

Review

Metabolic plasticity and radiotherapy response in prostate cancer: Emerging roles for extracellular vesicles

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Abstract

Radiotherapy (RT) is a mainstay of treatment for localised prostate cancer (PCa), yet its efficacy is fundamentally challenged by the inherent and adaptive heterogeneity of tumours. RT acts as a potent selective pressure on tumour cell populations, driving phenotypic plasticity and fostering the evolution of resistant subclones. Extracellular vesicles (EVs) have emerged as pivotal mediators in this adaptive process, serving as nanoscale messengers that transfer molecular cargo, including metabolites, metabolic regulators, and regulatory RNAs, to reshape the tumour microenvironment and propagate survival signals. At the same time, advances in metabolomics offer a powerful tool to elucidate the dynamic metabolic reprogramming orchestrated by EVs in response to RT. This review synthesises current knowledge on the interplay between RT, EV-mediated signalling, and metabolic adaptation in PCa. We examine how radiation stress alters EV biogenesis and cargo, and evaluate the evidence linking EV signalling to the glycolytic, lipid and amino acid pathways implicated in radioresistance, including emerging RT-ferroptosis-EV cross-talk. We argue that this EV-driven metabolic reprogramming is a potential mechanism underlying intra-tumoural heterogeneity and clonal evolution post-treatment. We organise these observations within a unifying framework in which EVs may act as drivers that actively confer radioresistance, amplifiers that propagate resistant phenotypes across the tumour, and readouts whose metabolite signatures report tumour state and RT response, which positions EV metabolomics as a candidate dynamic liquid biopsy and a plausible therapeutic target, and we consider how single-EV analysis could resolve the

subclonal heterogeneity central to this model. Finally, we highlight the technical and conceptual challenges in the field that must be addressed to define whether EV metabolomics can provide clinically meaningful insight into RT-driven tumour evolution and support future precision oncology strategies.

Keywords: prostate cancer; radiotherapy; extracellular vesicles; phenotypic plasticity; metabolic reprogramming

1. Introduction

1.1. PCa heterogeneity is a core therapeutic challenge

Globally, prostate cancer (PCa) represents a substantial health burden among men, ranking as the second most frequently diagnosed malignancy in males worldwide [1]. In the United States, PCa is projected to account for approximately 30% of all newly diagnosed cancers in males in 2026, with an estimated 333,830 new cases and 36,320 associated deaths [2]. Although the 5-year survival rate for localised PCa exceeds 95% when detected at an early stage, a considerable proportion of patients experience disease recurrence or treatment failure, ultimately progressing to metastatic PCa (mPCa). This advanced disease stage is associated with a markedly reduced 5-year relative survival of 30–40% [3,4].

This variability in clinical outcomes, in part, reflects the marked biological heterogeneity of PCa. PCa is typically multifocal, comprising spatially and morphologically distinct foci that may harbour divergent genetic mutations and exhibit variable degrees of aggressiveness [5]. High-throughput sequencing studies have shown that heterogeneity not only exists within individual primary tumours (intra-tumoural heterogeneity), but also between patients (inter-patient heterogeneity) and across metastatic lesions (inter-tumoural heterogeneity) [5–8]. Accumulating evidence indicates that tumour heterogeneity increases with disease progression and constitutes a critical determinant of patient prognosis and survival [9–12]. Such diversity has important clinical implications, as it contributes to variable treatment response, disease progression and the emergence of resistant phenotypes. However, current prognostic factors, such as PSA, Gleason scores and TNM staging, offer limited insight into the molecular heterogeneity that underpins therapeutic response [13]. This highlights an urgent need for novel biomarkers capable of improving diagnostic precision and enabling more accurate monitoring of PCa progression.

1.2. RT as a driver of PCa plasticity

Radiotherapy (RT) is a cornerstone treatment for PCa and is administered via external beam radiotherapy or brachytherapy [14]. Despite advances in RT techniques, approximately 20–40% of patients treated with RT experience biochemical recurrence and metastatic progression within 5 years [15]. Radioresistance in PCa is frequently associated with metastatic dissemination and development of castration-resistant prostate cancer (CRPC) with a median survival of less than 2 years [16]. While RT is intended to eradicate tumour cells, it may also impose selective pressure on heterogeneous tumour populations, favouring the survival and expansion of subclones with adaptive advantages [17,18]. This adaptive response is characterised by increased phenotypic

plasticity [19] which enables PCa cells to reprogramme DNA repair pathways, metabolic processes, and cellular states in response to RT-induced stress [17]. Over time, these adaptations facilitate the emergence of radioresistant and more aggressive tumour phenotypes, ultimately driving disease recurrence, metastatic progression, and the transition to CRPC [20].

1.3. EVs as dynamic mediators of tumour-stroma crosstalk and adaptive signalling

The emergence of radioresistant phenotypes following RT is not solely driven by intrinsic tumour cell adaptations but is also due to therapy-induced communication between PCa cells and the tumour microenvironment (TME) [21]. Increasing evidence indicates that extracellular vesicles (EVs) are important mediators of this crosstalk. EVs are cell-released, lipid-bound, nano-sized vesicles which mediate bidirectional communication between cancer cells and stromal, immune, and endothelial components of the TME through the transfer of bioactive molecular cargo [22], including miRNAs, mRNAs, proteins, lipids and metabolites. Through transfer of this cargo, EVs can alter the phenotype and behaviour of recipient cells and thereby influence tumour progression, stromal remodelling, immune regulation and treatment response. Consequently, profiling dynamic changes in EV cargo following RT may provide emerging insight into the cellular and molecular mechanisms underpinning PCa plasticity and radioresistance.

1.4. Metabolomics: deciphering the functional output of cellular plasticity

Among the various types of cargo carried by EVs, metabolites are significant molecules of interest, as they represent the immediate functional state and biochemical activity of their origin cell and metabolic reprogramming is a recognised hallmark of cancer [23]. Metabolomics captures both the downstream output of genomic and proteomic regulation while also integrating upstream environmental inputs, thereby providing a direct readout of gene-environment interactions [24]. Unlike other static molecules, metabolic profiles are highly dynamic and respond rapidly to environmental influences, making metabolomics particularly well-suited for studying the RT adaptive responses and tumour plasticity [25,26]. Accordingly, analysis of EV-associated metabolites may provide insight into how tumours adapt to RT and may help identify biomarkers of response, early resistance and potential therapeutic vulnerabilities.

This review explores the emerging intersection between radiotherapy, EV biology and metabolic adaptation in PCa. Specifically, it considers how radiation-induced stress may reshape EV secretion and cargo composition, and how these changes may contribute to tumour plasticity, TME remodelling and the evolution of treatment-resistant phenotypes. In this context, particular emphasis is placed on addressing the role of EV cargo in facilitating metabolic reprogramming linked to tumour survival, heterogeneity and radioresistance. Further, this review evaluates the translational relevance of EV metabolomics as a minimally invasive approach for monitoring disease status and treatment response. By integrating current evidence from PCa and the broader literature, this review aims to define the conceptual framework of this field, highlight key biological and methodological challenges and identify priorities in establishing the clinical utility of EV metabolic profiling in precision oncology.

2. Radiation Stress Reshapes the EV Landscape: Biogenesis, Release and Altered Cargo

2.1. RT induces EV secretion and TME reshaping

EVs are increasingly recognised as critical mediators of cellular responses to RT. In return, RT has been shown to enhance EV secretion and to modulate EV cargo composition in both malignant and non-malignant cells [27–30].

For instance, exposure to X-rays increases the release of EVs from neuroblastoma cells, which are then taken up by non-irradiated cells, enhancing their viability and migration [27]. Similarly, gamma radiation significantly enhances EV release from both naïve and polarised macrophages [31]. These alterations are, in part, driven by DNA damage-induced activation of p53 signalling pathways, which promote the selective export of growth-regulatory proteins and other bioactive factors via EVs [32]. Importantly, EV-mediated responses to RT are not restricted to tumour cells. Stromal components, including cancer-associated fibroblasts (CAFs), also exhibit increased EV release following irradiation, suggesting that RT may also reshape TME dynamics via EV-mediated crosstalk [27,28]. Furthermore, RT enhances the uptake and internalisation of tumour-derived EVs by neighbouring recipient cells, thereby amplifying intercellular signalling within the irradiated microenvironment [33–35]. In summary, these findings indicate that RT-induced modulation of EV biogenesis, cargo loading, and intercellular transfer may promote adaptive responses that increase the radioresistant and metastatic potential of cancer cells; whether this applies in PCa remains to be confirmed.

2.2. Systematic reprogramming of PCa EV cargo post-RT

RT induces substantial alterations in the biomolecular cargo of EVs, which not only reflect acute cellular stress responses but may also represent adaptations in tumour phenotype.

The immune checkpoint molecule B7-H3 (CD276), a validated marker for distinguishing benign from aggressive PCa [36], has been shown to be enriched in EVs secreted by RT-induced senescent PCa cells. B7-H3 is implicated in the negative regulation of T-cell activation and effector function, thereby contributing to the suppression of anti-tumour immunity [37,38]. In parallel, RT has been reported to induce higher levels of PD-L1 in PCa-derived EVs compared with hormone therapy and chemotherapy [39], suggesting that RT may promote immune-evasive phenotypes. This has clear translational relevance, particularly given the ongoing interest in combining RT with immune checkpoint blockade in PCa. Beyond immune modulation, EV-mediated signalling may directly facilitate adaptive radioresistance. Prostatic stromal cells have been shown to promote radioresistance in PCa cells through EV-mediated transfer of interleukin-8 (IL-8). IL-8 engages CXCR1 and CXCR2 receptors on recipient tumour cells, activating AMP-activated protein kinase (AMPK)-dependent autophagy, which confers a survival advantage under RT-induced stress [40]. Such intercellular signalling mechanisms highlight how EVs can facilitate stress-driven phenotypic adaptation within TME. RT has also been found to upregulate the EV expression of cancer stem-cell (CSC)-associated gene markers (*CD133*, *CD44*, *ALDH1* and *GLUT1*), which suggests RT may select for more aggressive, metabolically active CSC phenotypes [41].

