



Deposited via The University of Sheffield.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/233302/>

Version: Published Version

Article:

Rainero, E. (2024) Macropinocytosis at the crossroad between nutrient scavenging and metabolism in cancer. *Current Opinion in Cell Biology*, 88. 102359. ISSN: 0955-0674

<https://doi.org/10.1016/j.ceb.2024.102359>

Reuse

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here:

<https://creativecommons.org/licenses/>

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



Macropinocytosis at the crossroad between nutrient scavenging and metabolism in cancer

Elena Rainero

Abstract

Macropinocytosis (MP), the actin-dependent bulk uptake of extracellular fluids, plays a central role in nutrient scavenging, allowing cancer cells to sustain their growth in the hypoxic and nutrient-deprived microenvironment often found in solid tumours. The lack of soluble nutrients and several oncogenic signalling pathways, with RAS being the most studied, push MP-dependent internalisation of extracellular proteins, which are then digested in the lysosomes, replenishing the intracellular nutrient pools. This review will highlight recent advances in understanding how MP is regulated in hypoxic cancers, how it impinges on chemoresistance, and how different MP cargos facilitate tumour growth. Finally, I will highlight the crosstalk between MP and extracellular matrix receptors.

Addresses

School of Biosciences, University of Sheffield, Sheffield, S10 2TN, UK

Corresponding author: Rainero, Elena (e.rainero@sheffield.ac.uk)

Current Opinion in Cell Biology 2024, 88:102359

This review comes from a themed issue on **Membrane Trafficking 2024**

Edited by **Min Wu** and **Patrick Caswell**

For complete overview of the section, please refer the article collection - [Membrane Trafficking 2024](#)

Available online 15 April 2024

<https://doi.org/10.1016/j.ccb.2024.102359>

0955-0674/© 2024 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Abbreviations

MP, macropinocytosis; TME, tumour microenvironment; mTOR, mammalian target of Rapamycin; AMPK, AMP-activated protein kinase; ECM, extracellular matrix; PDAC, pancreatic ductal adenocarcinoma; HIF1A, hypoxia-inducible factor 1A; KRAS*, mutant KRAS; SDC1, syndecan 1; NHE1, sodium/proton exchanger 1; HCC, hepatocellular carcinoma; TCA, tricarboxylic acid cycle; ACLY, ATP citrate lyase; DNM2, dynamin 2; ATM, ataxia-telangiectasia; ATR, Ataxia telangiectasia and Rad3-related protein; MMP, matrix metalloproteinase; DDR1, Discoidin Domain Receptor 1; HA, hyaluronic acid; HBP, hexosamine biosynthetic pathway.

Introduction

The movement of cargo within the cells is controlled by membrane trafficking, a complex network of tubular and vesicular compartments [1]. Vesicular trafficking can impinge on cell metabolism through the regulation of

nutrient uptake mechanisms and by controlling nutrient signalling. The plasma membrane levels of nutrient transporters are controlled by the balance between internalisation and recycling, and multiple endocytic pathways have been involved in these processes [2]. In recent years, macropinocytosis (MP) has taken the centre stage as a controller of nutrient scavenging under the limited nutrient availability conditions found in the tumour microenvironment (TME) [3]. MP is defined as the bulk uptake of extracellular fluids, and it is mediated by the extension of actin-rich protrusions, eventually forming a vesicle called the macropinosome. These vesicles are transported through the endosomal system and eventually fuse with lysosomes, allowing for their content to be degraded by lysosomal proteases [4,5]. The complex branched glucan dextran, in its high molecular weight form, has been extensively used as a MP marker, as it is too large to fit into smaller endocytic vesicles [6]. MP has been shown to be controlled by a variety of mechanisms, including oncogenic signalling, nutrient availability, autophagy, and nutrient signalling by mammalian targets of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) pathways [5]. Here I will present recent advances highlighting how MP is regulated in cancer, including under hypoxic conditions, how MP can support drug resistance, and the different cargos that can be internalised through MP. I will conclude by describing the crosstalk between cell/extracellular matrix (ECM) adhesion and MP, raising the intriguing possibility of an ECM-driven MP component.

