respiration and intracellular ATP levels [15]. In addition, crosstalk between the mitochondria and nucleus is required for normal cellular function, therefore dysfunction in the mitochondria can lead to alterations in nuclear gene expression and *vice versa* [81]. A number of studies have shown that alteration of nuclear encoded genes and transcription factors in cancer, which regulate mitochondria processes, can lead to mitochondrial dysfunction and to radioresistance [15,112,147]. In this review we detailed the mechanisms by which cancer rewires the function of the mitochondria and cellular metabolism to enhance resistance to IR. Fig. 1 shows the various processes and mechanisms described in this article by which the alterations in mitochondrial function and metabolism play a role in radioresistance. Importantly, there are no available radiosensitisers on the market that can be used to increase response in radioresistant cancer, thus, there is increasing interest in identifying the mechanisms regulating radioresistance in order to develop targeted novel treatments to enhance radiosensitivity. In this scenario, a number of studies showed that drugs targeting mitochondria bioenergetics such as metformin [137–141] and pyrazinib [146] might have some promise as radiosensitisers. Research focused on development of therapeutics targeting radioresistance through rewiring of mitochondria dysfunctions and altered metabolism in cancer will translate to the development of novel radiosensitisers, with the ultimate goal of improving response to radiotherapy in cancer patients.

Declaration of Competing Interest

The authors declare no competing interests.

CRediT authorship contribution statement

Emma McCann: Investigation, Writing - original draft. **Jacintha O'Sullivan:** Conceptualization, Writing - review & editing. **Simone Marcone:** Conceptualization, Writing - review & editing.

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