2.3. EV-mediated RIBE

RT can induce off-target effects in non-irradiated cells via signal transduction from irradiated cells, a phenomenon termed as the radiation-induced bystander effect (RIBE) [42]. EVs have emerged as important mediators of this process owing to their capacity to facilitate intercellular communication and propagate stress signals. EV-mediated bystander signalling has been shown to trigger diverse biological responses following RT, including the activation of stress pathways, genomic instability, and alterations in cell proliferation and apoptosis [30,43–46]. This is supported by a study which showed that irradiated mice serum-derived EVs were found to contain mitochondrial DNA (mtDNA) which, upon transfer to recipient healthy cells, induced DNA damage [47]. Consistent with these findings, an *in vivo* study found that EVs derived from the bone marrow of irradiated mice induced DNA double-strand breaks (DSBs) in non-irradiated recipient mice [48]. These systemic alterations were accompanied by increased chromosomal aberrations and reductions of haematopoietic and immune cell populations. Another study found that EVs released from irradiated PCa cells significantly promoted epithelial–mesenchymal transition (EMT) in non-irradiated PCa cells, characterised by upregulation of mesenchymal markers and downregulation of epithelial markers [41]. This suggests RT-induced EVs promote EMT and metastatic ability in untreated PCa cells, propagating PCa plasticity across distinct tumour regions. Thus, EV-mediated RIBE may contribute to spatially heterogeneous responses to RT, which can influence tumour evolution, metastatic dissemination and overall treatment outcomes.

Taken together, these findings support a conceptual shift toward a more expansive and biologically realistic understanding of RT response in PCa: RT should be regarded not only as a cytotoxic modality, but also as a systems-level adaptation capable of reshaping intercellular communication within the tumour and its microenvironment (**Figure 1**). In this context, EVs have emerged as a plausible interface through which radiation-induced stress is distributed and potentially stabilised across heterogeneous cell populations. It is clear that increased EV release, altered cargo and RIBE are all consistent with adaptive reprogramming; however, what remains less clear is whether these changes are mechanistic drivers, amplifiers of pre-existing signals or merely molecular readouts of cellular stress. This distinction is fundamental to understanding whether and how such alterations meaningfully contribute to heterogeneity, microenvironment remodelling and long-term therapeutic resistance.

3. EV-driven Metabolic Reprogramming: Fueling Plasticity and Therapy Resistance

Cancer exerts profound effects on cellular metabolism, including the reprogramming of intracellular metabolic pathways to enable tumour cells to sustain proliferation and adapt to therapeutic pressure [49]. This is of particular interest in PCa, as rather than conforming uniformly to a glycolysis-dominant phenotype, PCa is characterised by dynamic and stage-dependent metabolic states shaped by lineage context, androgen receptor (AR) signalling and TME constraints. Furthermore, oncogenic metabolic reprogramming can generate distinct metabolic dependencies, rendering tumour cells selectively reliant on specific pathways for survival and growth. These acquired vulnerabilities

present opportunities for precision medicine approaches, including the development of therapeutics targeting key metabolic enzymes or pathways essential for tumour maintenance [50,51].

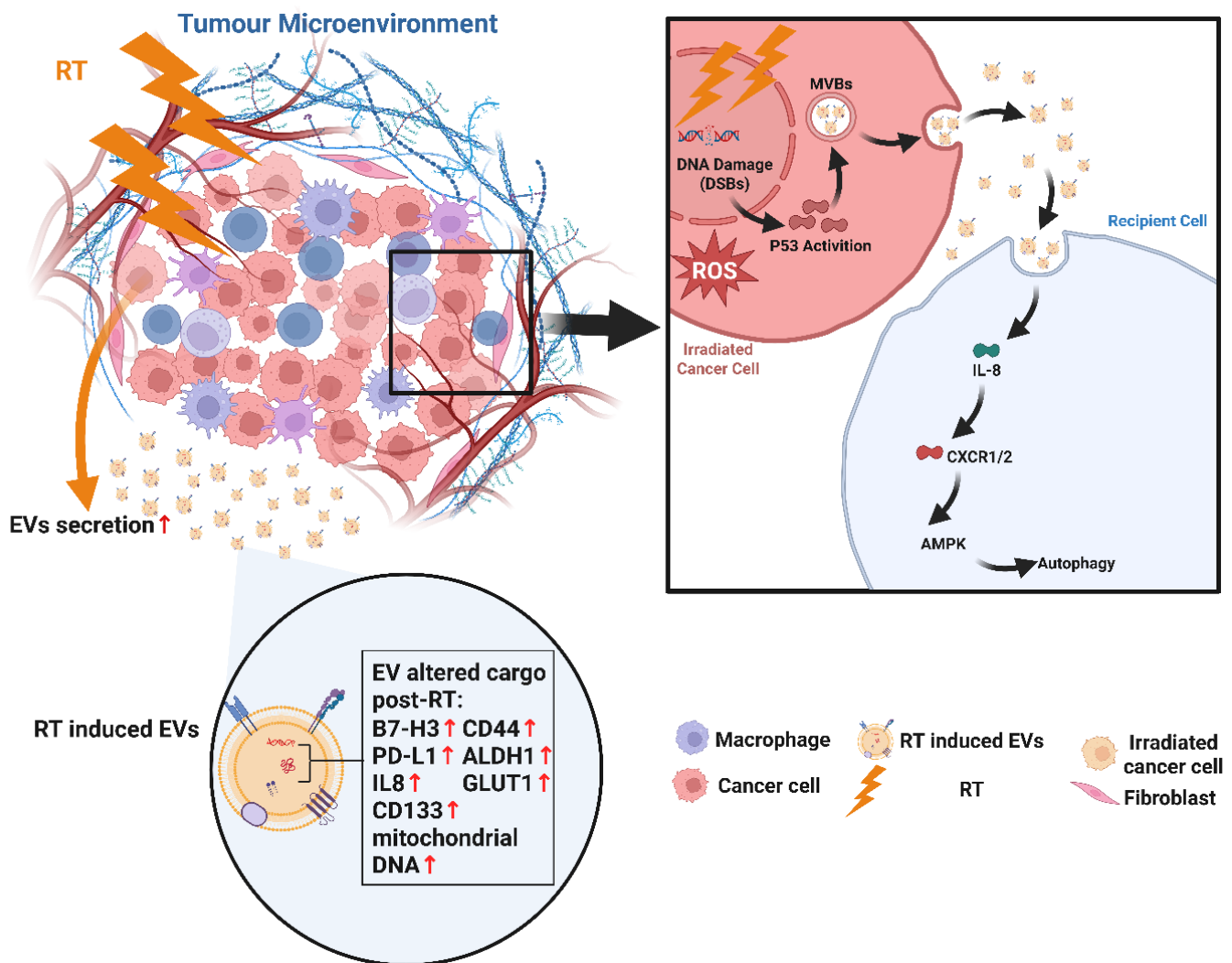


Figure 1. RT stress reshapes EV secretion and cargo to modulate the TME in PCa. RT induces cellular stress in PCa by causing DNA damage, including double-strand breaks and increased production of ROS, which activates stress-response pathways including p53 signalling. These changes promote enhanced biogenesis and secretion of EVs via MVBs into the TME. Following RT, EVs exhibit altered cargo composition, including the upregulation of oncogenic and stress-associated molecules such as B7-H3, CD44, PD-L1, ALDH1, IL-8, GLUT1, CD133, and mitochondrial DNA. These EVs are taken up by recipient cells within the TME, including neighbouring cancer cells, fibroblasts, and immune cells, where they activate downstream signalling pathways such as IL-8/CXCR1/2 and AMPK and reprogramme recipient-cell metabolism. By transferring metabolic cargo between cells, EVs propagate metabolic plasticity across the tumour, favouring the selection and clonal expansion of radioresistant subpopulations. In this way, RT-induced EV signalling links altered cargo to metabolic adaptation and radioresistant subclonal evolution, ultimately contributing to tumour progression and radioresistance. (Created with BioRender.com). Abbreviations: ALDH1, aldehyde dehydrogenase 1; AMPK, AMP-activated protein kinase; B7-H3, B7 homolog 3; CD44, cluster of differentiation 44; CD133, cluster of differentiation 133; CXCR1/2, C-X-C motif chemokine receptor 1/2; DNA, deoxyribonucleic acid; EVs, extracellular vesicles; GLUT1, glucose transporter 1; IL-8, interleukin-8; MVBs, multivesicular bodies; PD-L1, programmed death-ligand 1; ROS, reactive oxygen species; RT, radiotherapy; TME, tumour microenvironment.

3.1. Metabolic hallmarks of PCa and their modulation by EVs

Metabolism adaptation in tumour cells arises from increased demands for energy production, biomass synthesis, cofactor generation and redox

homeostasis. To sustain rapid proliferation and survival under environmental stress, cancer cells reprogramme central metabolic pathways to support these biosynthetic and bioenergetic requirements. While enhanced aerobic glycolysis (commonly known as the Warburg effect) is the most widely recognised metabolic alteration in cancer, PCa exhibits a distinct metabolic phenotype that diverges from this classical paradigm. Normal prostate epithelium is specialised for citrate production and secretion, a state maintained by high intracellular zinc concentrations that inhibit mitochondrial aconitase and truncate tricarboxylic acid (TCA) cycle activity [52–54]. During malignant transformation, this citrate-oriented metabolism is reprogrammed, leading to unique metabolic adaptations that distinguish PCa from other solid tumours. As a consequence, primary prostate tumours rely on oxidative phosphorylation (OXPHOS) and *de novo* lipogenesis rather than relying predominantly on glycolysis [55,56]. Enhanced fatty acid (FA) synthesis is evident early in PCa tumourigenesis and is strongly associated with disease progression and poor clinical outcome [57]. With disease progression, however, particularly under androgen deprivation, this metabolic configuration becomes increasingly plastic. In CRPC, glycolytic flux becomes markedly elevated [58]. This indicates that metabolic progression in PCa is best understood not as a linear shift from one dominant pathway to another, but as progressive expansion of metabolic adaptability.