Macropinocytosis regulation in the tumour microenvironment

Most solid tumours are characterised by a hypoxic TME, which has been associated with drug resistance and a poor prognosis [7]. Aspartate represents an endogenous metabolic limitation under hypoxia. Interestingly, GOT2, a mitochondrial aspartate synthesis enzyme, is required for pancreatic ductal adenocarcinoma (PDAC) cell growth *in vitro*, while *in vivo* this requirement is bypassed by albumin internalisation mediated by MP. Indeed, in PDAC tumour xenografts, there was a marked increase in dextran uptake in hypoxic regions, while *in vitro* hypoxia led to a hypoxia-inducible factor 1A (HIF1A)-dependent increase in dextran uptake in PDAC cells harbouring different KRAS mutations (KRAS*) but not in wild-type (WT) KRAS cells. It would be important to confirm these data in orthotopic

settings, closely recapitulating the PDAC microenvironment, as opposed to xenograft experiments. Mechanistically, the canonical HIF1A target carbonic anhydrase 9 (CA9) promoted MP through a bicarbonate/soluble adenylate cyclase/protein kinase A axis [8], as previously shown [9]. Finally, the loss of CA9 significantly reduced the ability of GOT2 KO cells to grow in hypoxic tumour regions without affecting the proliferation of WT cells. This highlights the importance of MP in maintaining the metabolic fitness of the cells and compensating for the lack of nutrients. Intriguingly, hypoxia induction mediated by CoCl₂ treatment in KRAS^{*G12D} PDAC cells has been shown to promote MP through NRF2-dependent expression of MP-related proteins, including syndecan 1 (SDC1), CDC42, and sodium/proton exchanger 1 (NHE1) [10]. This indicates that, at least in PDAC, hypoxia can elicit the activation of MP through different signalling pathways (Figure 1a).

A similar correlation between hypoxia and dextran uptake was observed in hepatocellular carcinoma (HCC), both in *in vivo* orthotopic xenografts and *in vitro*. Interestingly, MP-dependent albumin uptake supported cell proliferation under low glutamine in hypoxia but not in normoxia. However, MP has been shown to support HCC cell growth under serum starvation in normoxia [11], suggesting a potential crosstalk between nutrient levels, MP, and oxygen levels, which requires further evaluation. Mechanistically, HIF1A directly induced the expression of the dynamin-related ATPase EHD2, required for the maintenance of plasma membrane curvature to induce membrane fission and macropinosome formation (Figure 1a). Several *in vivo* models showed that hypoxia- and EHD2-dependent MP is a general phenomenon in HCC, not linked to a specific oncogenic mutation [12], while in PDAC hypoxia-induced MP is specifically linked to KRAS*. It is therefore likely that different mechanisms are underpinning hypoxia-mediated MP in different cancer types. In PDAC, KRAS*-independent MP has been described [13], but it is possible that hypoxia does not play a role in this context. The deubiquitinase USP21 has been shown to promote KRAS*-independent tumour growth by driving MARK3-dependent MP, which in turn maintains intracellular amino acid levels and activates mTORC1. Interestingly, MARK3 is a regulator of microtubule dynamics, and evidence from this work strongly supports the idea that, in addition to the actin cytoskeleton, microtubule dynamics can foster MP [14]. Consistently, the inhibition of microtubule dynamics by nocodazole treatment opposed ruffle formation and macropinocytosis in macrophages [15], and microtubules were shown to be required for macropinosome formation and inward movement in fibrosarcoma cell lines [16]. Evidence suggests the existence of a crosstalk between hypoxia and microtubules, whereby on the one

hand hypoxia promotes microtubule stabilisation [17], while on the other hand microtubules can regulate HIF1A trafficking and activity [18]. It would therefore be interesting to characterise in more detail the role of microtubules in hypoxia-driven MP.