AR signalling is a central regulator of the core metabolic pathways in PCa [59]. Beyond its established role in driving cellular proliferation, AR directly influences mitochondrial respiration, lipid biosynthesis and redox homeostasis to sustain tumour growth and progression. AR activation induces OXPHOS and *de novo* lipogenesis in parallel with cellular proliferative signalling [60–62]. In addition, AR promotes metabolic flux through the pentose phosphate pathway (PPP), partly via the mechanistic target of rapamycin (mTOR)-mediated upregulation of glucose-6-phosphate dehydrogenase (G6PD) [63,64]. Increased G6PD activity augments ribose-5-phosphate synthesis to support nucleotide production while elevating NADPH generation, thereby maintaining reductive biosynthesis and redox balance necessary for sustained lipogenesis and tumour cell survival [65]. AR is also associated with a downregulation of zinc transporter proteins, which reduces intracellular zinc accumulation and relieves inhibition of m-aconitase. This promotes increased TCA flux and ATP production in PCa compared with normal prostate epithelium [54,66], further enhancing bioenergetic efficiency and supporting malignant progression.

Within this framework, emerging evidence indicates that EVs may actively shape and maintain metabolic phenotypes in PCa. One study found that CAF-derived EVs reprogramme the metabolism of recipient PCa cells [67], characterised by decreased OXPHOS and a concomitant increase in glycolysis and glutamine-dependent reductive carboxylation, a metabolic feature so far described in other tumour models [68,69]. Another study in mice found that PCa EVs exhibit marked increases in enzymes involved in PCa metabolic pathways including glycolysis, amino acid metabolism, carbon and pyruvate metabolism [70]. Similarly, EVs released from acid-resistant PCa cells have been shown to be enriched in glycolytic enzymes. Upon uptake by recipient cells, these EVs enhanced glycolytic flux and increased cell proliferation, resulting in a shift towards a glycolysis-dependent metabolic phenotype, associated with advanced PCa [58,71]. Another study found that EVs derived from enzalutamide-resistant PCa cells exhibit increased expression of the transcriptional regulator Yes associated protein (YAP)-1 which drives cancer

stemness and lipid metabolism [72]. Notably, treatment of androgen-sensitive LNCaP cells with these EVs not only promotes enzalutamide resistance but also enhances stem-like properties and lipid metabolic activity. These findings suggest that EVs secreted from metabolically or therapeutically adapted tumour subpopulations can disseminate metabolic traits to neighbouring cells, therefore reinforcing metabolic plasticity within the TME. Such EV-mediated metabolic crosstalk may contribute to disease progression, therapeutic resistance, and intra-tumoural heterogeneity in PCa.

Clinically, the metabolic dependence of PCa on AR signalling is shown by the rapid regression of PCa following androgen deprivation therapy (ADT) [73,74]. However, tumours can frequently develop mechanisms to restore AR activity or reprogramme core metabolic pathways, resulting in progression to CRPC [75–80]. The ability to reactivate AR-driven signalling and metabolism in the absence of androgens poses a significant clinical challenge and highlights the intrinsic metabolic plasticity of advanced PCa. While many CRPC tumours maintain reactivated AR signalling, some may undergo lineage plasticity, transdifferentiating into neuroendocrine prostate cancer (NEPC), which has an even worse prognosis than classic CRPC [20,81]. This represents an extreme manifestation of tumour plasticity, where metabolic pathways are fundamentally restructured. EVs may represent an important, though not yet fully defined, mechanism by which adaptive traits are propagated. Thus, the transition from hormone-sensitive disease to CRPC or NEPC should be understood not only as a cell-intrinsic evolutionary process but also as one that may be shaped by EV-mediated metabolic reprogramming.

3.2. Radiation-induced metabolic rewiring via EVs: A mechanism of adaptive survival

RT exerts profound oxidative and metabolic stress on tumour cells through DNA double-strand breaks, the generation of reactive oxygen species (ROS), and mitochondrial dysfunction [82,83]. While these effects underpin the cytotoxic efficacy of RT, irradiation can also impose selective pressure that favours the survival of tumour cells capable of adaptive metabolic reprogramming and enhanced DNA repair [84]. Emerging evidence suggests that EVs may function as amplifiers of these adaptive responses, facilitating the transfer of stress-associated metabolic signals and thereby reinforcing radioresistance (**Figure 2**).

3.2.1. Glycolytic shift and antioxidant defence

A shift toward glycolysis and enhanced antioxidant capacity is an important metabolic programme through which tumour cells survive RT-induced stress. In PCa specifically, this adaptive capacity appears to converge on two interrelated metabolic axes: enhanced aerobic glycolysis and augmented antioxidant defence via the PPP, both of which are transcriptionally coordinated by hypoxia-inducible factor-1 (HIF-1).

Emerging evidence indicates that enhanced glycolytic activity is associated with radioresistance in PCa. Mechanistically, this association reflects several converging effects. By diverting glucose-derived carbon into the PPP, enhanced glycolysis increases NADPH production, which sustains glutathione-dependent scavenging of ROS generated by irradiation and thereby limits oxidative DNA damage [85]. The same flux supplies ribose-5-phosphate and ATP required for

nucleotide synthesis and the DNA damage response, supporting more efficient repair of radiation-induced lesions [86,87]. In addition, lactate and pyruvate provide direct antioxidant buffering, while HIF-1-driven glycolysis enables the survival of hypoxic cells that are intrinsically radioresistant, owing to the reduced oxygen-mediated fixation of DNA damage (the "oxygen effect") [21]. Chang *et al.* reported that radioresistant DU145 and PC3 cells as well as PCa xenograft models exhibit significantly elevated glycolytic activity [88], accompanied by upregulation of the key glycolytic effector aldolase A (ALDOA) [89]. HIF-1, a central regulator of the cellular hypoxic response, is frequently overexpressed in PCa [90] and has been demonstrated to promote radioresistance in PCa cells [91,92]. Notably, HIF-1 drives a metabolic shift from mitochondrial OXPHOS towards accelerated glycolysis and activation of the PPP, thereby enhancing the survival of hypoxic cancer cells under radiation stress [21]. HIF1 directly regulates the expression of LDHA, the key enzyme responsible for the conversion of pyruvate to lactate during anaerobic glycolysis [93]. The clinical relevance of LDHA in this context is underscored by its association with biochemical recurrence and local relapse following RT in patients with PCa [94], and by functional studies demonstrating that its pharmacological or gene silencing significantly restores radiosensitivity [95]. In summary, these findings suggest that hypoxia-driven metabolic reprogramming towards increased glycolysis contributes to the development of radioresistance in PCa.

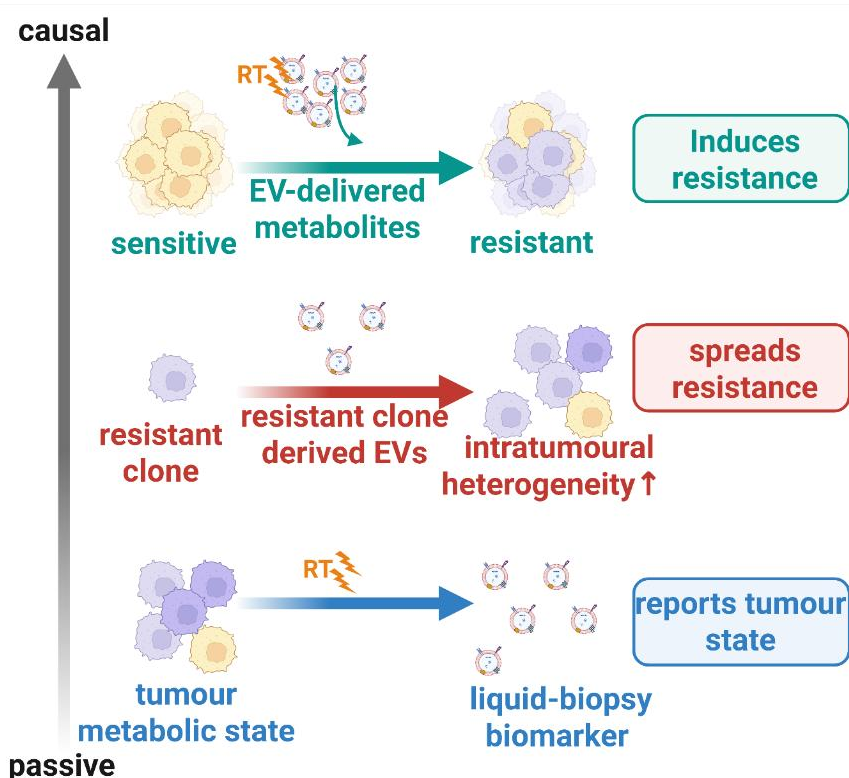


Figure 2. EV metabolomics as a driver, amplifier, or readout of radioresistance. Three non-mutually-exclusive roles are proposed for EV metabolomics in RT-driven prostate cancer evolution, ordered from active/causal (top) to passive (bottom). As a driver, EV-delivered metabolites and metabolic regulators may actively induce a radioresistant phenotype in recipient cells. As an amplifier, EVs released from already-resistant subpopulations may propagate a pre-existing resistant phenotype across the tumour, reinforcing intratumoural heterogeneity. As a readout, the circulating EV metabolome may passively reflect tumour metabolic state and RT response, serving as a liquid-biopsy biomarker without a causal role. Distinguishing among these roles is a central open question for the field. (Created with BioRender.com.) Abbreviations: EV, extracellular vesicle; RT, radiotherapy.