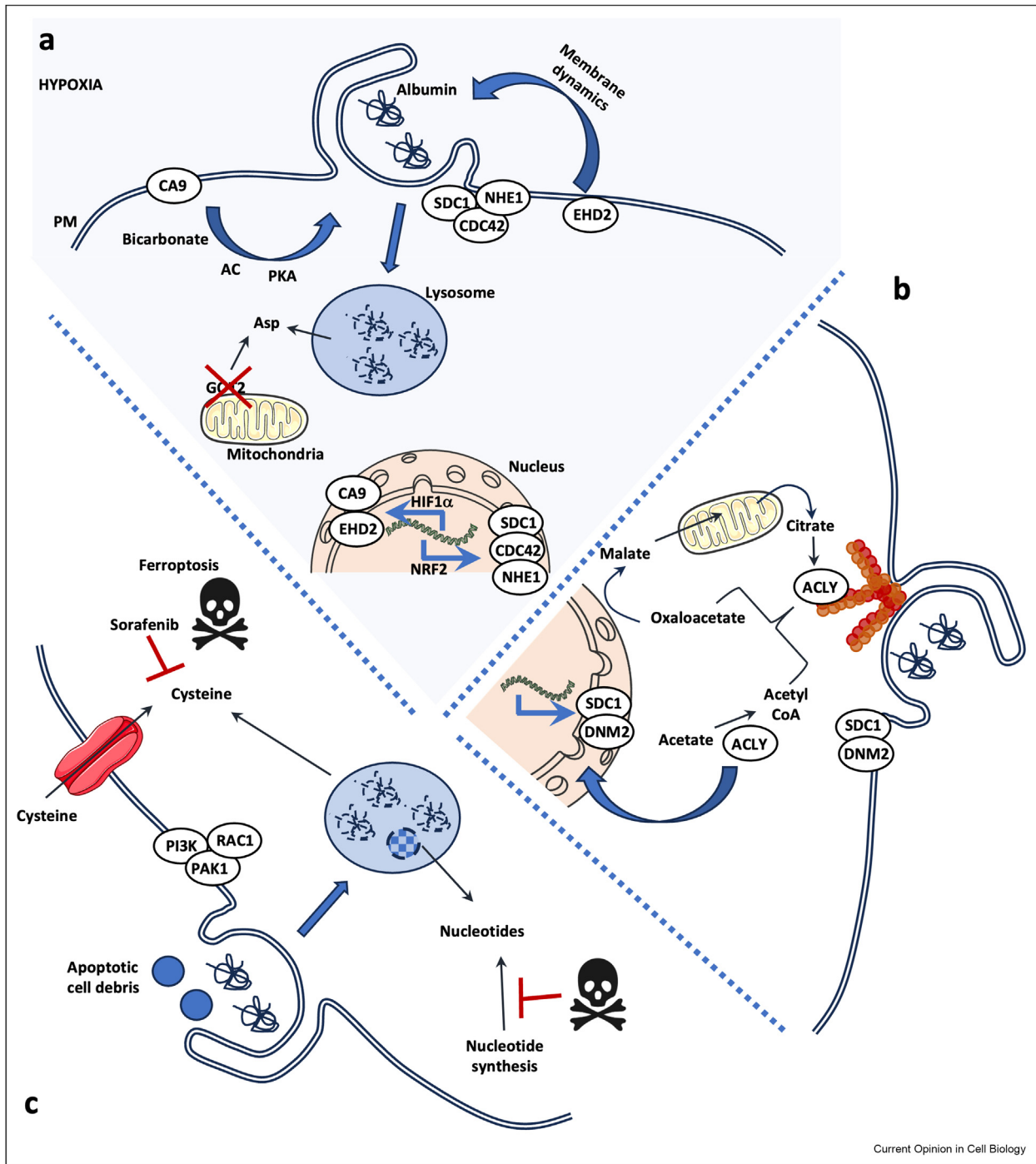
Cellular bioenergetics and extracellular protein-scavenging are interconnected processes. Acetyl coenzyme A (acetyl-CoA) plays a central role in cellular metabolism. Being produced by nutrient catabolism, it fuels the tricarboxylic acid (TCA) cycle, provides building blocks for lipid biosynthesis, and is involved in the acetylation of histones and other proteins. Acetyl-CoA metabolic enzymes are often upregulated in cancer [19]. Interestingly, the acetyl-CoA-producing enzyme adenosine triphosphate (ATP) citrate lyase (ACLY) is associated with the actin cytoskeleton, coupling citrate exported from mitochondria located in close proximity to membrane ruffles with actin polymerisation, resulting in macropinosome formation (Figure 1b). Indeed, the blockade of citrate mitochondria export, ACLY KO, or its pharmacological inhibition, prevented dextran uptake in a panel of RAS* cell lines [20]. Similarly, the acetyl-CoA enzyme short chain family member 2 (ACSS2) was upregulated by metabolic stress, promoting the expression of SDC1 and dynamin 2 (DNM2), which in turn stimulated MP in KRAS^{*G12D} or G12V PDAC cells (Figure 1b). Noteworthy, ACSS2 KO suppressed tumour growth in an orthotopic xenograft mouse model [21].