In this mechanistic backdrop, whether RT-induced metabolic adaptations are disseminated through EVs, and whether such dissemination contributes meaningfully to radioresistance, represents a critical question to answer. Irradiation of PC-3 PCa cells has been shown to enrich secreted EVs with miR-378a-3p, a strand of miR-378a whose glycolytic role has so far been shown only in breast cancer [96], and whose elevation in circulating EVs was detectable in irradiated mouse models [97]. Although this has not yet been examined in PCa, another study reported that EVs released from irradiated lung cancer cells exhibited elevated expression of the critical glycolytic enzyme ALDOA, alongside ALDH3A1. Co-culture of recipient cancer cells with these EVs resulted in increased expressions of these enzymes, accompanied by enhanced glycolytic activity, cell motility and metastatic potentials [98]. Similarly, Wu *et al.* demonstrated that latent membrane protein 1 (LMP1) packaged within EVs derived from nasopharyngeal carcinoma (NPC) cells activated normal fibroblasts into CAFs via NF-kb signalling. This activation promoted enhanced aerobic glycolysis and increased expression of lactate transporters in CAFs, which subsequently supported the proliferation and radiation resistance of co-cultured NPC cells [99]. Another study on rectal cancer also highlights the association between EV cargo and treatment response. The glucose transporter SLC2A1/GLUT1, which is a critical regulator in glucose metabolism, was significantly overexpressed in EVs derived from patients who responded poorly to RT, accompanied by significantly elevated glucose levels [100]. Elevated GLUT1 expression has previously been observed in radioresistant tumour cells and is frequently associated with hypoxia and activation of MAPK and PI3K/AKT signalling pathways [101,102]. Together, these findings indicate that EV-mediated transfer of metabolism-associated molecules may contribute to tumour metabolic plasticity and the propagation of radioresistant metabolic phenotypes by upregulating glycolytic reprogramming following RT. These findings, however, are drawn mostly from other irradiated tumour types; the only direct PCa observation to date is the enrichment of miR-378a-3p in irradiated PC-3 EVs, and functional confirmation in PCa is still needed.

3.2.2. Lipid metabolism remodelling

PCa is characterised by pronounced alterations in lipid metabolism, including increased *de novo* lipogenesis, FA synthesis and oxidation, arachidonic acid metabolism and cholesterol synthesis [85]. This characteristic is particularly important in terms of radioresistance, given the mechanistic intersection between lipid anabolism and AR signalling, with androgens being themselves derived from cholesterol through a multi-step biosynthetic pathway [103], as well as the well-established involvement of AR signalling in the development of radioresistance via the upregulation of DNA repair genes which facilitates repair of RT-induced damage and attenuates cytotoxic effects [104–106].

The principal effectors of enhanced lipogenesis in PCa, namely fatty acid synthase (FASN), stearoyl-CoA desaturase (SCD), ATP-citrate lyase and acetyl-CoA carboxylase (ACC) are upregulated in radioresistant tumours, facilitating increased production of plasma membrane phospholipids and bioactive lipid-derived signalling molecules [107]. In PCa cells, overexpression of FASN has been shown to upregulate AR signalling via activation of the Akt/NF-kB pathway, leading to cell cycle arrest and improved DNA repair capacity, thereby resulting in radioresistance. Furthermore, pharmacological inhibition of FASN has been demonstrated to increase the radiosensitivity of PCa cells by altering cell cycle phases [108].

Arachidonic acid metabolism also contributes to PCa progression and treatment resistance. Arachidonic acid is synthesised from membrane phospholipids by cytosolic phospholipase A2 and subsequently converted into bioactive substances such as prostaglandins, prostacyclins and thromboxanes via the enzymatic activity of lipoxygenases (LOXs) and cyclooxygenases. In PCa, it has been shown that increased LOX-12 expression is associated with advanced disease and poor prognosis and pharmacological inhibition of LOX-12 has been shown to increase the radiosensitivity of PCa cells significantly [109,110].

Cholesterol biosynthesis, regulated by the rate-limiting enzyme HMG-CoA reductase, similarly contributes to radioresistance. Statin-mediated inhibition of HMG-CoA reductase has been associated with reduced incidence of advanced and radioresistant PCa [111,112], and combined simvastatin-RT treatment has demonstrated enhanced cytotoxicity in radioresistant PCa models relative to RT alone, characterised by impaired DNA double-strand break repair and increased apoptotic signalling [113]. Taken together, these findings delineate a coherent and complex picture in which multiple interconnected lipid metabolic programmes collectively sustain the radioresistant phenotype of PCa.

EVs may play a role in the regulation of lipid metabolism in response to RT, however, this is also an area in which the evidentiary gap is apparent. Direct support for EV-mediated lipid remodelling in irradiated PCa remains limited, and much of the current narrative relies on associative findings in PCa or inference from other tumour types. A study by Malla *et al.* reported that hsa-miR-21-5p was significantly upregulated in serum EVs from high-risk compared to intermediate-risk PCa patients after RT [114]. miR-21-5p has previously been associated with insulin resistance and increased levels of triglycerides and triacylglycerols in patients with hepatocellular carcinoma, suggesting a potential link between EV-associated miRNAs and lipid metabolic regulation [115]. Another study on NPC found that high EV expression of circMYC is an independent predictor of patient survival and disease recurrence and can differentiate radioresistant tumours from radioresistant counterparts [116]. Mechanistically, circMYC has been shown to enhance fatty acid synthesis in breast cancer via activation of SREBP1 [117]. Similarly, irradiated glioblastoma cells have been reported to release EVs enriched with miR-603, upregulating the MGMT protein which is strongly associated with poor responses to RT [118]. Notably, unmethylated-MGMT status has been linked to increased lipid metabolic activity in glioblastoma, specifically enriching unsaturated FAs and enhancing the mobilisation of lipid droplets [119]. In PCa, YAP protein has been found to be enriched in EVs following chemotherapy (rather than RT) exposure, where it promotes lipid metabolism via upregulation of HMG-CoA reductase and enhances cancer stemness and treatment resistance [72]. Importantly, YAP has been extensively implicated in AR signalling and castration-resistant PCa growth [120,121] and radioresistance in several other malignancies including glioma, medulloblastoma, NPC and non-small cell lung carcinoma [122–125]. Thus, these findings suggest that EV-mediated transfer of metabolic regulators such as miRNAs, circular RNAs, and transcriptional co-activators may contribute to lipid metabolic reprogramming following RT.

A further, emerging dimension of RT-lipid crosstalk is ferroptosis – a non-apoptotic, iron-dependent form of regulated cell death driven by the lipid peroxidation of polyunsaturated fatty acid (PUFA)-containing phospholipids.

When the intracellular levels of lipid ROS exceed the antioxidant capacity of glutathione-dependent peroxidase (GPX4), this leads to the collapse of cellular redox homeostasis and subsequent cell death [126]. Because RT generates ROS and promotes lipid peroxidation, ferroptosis contributes to RT-induced cell death [127]. Tumour cells that resist ferroptosis may therefore be more likely to survive irradiation. EVs have been shown to modulate this process by transferring ferroptosis-regulatory cargo between cells. In non-squamous cell lung cancer (NSCLC), EVs released from hypoxic tumour cells were shown to transfer angiopoietin-like 4 protein to neighbouring normoxic cells, conferring radioresistance through a GPX4-dependent inhibition of ferroptosis [128]. EVs have also been shown to contribute to chemotherapy resistance via the inhibition of ferroptosis in various non-PCa cancer models. In NSCLC, EV delivery of miR-4443 to cisplatin-sensitive NSCLC cells upregulates ferroptosis suppressor protein 1 (FSP-1) expression and subsequent chemoresistance. The suppression of ferroptosis by FSP-1 is mediated by ubiquinol (CoQ10), whose reduced form, ubiquinol, traps lipid peroxy radicals that mediate lipid peroxidation, and FSP-1 catalyses the regeneration of CoQ10 via NADPH. In lung adenocarcinoma cells, EV-mediated transfer of circRNA_101093 increases fatty-acid binding protein 3 to reduce global arachidonic acid (AA) and AA incorporation into the basement plasma membrane, leading to ferroptosis resistance [129]. In gastric cancer (GC), chemotherapeutic drug toxicity stimulates CAFs to release EV-derived miR-522 which blocks the accumulation of lipid ROS by targeting ALOX15, thus inhibiting ferroptosis and inducing chemotherapy resistance [130]. A separate study in GC found that EV-derived lncFERO enhanced SCD expression while recruiting heterogeneous nuclear ribonucleoprotein A1, which led to dysregulated PUFA levels and suppressed ferroptosis, thus reducing chemosensitivity of CSCs [131]. In pancreatic ductal adenocarcinoma, CAF-derived EVs promoted chemoresistance via the transfer of miR-3173-5p which decreased ACSL4 expression and subsequent ferroptosis [132]. In colorectal cancer (CRC), adipose-derived EVs deliver microsomal triglyceride transfer protein, a major intracellular lipid transfer protein, to inhibit ferroptosis in recipient CRC cells by upregulating GPX4 and xCT which promotes chemoresistance [133]. Although much of the current EV-ferroptosis literature derives primarily from chemoresistance models rather than RT-specific studies, these findings remain mechanistically relevant to radioresistance since ferroptosis is regulated by shared redox and lipid-peroxidation pathways.

Therefore, EVs can transfer anti-ferroptotic effectors linked to glutathione peroxidase 4 (GPX4), components of the SLC7A11/xCT cystine-glutathione system, ferritin and regulatory miRNAs, conferring ferroptosis resistance on recipient cells, thereby linking ferroptosis to the NADPH- and glutathione-dependent redox programmes discussed in Section 3.2. The EV-mediated dysregulation of PUFAs and lipid-remodelling enzymes such as ACSL4 and SCD may further alter the susceptibility of recipient-cell membranes to peroxidation; consistent with this, the MUFA-enriched, PUFA-poor lipid profile reported for aggressive PCa-derived EVs is consistent with a ferroptosis-resistant phenotype [134–140]. Although this RT-ferroptosis–EV crosstalk is currently inferred from non-PCa models and remains to be demonstrated directly in irradiated PCa, it represents a plausible mechanism by which EVs could influence radiosensitivity and warrants future investigation.