MP has been shown to be associated with resistance to therapy. In HCC, sorafenib treatment induces cell death through ferroptosis, via cysteine depletion. In sorafenib-resistant cells, the stimulation of MP-dependent protein scavenging replenished cysteine levels, preventing ferroptosis (Figure 1c). *In vivo*, the inhibition of MP by amiloride treatment enhanced sorafenib anti-tumour effects [22]. Consistently, in fibrosarcoma, lung, and PDAC cells, MP-dependent albumin uptake prevented ferroptosis [23]. This was observed in both KRAS* and WT cells, and it is possible that other mechanisms, in addition to MP, contributed to albumin internalisation. Similarly, in breast cancer cells, MP-dependent uptake of necrotic cell debris has been shown to support resistance to drugs targeting nucleotide biosynthesis by replenishing the cellular nucleotide pool (Figure 1c) [24]. In PDAC cells, protein scavenging by MP, followed by lysosomal degradation, mediated mTOR inhibitor resistance in PTEN null cells. Interestingly, in this context, MP was predominantly driven by mTORC2 [25]. Together, this indicates that inhibition of MP could represent a strategy to overcome therapy resistance in different contexts.

Macropinocytosis cargos in the tumour microenvironment

MP as a nutrient-scavenging mechanism has been implicated in the uptake of a variety of cargos.