3.2.3. Amino acid and nutrient scavenging

Amino acid metabolism plays a key role in core cancer processes, including but not limited to energy production, redox homeostasis and nucleotide synthesis [141]. Glutamine is one of the most important nutrients supporting these processes [142]. Glutamine functions simultaneously as a nitrogen donor for nucleotide synthesis, a carbon source for the TCA cycle and a precursor for glutathione biosynthesis that is essential for ROS detoxification under conditions of RT-induced oxidative stress [142,143]. RT has been reported to increase GLS activity in several cancers, including PCa. One study found that radioresistant PCa cells and prostate CSCs exhibit a high glutamine demand, not only for energy production but also for the maintenance of redox homeostasis. Furthermore, high GLS expression is associated with decreased relapse-free survival in patients after RT [144]. Serine and glycine metabolism represent a further dimension of amino acid-mediated adaptation. Under hypoxic conditions, which, as previously discussed, are prevalent in PCa and strongly predictive of RT failure, HIF-1/2 activation and the PERK-eIF2 α -ATF4 axis cooperate to upregulate key serine/glycine-synthesising enzymes, including PHGDH, PSTA1, PSPH and SHMT2 [145–147]. The resultant increase in serine/glycine metabolism elevates NADPH and glutathione levels, promoting ROS elimination [85]. In NEPC, loss of the tumour suppressor protein kinase C rewires cellular metabolism towards serine biosynthesis via an mTORC1/ATF4-driven pathway. This increases intracellular S-adenosylmethionine levels, promoting epigenetic changes and DNA methylation patterns which are conducive to NEPC differentiation [148]. Arginine metabolism has also been implicated in PCa progression and RT response. In murine models, irradiated PCa cells recruit tumour-associated macrophages (TAMs) with higher levels of arginase, cyclooxygenase and nitric oxide synthase. Subsequently, crosstalk between TAMs and tumour cells promotes PCa aggressiveness post-RT [149].

EVs may play a role in amino acid metabolism reprogramming in PCa after RT. Evidence from other tumour types suggests that RT-induced EV signalling can enhance amino acid utilisation in recipient cells. Although not yet shown in PCa, in oral squamous cell carcinoma, RT has been shown to increase the release of EVs enriched in SLC1A5, a critical glutamine transporter. Uptake of these EVs by unirradiated cells enhanced glutamine metabolism, while pharmacological inhibition of SLC1A5 increased tumour radiosensitivity, suggesting that RT-induced EVs may promote glutamine utilisation and radioresistance [150]. In a non-RT setting, another study found that CAFs in lung adenocarcinoma release EVs containing the long non-coding RNA LINC01614, which directly interacts with annexin A2 and p65 to activate the NF- κ B pathway in recipient cells, leading to the upregulation of glutamine transporters SLC38A2 and SLC7A5 and enhanced glutamine metabolism, which was associated with poorer patient survival [151]. Collectively, these findings from other cancer models suggest that EVs can regulate amino acid transport and metabolism through the transfer of transporters, regulatory RNAs, and metabolic enzymes.

3.2.4. EV-mediated mitochondrial transfer

Beyond soluble metabolites and regulatory RNAs, EVs and related vesicular structures can mediate the horizontal transfer of mitochondria and mitochondrial components, including mtDNA and respiratory-chain proteins, between cells. Recent evidence indicates that EVs can carry mitochondrial cargo

and transfer functional mitochondria to recipient cells, which can restore or augment oxidative phosphorylation, rescue bioenergetics under metabolic stress, buffer reactive oxygen species and potentially support survival and proliferation [152,153]. This mechanism has been implicated in tumour progression and in resistance to chemotherapy and RT across other cancer types, including breast cancer [154] and NSCLC [155]. Such bioenergetic rescue may be especially relevant in PCa, where primary tumours depend substantially on oxidative phosphorylation (see Section 3.1), suggesting that EV-mediated mitochondrial transfer could contribute to metabolic plasticity and adaptive survival following RT. This metabolic role is distinct from, and complementary to, the transfer of EV-borne mtDNA as a genotoxic bystander signal discussed earlier (Section 2.3). Direct evidence for mitochondrial transfer in irradiated PCa, however, is currently lacking and represents an important avenue for future investigation.

Across glycolytic, lipid and amino acid metabolic domains, a consistent mechanistic theme emerges: RT acts not only as a cytotoxic modality but as a selective pressure that enriches for tumour cell populations capable of coordinated metabolic adaptation. Although presented pathway-by-pathway above, these programmes are not isolated; they converge on a shared set of effectors that together sustain the radioresistant phenotype (**Figure 3**). They reinforce redox control, as PPP-derived NADPH together with glutamine- and serine/glycine-derived glutathione buffers the reactive oxygen species generated by irradiation. They support DNA repair, with ribose-5-phosphate sustaining nucleotide synthesis while AR- and FASN-driven signalling enhances the repair of RT-induced damage. Through lipogenesis, they drive membrane remodelling, generating the phospholipids and bioactive lipid signalling molecules characteristic of radioresistant tumours. These activities are coordinated by overlapping regulatory nodes, most prominently AR signalling, a master regulator of glycolytic, lipogenic and redox metabolism in PCa, and HIF-1, which, under the hypoxic conditions prevalent in PCa, redirects metabolism towards glycolysis and the PPP to enable survival under hypoxia. Finally, this metabolic plasticity sustains stemness, supporting the glutamine-dependent, YAP-driven stem-like states associated with radioresistance. Mapped onto the classical radiobiological framework, these EV-propagated programmes act mainly on Repair (enhanced DNA-damage repair), intrinsic Radiosensitivity (ROS buffering), Reoxygenation and hypoxic survival, and Repopulation (via stem-like states), while EV-borne immune-checkpoint cargo (Section 2.2) may additionally impair Reactivation of anti-tumour immunity. EV-mediated regulation of key metabolic pathways and their roles in radioresistance are summarised in **Table 1**. This regulatory architecture makes it unlikely for radioresistance to be overcome by targeting any single metabolic pathway in isolation, and underscores the need for an integrative framework that accounts for resistance driven by coordinated metabolic remodelling.

Such a framework must also consider the intratumoural heterogeneity in the context of PCa. When the tumour is treated with RT, irradiation targets a spatially structured ecosystem in which subpopulations, for example, tumour cells and CSCs, stromal cells, differ substantially in their baseline metabolic state and adaptive capacity. Under these conditions, EVs assume their greatest potential significance: by packaging and transferring glycolytic enzymes, lipid metabolic regulators, amino acid transporters, and the transcriptional and epigenetic effectors that coordinate their expression, EVs released from radioresistant

subpopulations may extend adaptive metabolic capacity beyond their cell of origin and disseminate resistance across the whole tumour ecosystem.

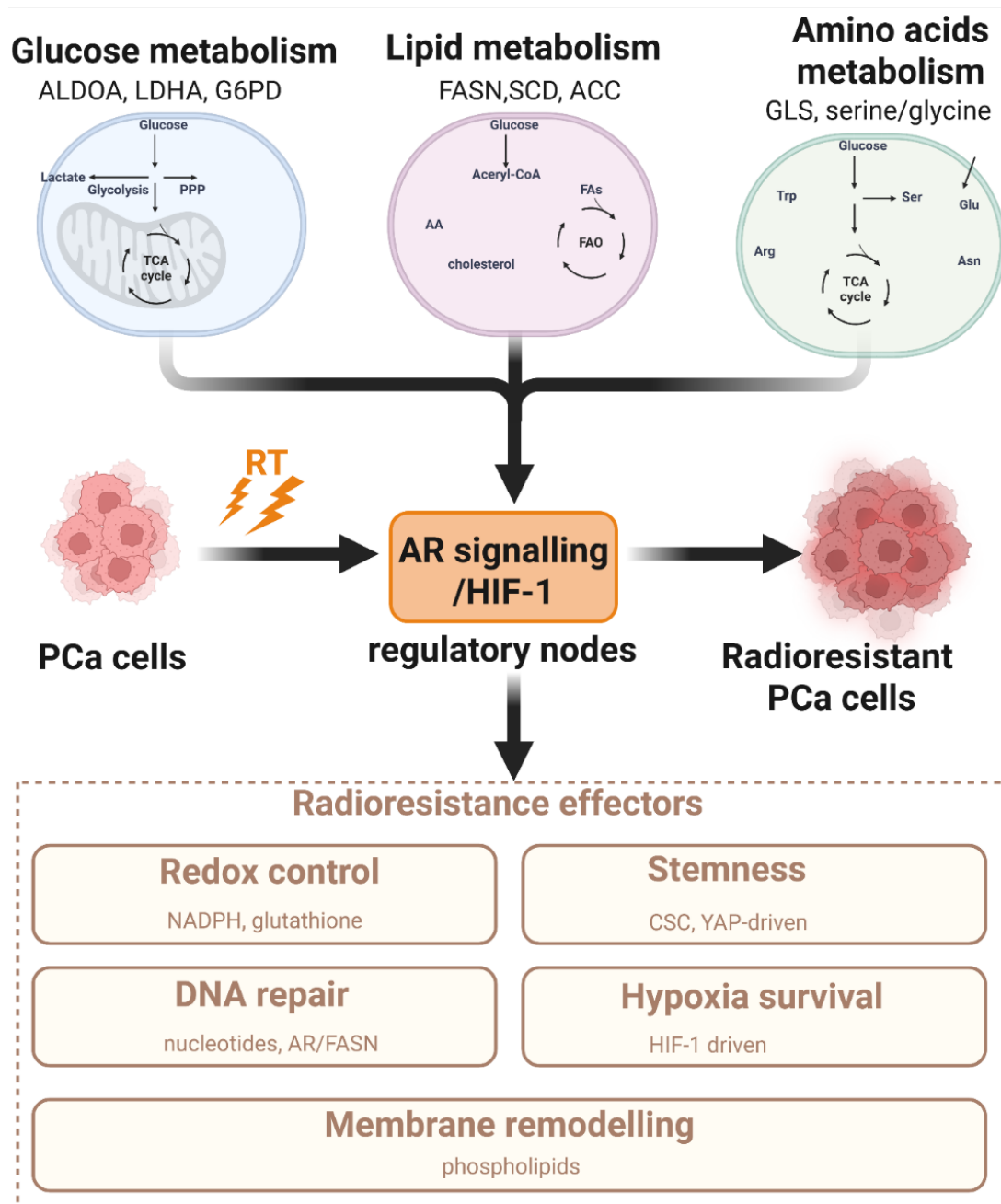


Figure 3. Convergence of metabolic pathways on radioresistance in PCa. The glycolytic/pentose phosphate, lipid and amino acid metabolic programmes upregulated after radiotherapy are not independent but converge on a shared set of effectors that sustain the radioresistant phenotype. They are coordinated by two overlapping regulatory nodes: androgen receptor (AR) signalling, a master regulator of glycolytic, lipogenic and redox metabolism in PCa, and HIF-1, which, under hypoxic conditions, redirects metabolism towards glycolysis and the PPP. Through these nodes, the three pathways jointly drive redox control (PPP-, glutamine- and serine/glycine-derived NADPH and glutathione that buffer radiation-induced ROS), DNA repair (nucleotide supply and AR-/FASN-enhanced repair), membrane remodelling (phospholipid and lipid-signalling synthesis), cancer stem-like states (CSC/YAP-driven stemness) and survival under hypoxia, together producing a radioresistant phenotype and supporting the survival of resistant subclones. Abbreviations: ACC, acetyl-CoA carboxylase; ALDOA, aldolase A; AR, androgen receptor; CSC, cancer stem cell; FASN, fatty acid synthase; G6PD, glucose-6-phosphate dehydrogenase; GLS, glutaminase; GSH, glutathione; HIF-1, hypoxia-inducible factor 1; LDHA, lactate dehydrogenase A; NADPH, nicotinamide adenine dinucleotide phosphate; PCa, prostate cancer; PPP, pentose phosphate pathway; ROS, reactive oxygen species; SCD, stearoyl-CoA desaturase; YAP, Yes associated protein. (Created with BioRender.com).

Table 1 – Summary of key metabolic pathways, their role in radioresistance, and EV-mediated regulation. 6 Rs of radiotherapy response: Repair (of sublethal DNA damage), Redistribution (within the cell cycle), Repopulation, Reoxygenation, intrinsic Radiosensitivity, and Reactivation of anti-tumour immunity. Abbreviations: AKT, protein kinase B; ALDH3A1, aldehyde dehydrogenase 3 family member A1; ALDOA, aldolase A; AR, androgen receptor; CAF, cancer-associated fibroblast; circMYC, circular MYC; CSC, cancer stem cell; EV, extracellular vesicle; GLUT1, glucose transporter 1; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; LINC01614, long intergenic non-protein coding RNA 1614; LMP1, latent membrane protein 1; MAPK, mitogen-activated protein kinase; MGMT, O6-methylguanine-DNA methyltransferase; NF-κB, nuclear factor kappa B; PI3K, phosphoinositide 3-kinase; RT, radiotherapy; SLC1A5, solute carrier family 1 member 5; SLC2A1, solute carrier family 2 member 1; SLC7A5, solute carrier family 7 member 5; SLC38A2, solute carrier family 38 member 2; SREBP1, sterol regulatory element-binding transcription factor 1; YAP, Yes associated protein 1. (please cite/mention Table 1 in the main text where it was first discussed)

Metabolic Pathway	Cancer Type / Model	EV Cargo (Source)	Functional Effect/Mechanism	Impact on RT Response (Relevant Rs)	Evidence Type	References
Glycolysis	Prostate cancer (PC3; mouse model)	miR-378a-3p (Irradiated tumour cells)	miR-378-mediated metabolic reprogramming → ↑ glycolytic shift → NADPH/ROS buffering and DNA-repair support → radioresistance	Potential radioresistance (Repair; Radiosensitivity)	<i>In vitro + in vivo</i>	[96,97]
Glycolysis and stemness (CSC)	Prostate cancer	CD133, CD44, ALDH1, GLUT1 (Irradiated tumour cells)	↑ CSC markers → promotes stem-like, glycolytic, metabolically active phenotype and EMT in recipient cells	Promotes aggressive, radioresistant phenotype (Repopulation; Radiosensitivity)	<i>In vitro</i>	[41]
Glycolysis	Lung cancer	ALDOA, ALDH3A1 (Irradiated tumour cells)	↑ glycolysis, ↑ motility, ↑ metastasis (Glycolytic enzyme transfer → NADPH/ROS buffering and DNA-repair support → radioresistance)	Promotes resistance (Repair; Radiosensitivity)	<i>In vitro</i>	[98]
Glycolysis (tumour–stroma crosstalk)	Nasopharyngeal carcinoma	LMP1 (Tumour-derived EVs)	LMP1 activates CAFs via NF-Kb siognalling → ↑ aerobic glycolysis, ↑ lactate transport → metabolic fuel transfer supporting survival and repopulation	Supports resistance (Repair; Repopulation)	<i>In vitro</i>	[99]
Glucose metabolism	Rectal cancer (patients)	SLC2A1/GLUT1 (Circulating EVs)	↑ glucose uptake and metabolism → ↑ NADPH/ROS buffering, nucleotide synthesis and hypoxic-cell survival (MAPK, PI3K/AKT pathway; hypoxia-associated)	Poor RT response (Repair; Reoxygenation)	Clinical	[100–102]

Lipid metabolism	Prostate cancer (patients)	miR-21-5p (Serum EVs post-RT)	MiR-21-5p associated with lipid dysregulation → possible membrane/lipid-signalling adaptation → enhanced DNA repair and survival	Potential resistance biomarker (Repair)	Clinical	[114,115]
Lipid metabolism	Nasopharyngeal carcinoma	circMYC (Tumour-derived EVs)	circMYC/SREBP1 activation → ↑ fatty acid synthesis → membrane remodelling and lipid-signalling support for repair/survival	Radioresistance (Repair)	Clinical + mechanistic	[116,117]
Lipid metabolism	Glioblastoma	miR-603 (Irradiated tumour cells)	miR-603 → ↑ MGMT expression and lipid metabolic shift → enhanced DNA damage repair and survival	Poor RT response (Repair)	<i>In vitro</i>	[118,119]
Lipid metabolism	Prostate cancer	YAP (Therapy-induced EVs)	YAP → ↑ cholesterol synthesis; ↑ stemness via HMG-CoA reductase/AR signalling → DNA-repair support and repopulation	Therapy resistance (Repopulation; Repair)	<i>In vitro</i>	[72,121–125,156]
Amino acid metabolism (glutamine)	Oral squamous cell carcinoma	SLC1A5 (Irradiated tumour cells)	Glutamine transporter transfer → ↑ glutamine uptake and metabolism → GSH synthesis/ROS buffering and nucleotide biosynthesis → increased repair and survival	Promotes resistance (Radiosensitivity; Repair)	<i>In vitro</i>	[150]
Amino acid metabolism (glutamine)	Lung adenocarcinoma (CAF-tumour)	LINC01614/lncRNA(CAF-derived EVs)	LINC01614 → NF-κB activation → ↑ SLC38A2, SLC7A5 → ↑ glutamine uptake and metabolism → GSH synthesis/ROS buffering and nucleotide biosynthesis → increased repair and survival	Poor survival/resistance (Radiosensitivity; Repair)	<i>In vitro</i> + clinical	[151]

The EV-specific mechanistic evidence above is drawn predominantly from other tumour types and is largely correlative; direct evidence in irradiated PCa remains sparse. We must also acknowledge that the mechanistic studies cited derive predominantly from tumour types with distinct metabolic dependencies compared to PCa. Furthermore, the evidence is largely correlative, but not causal in nature. The additional intersection of EV-mediated metabolic signalling with tumour plasticity, including lineage switching and acquisition of stem-like features, further complicates this research field. Resolving these questions will require integrated metabolomics in tandem with other multi-omic profiling of EVs derived from irradiated PCa cells, combined with functional recipient-cell assays, *in vivo* validation and clinical outcome correlation, which remain largely missing from the current literature.

4. EVs as Metabolic Biosensors: Clinical Translation for Precision Oncology

4.1. EV metabolomics in liquid biopsy: capturing dynamic heterogeneity

A significant challenge in precision oncology is that clinically actionable tumour biology is neither spatially uniform nor temporally stable. Molecular profiling of tumours in patients has been shown to improve the selection of personalised cancer treatments, facilitate the detection of treatment resistance, and enable monitoring for tumour relapse [157,158]. Yet the utility of molecular profiling in PCa is complicated by the spatial and temporal heterogeneity that defines the disease. As a result, tissue biopsy, although still the gold standard for diagnosis and pathological assessment, provides only a limited and static representation of a biologically dynamic disease [159]. Moreover, tumour profiles evolve over time, meaning that clinical decisions based on historical biopsy data may be misleading [160,161]. Repeated tissue sampling is also constrained by procedural invasiveness, cost, patient burden, and feasibility.

In response to these limitations, liquid biopsy has emerged as a promising, non-invasive approach within precision medicine. Liquid biopsy involves the analysis of bodily fluids, including blood and urine, to detect molecular biomarkers for early cancer detection, surveillance, and monitoring for post-treatment recurrence [162,163], where tumour biology could be captured in a manner that is serial, systemic and ongoing. This enables continuous monitoring of cancer evolution and treatment response, supporting real-time clinical decision-making [164,165].

As discussed above, EV-derived metabolomics represents a promising yet underexplored analytical strategy for liquid biopsy. Biologically, this may be particularly relevant in the context of RT response: metabolic adaptation to RT can proceed through genetically and transcriptionally diverse mechanisms that converge on shared outputs, which means metabolomic profiling could, in principle, detect early radioresistant signals that may be invisible to mutation- or transcript-based approaches.