Figure 1

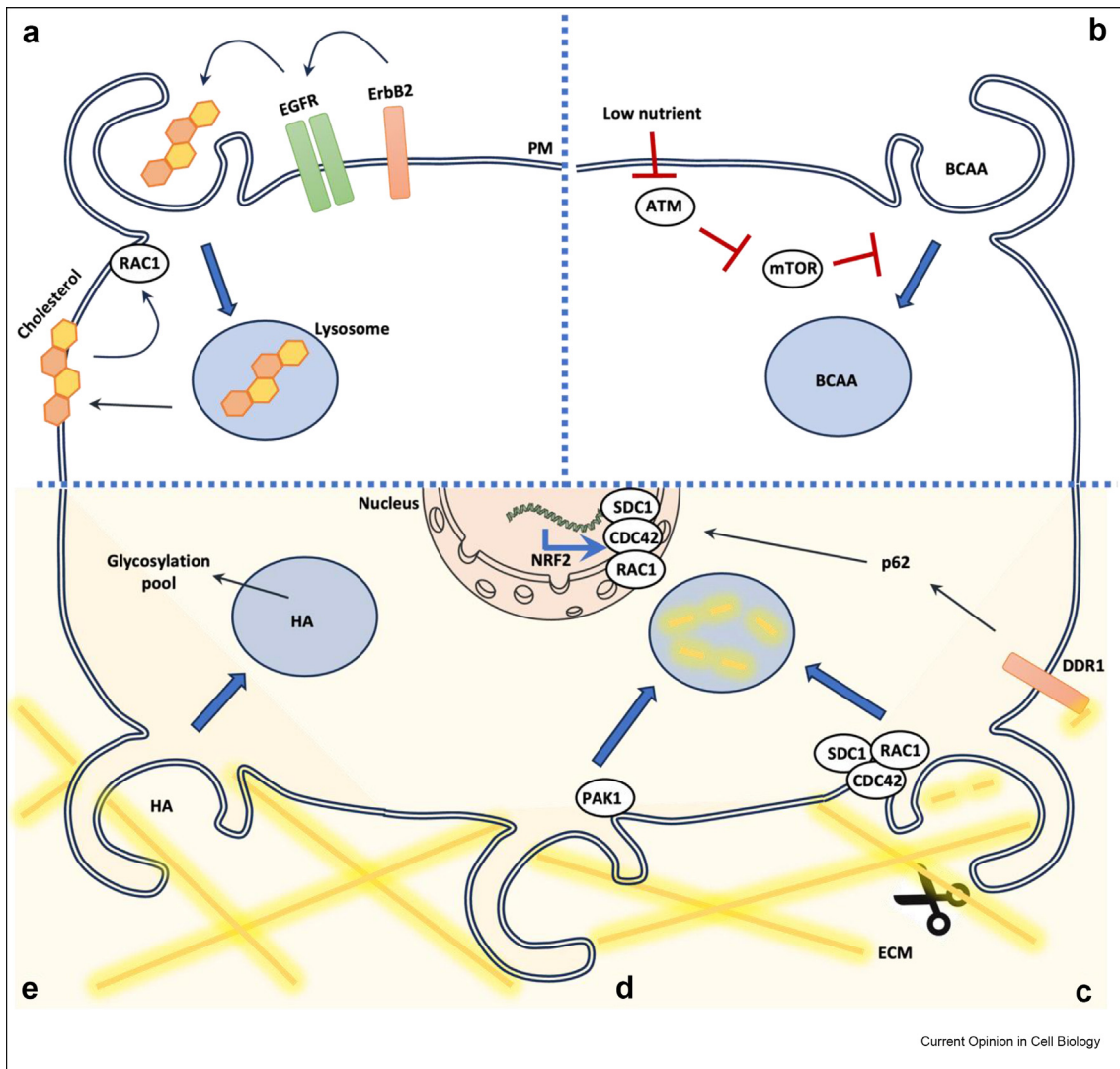


MP regulators in the TME. (a) Hypoxia promotes MP via different mechanisms. Blockade of the aspartate (Asp) synthesis enzyme GOT2 depletes cellular Asp pools in KRAS⁺ PDAC cells. HIF1A-dependent expression of carbonic anhydrase 9 (CA9) promotes albumin MP via bicarbonate, adenylate cyclase (AC) and protein kinase A (PKA). Albumin lysosomal degradation restores Asp levels. NRF2-dependent expression of syndecan 1 (SDC1), CDC42 and NHE1 also promote MP in KRAS⁺ PDAC cells. In hepatocellular carcinoma (HCC), HIF1A-dependent EHD2 expression promotes MP. (b) The acetyl-CoA producing enzyme ATP citrate lyase (ACLY) promotes MP by controlling actin polymerisation at membrane ruffles. ACS2, another acetyl-CoA generating enzyme, drives MP by promoting the expression of SDC1 and dynamin 2 (DNM2). (c) MP confers resistance to sorafenib-induced ferroptosis and cell death by nucleotide synthesis inhibitors by providing a source of cysteine (via a phosphatidylinositol 3 kinase (PI3K)/RAC1/PAK1 signalling pathway) and nucleotides, respectively.

Extracellular protein scavenging is a well-known regulator of cancer cell growth, and it is well established that extracellular proteins are targeted to lysosomes for

degradation [26]. It is therefore not surprising that, when cells rely on extracellular protein sources, lysosomal cathepsins, as well as lysosomal enzyme

Figure 2



MP cargos. (a) ErbB2/EGFR signalling drives cholesterol MP. Cholesterol at the plasma membrane (PM) can activate RAC1, with a potential feedback loop driving further MP. (b) ATM inhibition promotes branched chain amino acids (BCAA) MP in ovarian cancer cells. (c) DDR1 binding to collagen I fragments promotes collagen I MP, by stimulating p62-dependent expression of the NRF2 targets SDC1, CDC42 and RAC1. (d) In breast cancer cells, PAK1 drives ECM component MP. (e) Hyaluronic acid (HA) uptake via MP maintains the glycosylation pool in PDAC cells.

trafficking factor (LYSET), an enzyme mediating lysosomal enzyme targeting, are required for scavenging-dependent cell growth [27,28].

In addition to the role of MP in extracellular proteins/albumin internalisation, other MP cargos have been identified. In ovarian and breast cancer cells, cholesterol uptake is required for cell invasion [29]. A constitutively active and therapy-resistant form of ErbB2 (p95ErbB2) was shown to increase MP-dependent cholesterol uptake and promote cell invasion (Figure 2a) [30]. Interestingly, in HCC cells, the accumulation of cholesterol at the plasma membrane was shown to promote RAC1 activation and MP, supporting ATP production and cell

proliferation under conditions in which cell growth is dependent on extracellular protein uptake [11]. These observations might suggest the existence of a positive feedback loop whereby MP-driven cholesterol uptake further activates MP to promote nutrient scavenging.