Moreover, the capacity of EV metabolomics to capture intratumoral heterogeneity is further enhanced by the composite nature of circulating EV populations. The aggregate EV metabolome, therefore, reflects a systems-level diversity that is inaccessible to single-site tissue biopsy. Longitudinal profiling of this signal could enable the early detection of metabolic shifts associated with the emergence of

radioresistant clones prior to biochemical failure or clinical relapse, and may, with validation, offer a possible clinical window for therapeutic personalisation.

A complementary strategy for resolving this heterogeneity is single-EV analysis. Since bulk and aggregate measurements average signals across heterogeneous EV populations, they can obscure rare but uniquely informative subsets, such as tumour- or radioresistant-clone-derived vesicles. Single-EV technologies, including nano-flow cytometry (nFCM) [166–173], single-particle interferometric reflectance imaging (SP-IRIS) (e.g., SP-IRIS/ExoView) [174–178], super-resolution and total internal reflection fluorescence microscopy (TIRF) [179–182], microfluidic platforms and emerging single-EV proteomic approaches, can phenotype individual vesicles, co-localise multiple cargoes on the same EV and detect rare subpopulations [183]. In PCa, single-EV nFCM analysis was shown to have diagnostic utility in differentiating healthy patients from PCa, by measuring levels of the metalloredutase six-transmembrane epithelial antigen of the prostate 1 (STEAP1), with an AUC of 0.95 [166]. Another study showed that nFCM was able to separate intermediate-risk (Gleason score <8) from high-risk PCa (Gleason score of 8 or above) by measuring PSMA-positive prostate EV levels in plasma [167]. nFCM was also able to distinguish between prostate EVs of exocytic origin versus membrane origin (microvesicles) by co-expression of surface markers CD9, CD63 and CD81 [184]. In NPC, nFCM was able to determine the concentration of 5 surface proteins (LMP1, LMP2A, PD-L1, EGFR and EpCAM) on individual plasma EVs, and, in a combined panel, differentiate NPC from both healthy donors and nasopharyngitis with 96.3% and 83.1% accuracy, respectively, which was significantly superior to the traditional VCA-IgA assay [168]. Another study on intraductal papillary mucinous neoplasms (IPMN) showed that FCM could differentiate invasive from indolent IPMN with 82% specificity and 100% sensitivity by measuring mucin 5AC levels in plasma EVs [170]. In NSCLC, TIRF was able to distinguish good responders from poor responders to immunotherapy by quantifying single-EV PD-1/PD-L1 mRNA with an accuracy of 72.2% and could diagnose NSCLC with an accuracy of 93.2% [179]. In PCa, these approaches could potentially identify and enrich tumour-derived EV subsets associated with metabolic adaptation and radioresistance, improving the specificity of liquid biopsy signals and helping to detect the emergence of radioresistant clones anticipated by our heterogeneity framework. However, within the current literature, single-EV analysis is used mainly for surface marker and particle characterisation; its application to the EV metabolome is constrained by the low abundance of metabolites and limited throughput, cost and standardisation. As such, bulk and single-EV approaches are likely to remain complementary in the near future.

4.2. Clinical biomarker application of EV metabolomics

The translational potential of EV metabolomics in PCa should span three important domains: primary diagnosis and risk stratification, monitoring of therapeutic response and early detection of treatment resistance. The available evidence provides meaningful proof-of-concept across several of these domains. An early proof-of-concept study investigating the diagnostic potential of urinary EV lipid profiles demonstrated that nine lipids were significantly different between PCa patients and healthy controls. Using EV lipid analysis, the groups could be distinguished with 93% sensitivity and 100% specificity [185]. However, the study cohort was small, including only 15 patients and 13 controls. Therefore, larger cohort studies are required to validate these findings.

Metabolomic analysis of urinary EVs has also shown promise in differentiating PCa from benign prostatic hyperplasia (BPH). One study reported that EV metabolites reflect metabolic adaptations characteristic of PCa, including changes in phosphatidylcholines, acyl carnitines, citrate and kynurenine [186]. Notably, acyl carnitine, an intermediate in lipid metabolism, was elevated in urinary EVs, suggesting increased β -oxidation of FAs which is a recognised feature of PCa metabolism reprogramming [187]. Furthermore, 3 β -hydroxyandrost-5-en-17-one-3-sulphate, a key precursor in androgen synthesis, was elevated in PCa-derived EVs compared to BPH EVs, further supporting the potential of EV metabolites as non-invasive diagnostic biomarkers [186].

Additional metabolomic studies have identified alterations in other metabolic pathways. One investigation reported reduced glucuronate levels in urinary EVs from PCa patients prior to prostatectomy compared with healthy controls and post-prostatectomy samples [188]. Importantly, these changes were detected in urinary EVs but not in whole urine, showcasing the potential of EV-based analyses to reveal tumour-specific metabolic signatures that may otherwise remain undetected. Another study found that EVs from highly metastatic PC-3 cell lines contain higher levels of n-9 oleic acid and monounsaturated fats than less metastatic LNCaP cell lines [134–136]. These lipids are associated with enhanced activity of the enzyme stearoyl-CoA desaturase-1, an enzyme linked to tumour invasiveness. Conversely, PC-3 EVs exhibited lower saturated fatty acids and polyunsaturated fatty acids levels than LNCaP EVs, indicating alterations in lipid signalling pathways associated with PCa aggression [137–140]. Beyond tumour-derived EVs, stromal cells within the tumour microenvironment may also contribute to metabolic support. PCa-associated fibroblasts have been shown to release EVs containing metabolites such as lipids and TCA-cycle intermediates, which can be utilised by cancer cells to sustain tumour growth under nutrient-deprived conditions [67]. Targeting this metabolic crosstalk between stromal cells and tumour cells may therefore represent a novel therapeutic strategy, as has already been explored through EV-associated miRNAs in other cancer types [189].

Despite growing interest in EV biology, most studies investigating EV-mediated responses to RT have focused on transcriptomic and proteomic cargo, with comparatively little attention given to the EV metabolome. To date, no studies have specifically investigated whether EV-derived metabolites can differentiate RT responses in PCa. Evidence from other tumour types, while requiring cautious extrapolation, is nonetheless instructive regarding the feasibility of this proposed approach. One study on small-cell lung cancer EVs found that RT led to decreased levels of EV metabolites involved in nucleotide metabolism and folate metabolism [190]. Similarly, metabolomic profiling of EVs from rectal cancer patients identified multiple metabolite differences between good and poor responders to RT, including significantly elevated glucose levels in the EVs from poor responders [100]. Increased glucose availability and upregulated glycolysis have been associated with radioresistant phenotype through enhanced DNA repair capacity [86,87]. Conversely, not all studies have reported consistent findings. In head and neck cancers, EV metabolomic analysis detected no significant metabolic alterations following RT, raising questions regarding the reliability of EV metabolomics for assessing RT response [191]. Such inconsistencies represent the challenges of reproducibility and specificity that must be resolved before EV metabolomics can be considered a clinically

viable biomarker. A summary of EV metabolomic studies with clinical relevance is provided in **Table 2**. For EV metabolomics to move beyond exploratory relevance towards clinical utility in PCa, several prerequisites must be met:

- (i) Standardised, reproducible EV isolation and characterisation, reported in line with the Minimal Information for Studies of Extracellular Vesicles (MISEV2023) [192] and the open-source knowledge base EV-TRACK, which centralises data of EV separation and characterisation [193].
- (ii) Longitudinal sampling before, during and after RT to capture treatment-induced dynamics
- (iii) Link to matched clinical outcomes such as biochemical recurrence, local control and survival.
- (iv) Robust metabolite normalisation, for example, to EV particle number, EV protein or sample volume [188].
- (v) Analytical and clinical validation in independent, external cohorts.

Until these conditions are satisfied, EV metabolomics in PCa should be regarded as a promising but pre-clinical, hypothesis-generating approach rather than a near-term clinical tool.

4.3. Therapeutic implications: targeting EV-mediated metabolic crosstalk

The recognition that EVs participate in metabolic adaptation following RT opens potential therapeutic avenues. If the EV-mediated transfer of metabolic enzymes or substrates contributes to radioresistant phenotypes, then targeting these metabolic dependencies may enhance radiosensitivity. The strategies can focus on two domains: pharmacological disruption of EV biogenesis and secretion and exploitation of EVs as precision delivery vehicles.

For example, EVs released by PCa cells have been shown to impair anti-tumour immune responses by upregulating PD-1 and TIM-3 expression in CD8⁺ T cells, thereby reducing their cytotoxic ability. Pharmacological inhibition of EV secretion using the neutral sphingomyelinase inhibitor GW4869 rejuvenated T cell function and subsequently suppressed tumour growth both *in vitro* and *in vivo* [194]. Similarly, other studies have reported that EV-associated PD-L1 contributes to PCa progression, and that inhibition of EV biogenesis suppresses tumour growth [195]. EV secretion has also been implicated in therapy resistance. GW4869 and dimethyl amiloride have demonstrated efficacy in reducing cell viability in enzalutamide-resistant PCa cells characterised by elevated EV secretion, with syntaxin-6 knockdown producing concordant reductions in EV release and increased apoptosis, suggesting that EV hypersecretion may itself constitute a targetable vulnerability in therapy-resistant disease [196]. Additional pharmacological strategies targeting EV production have been explored. The natural bacterial metabolite manumycin-A (MA), which impacts RAS/RAF/ERK1/2 by targeting farnesyltransferases (FTases) inhibited EV secretion in CRPC cells. Additionally, tipifarnib, another FTase inhibitor, was also found to disrupt RAS-mediated ERK activation and the endosomal sorting complex required for transport (ESCRT) which is critical in EV biogenesis, cargo sorting and secretion [197], leading to significantly decreased EV secretion in PCa cells [198]. Kholia *et al.* found that the nuclear translocation of peptidylarginine deiminase (PAD)2 and PAD4 was associated with EV secretion in PCa cells, and the pharmacological inhibition of PAD activity using Cl-amidine reduced EV secretion and increased the sensitivity of PCa cells to chemotherapy [199]. This was supported by another study on PC-3 cells

which found that treatment of PC-3 cells with 5-fluorouracil (5-FU) in combination with EV biogenesis inhibitor CI-amidine significantly enhanced PCa cell apoptosis, resulting in a 62% decrease in viable PC-3 cells compared with treatment with 5-FU alone [200]. Collectively, targeting EV biogenesis or secretion may represent a promising strategy to enhance the efficacy of existing therapies such as chemotherapy or RT.

On the other hand, EVs themselves can be exploited as therapeutic delivery vehicles. Engineered EVs are being explored as carriers for small molecules, RNA therapeutics and metabolic inhibitors, taking advantage of their inherent biocompatibility, stability in circulation and tumour-targeting capabilities. This approach may enable selective delivery of radiosensitising agents to metabolically active tumour subclones. For instance, EVs loaded with the glycolysis inhibitor FX-11, which targets LDH, were shown to significantly inhibit cellular energy metabolism in breast cancer cells and enhance the anti-tumour effects of sonodynamic therapy [201]. Another study found that aptamer-engineered EVs delivering SIRT6-targeting siRNA achieved selective PCa cell targeting and resulted in the inhibition of proliferation and metastasis [202]. Similarly, EVs derived from PCa cells have been used to deliver paclitaxel, achieving efficient intracellular uptake via the endocytic pathway and increased cytotoxicity [203]. In the RT context, this platform could enable the targeted delivery of radiosensitising metabolic inhibitors to the precise tumour subpopulations, such as hypoxic clusters or androgen-independent variants where metabolic radioresistance is most pronounced, while minimising systemic toxicity.

Despite this therapeutic promise, several challenges must be addressed before EV-based strategies can be implemented clinically. The foremost is EV heterogeneity: secreted EVs comprise diverse subpopulations (exosomes, microvesicles and apoptotic bodies) that differ in biogenesis, cargo and function, and preparations are frequently contaminated by co-isolated non-vesicular particles and protein aggregates, which confounds both mechanistic interpretation and reproducible therapeutic formulation. A second challenge is the lack of standardisation: different isolation methods (ultracentrifugation, size-exclusion chromatography, precipitation and immunoaffinity capture) yield EV populations of differing purity and composition, while pre-analytical variables: sample type, collection and anticoagulation protocol, platelet contamination and storage conditions, strongly influence the results [22]. For therapeutic deployment specifically, additional challenges include scalable, reproducible and Good Manufacturing Practices-compliant EV production, efficient and consistent cargo loading, control of biodistribution and off-target uptake, potential immunogenicity, and the absence of standardised potency and quality-control assays. These challenges may be mitigated by adopting harmonised reporting and methodological standards (MISEV2023 [192], reported via EV-TRACK [193]), orthogonal isolation strategies and reference materials, single-EV characterisation to resolve functionally relevant subpopulations and engineering approaches that improve EV targeting and cargo stability, followed by validation in well-controlled preclinical models and, ultimately, prospective multicentre clinical studies within clear regulatory frameworks. Addressing these issues in parallel with the biomarker-development priorities outlined in Section 4.2 will be essential to realise the clinical potential of EV-based approaches in PCa.

Table 2. Overview of EV metabolomic studies with clinical relevance. Abbreviations: BPH, benign prostatic hyperplasia; DNA, deoxyribonucleic acid; dTTP, deoxythymidine triphosphate; EV, extracellular vesicle; MUFA, monounsaturated fatty acid; PCa, prostate cancer; PPP, pentose phosphate pathway; PUFA, polyunsaturated fatty acid; RT, radiotherapy; SFA, saturated fatty acid; TCA, tricarboxylic acid; TME, tumour microenvironment.

Clinical Application	Sample Source	Cancer Type / Model	EV Metabolic Cargo	Key Findings	Clinical Relevance	Evidence Type	References
Diagnosis	Urine	Prostate cancer (patients)	Lipid panel (9 species)	Distinguishes prostate cancer vs healthy controls (93% sensitivity, 100% specificity)	Non-invasive diagnostic biomarker	Clinical	[185]
Diagnosis	Urine	Prostate cancer vs BPH	Phosphatidylcholines, acyl carnitines, citrate, kynurenine	Distinct metabolic signatures between PCa and BPH	Differential diagnosis	Clinical	[186]
Diagnosis (androgen metabolism)	Urine	Prostate cancer vs BPH	3β-hydroxyandrost-5-en-17-one-3-sulphate	Elevated in PCa-derived EVs	Reflects androgen biosynthesis activity	Clinical	[186]
Metabolic pathway inference	Urine	Prostate cancer (pre- vs post-prostatectomy)	Glucuronate	Reduced in PCa EVs; not detectable in whole urine	Indicates PPP activation; EV-specific sensitivity	Clinical	[188]
Tumour aggressiveness	Cell culture EVs	PC-3 vs LNCaP	n-9 oleic acid, MUFAs, reduced SFAs/PUFAs	Altered lipid composition linked to metastatic potential	Biomarker for tumour aggressiveness	In vitro	[134–140]
Tumour–stroma metabolic crosstalk	TME-derived EVs	Prostate cancer	Lipids, TCA intermediates	Stromal EVs support tumour growth under nutrient stress	Therapeutic target potential	In vitro	[67,189]
RT response biomarker (metabolites ↓)	Circulating EVs	Small-cell lung cancer	Nucleotide metabolites (xanthylic acid, dTTP), folate metabolites	Decreased post-RT	Indicator of impaired DNA synthesis	<i>In vitro</i> /preclinical	[190]
RT response biomarker (metabolites ↑)	Circulating EVs	Rectal cancer (patients)	Glucose	Elevated in poor responders	Associated with glycolysis-driven radioresistance	Clinical	[86,87,100]
Negative / inconsistent findings	Circulating EVs	Head and neck cancer	Global metabolome	No significant changes post-RT	Highlights variability and limitations	Clinical	[191]

5. Conclusion and Future Perspectives

In summary, this review highlights an emerging but underexplored interface between RT, EV biology and metabolic adaptation in PCa. The current literature supports that EVs are increasingly recognised as adaptive signalling and potentially informative readouts of treatment-induced metabolic change, by redistributing metabolic signals, stress-associated cargo and adaptive phenotypes across spatially and functionally heterogeneous cell populations. However, although metabolic rewiring after RT is well characterised, the specific contribution of EVs to this process in PCa remains poorly defined, and much of the current mechanistic narrative relies on associative or extrapolative evidence.

The translational advantage of EV metabolomics lies in its potential to capture tumour adaptation as a dynamic and evolving process rather than a static endpoint. This is especially valuable in a disease like PCa marked by ongoing shifts in AR dependence, lineage state and metabolic phenotype under treatment pressure. Yet this promise must be balanced against substantial technical and biological challenges. Variability in EV isolation, metabolite extraction and analytical workflows continues to limit reproducibility, while the intrinsic heterogeneity and temporal plasticity of PCa complicate the interpretation of EV-associated metabolic signals. Depending on the RT modality (external beam or brachytherapy), longitudinal studies with serial sampling will be preferable to define the temporal relationship between EV-associated metabolic changes and the emergence of resistant disease states. Functional studies will be equally important to determine the role of EV cargo as a driver of phenotypic plasticity, an amplifier of pre-existing heterogeneity, or a biomarker of evolving tumour state (**Figure 2**).

Whether EV metabolomics ultimately proves most valuable as a mechanistic framework, a biomarker platform, or a guide to targeted therapeutic strategies will depend on whether future work can define this interface with sufficient biological clarity and analytical standardisation to support meaningful clinical translation.

Abbreviations

The following abbreviations are used in this manuscript:

5-FU:	5-fluorouracil
ACC:	acetyl-CoA carboxylase
ADT:	androgen deprivation therapy
ALDOA:	aldolase A
AMPK:	AMP-activated protein kinase
AR:	androgen receptor
ASS1:	argininosuccinate synthase 1
BPH:	benign prostatic hyperplasia
CAF:	cancer-associated fibroblast
CAT:	cationic amino acid transporter
CRPC:	castration-resistant prostate cancer
CSC:	cancer stem cell
DSB:	double-strand break
EMT:	epithelial–mesenchymal transition

Enz:	enzalutamide
ESCRT:	endosomal sorting complex required for transport
EV:	extracellular vesicle
FA:	fatty acid
FASN:	fatty acid synthase
FTase:	farnesyltransferase
G6P:	glucose-6-phosphate
G6PD:	glucose-6-phosphate dehydrogenase
GLS:	glutaminase
HIF1:	hypoxia-inducible factor 1
IL-8:	interleukin 8
LDHA:	lactate dehydrogenase A
LOX:	lipoxygenase
M-aconitase:	mitochondrial aconitase
MA:	manumycin A
mPCa:	metastatic prostate cancer
MS:	mass spectrometry
mTOR:	mechanistic target of rapamycin
NEPC:	neuroendocrine prostate cancer
NPC:	nasopharyngeal carcinoma
OXPHOS:	oxidative phosphorylation
PAD:	peptidylarginine deiminase
PCa:	prostate cancer
PPP:	pentose phosphate pathway
PSA:	prostate-specific antigen
RIBE:	radiation-induced bystander effect
ROS:	reactive oxygen species
RT:	radiotherapy
SCD:	stearoyl-CoA desaturase
siRNA:	small interfering RNA
SIRT6:	sirtuin 6
TAM:	tumour-associated macrophage
TCA cycle:	tricarboxylic acid cycle
TME:	tumour microenvironment
TNM:	tumour-node-metastasis classification
YAP:	Yes-associated protein

Declarations

Ethics Statement

Not applicable.

Consent for publication

Not applicable.

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Competing Interests

The authors declare no conflicts of interest.

Author Contributions

K.N. and Q.W. conceived the structure of the manuscript. K.Y. and Q.W. wrote the manuscript and drew the figures. K.N. provided guidance throughout the preparation of this manuscript. R.G., J.B. and K.N. reviewed and revised the manuscript.

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