In ovarian cancer cells, the inhibition of ataxia-telangiectasia (ATM), but not ataxia-telangiectasia and Rad3-related protein (ATR), promoted the MP-dependent uptake of branched-chain amino acids (BCAA), potentially through a mechanism driven by the inhibition of mTOR (Figure 2b). It is quite well established that the blockade of mTORC1 promotes MP and growth in cells relying on extracellular protein scavenging

[31]. Interestingly, ATM-inhibited tumours were found to be associated with a reduction in BCAA levels in ascites and interstitial fluids, while the combined inhibition of ATM and MP impaired proliferation and induced cell death both *in vitro* and *in vivo* [32]. In glioblastoma, ATR has been shown to promote dextran uptake by MP and the retrograde transport of macropinosomes along the neurites, indicating that ATR likely regulates MP in a context-dependent manner. Interestingly, several integrin isoforms, including $\alpha 3$, $\alpha 6$, and $\alpha 5$, are internalised through MP and are required for neurite detachment and cell migration [33], supporting the idea that integrins can be selectively recruited in macropinocytic cups, as previously shown [34]. It is therefore tempting to speculate that the presence of integrins in cups could define a subtype of MP, which could impinge on the regulation of MP-dependent ECM uptake and invasive cell growth. Indeed, ECM receptors have been implicated in the control of MP and nutrient scavenging [35,36].

The internalisation of collagen I fragments generated by matrix metalloproteinase (MMP) activity supported PDAC cell growth *in vitro* and *in vivo*. This process was dependent on the collagen receptor discoidin domain receptor 1 (DDR1), which resulted in the activation of the NF κ B/p62/NRF2 cascade, eventually leading to the upregulation of MP-related genes, including SDC1, RAC/CDC42, and NHE1 (Figure 2c) [37], as previously described [10]. It is not clear whether DDR1 is internalised together with the cleaved collagen I fragments or whether the binding of collagen to DDR1 at the plasma membrane drives the downstream signalling pathway, resulting in the engulfment of soluble collagen I fragments.

SDC1 has been shown to be upregulated at the plasma membrane in KRAS^{G12D} mouse PDAC cells. Mechanistically, KRAS^{*} promotes ARF6-dependent recycling of SDC1 back to the plasma membrane, which in turn promotes RAC activation and MP, supporting albumin-dependent cell growth under glutamine starvation conditions [38]. Consistently, the KO of another member of the SDC family, SDC4, resulted in a 50% reduction in MP in PDAC and colon adenocarcinoma cells and led to a significant inhibition of xenograft tumour growth *in vivo* [39]. Interestingly, SDC4 was also identified among the proteins upregulated at the plasma membrane upon KRAS^{G12D} induction in mouse PDAC cells [38]. Both SDC1 and SDC4 are co-receptors for ECM components and have been shown to interact with integrins and growth factor receptors. While SDC1 mostly signals through the activation of Mitogen-activated protein kinase (MAPK) and PI3K/AKT signalling [38], SDC4 mainly results in the activation of protein kinase C alpha [40]. Since SDC4 binding to the ECM leads to RAC activation [41], it is possible that SDC4-dependent MP is also mediated by RAC activation, as in the case of SDC1. Therefore, it would be interesting

to elucidate whether SDC/ECM interaction plays any role in MP activation.

Our group recently demonstrated that in breast cancer cells grown under amino acid starvation, MP-dependent internalisation of ECM components supported cell proliferation (Figure 2d). Interestingly, ECM lysosomal degradation resulted in an increase in intracellular amino acid content, in particular tyrosine and phenylalanine. We found that phenylalanine catabolism was required for ECM-dependent cell growth and migration in both 2D and 3D culture systems. Interestingly, ECM internalisation was strongly associated with invasive cancer cells, and ECM-dependent cell growth under starvation was a specific feature of invasive and metastatic breast cancer cells [42]. To note, we found that in breast cancer cells, ECM internalisation and ECM-dependent cell growth were independent of MMP activity. Similarly, in lung cancer cells, MP-dependent collagen I uptake was not affected by MMP inhibition [43], suggesting that collagen I and ECM cleavage requirements could be context-dependent.

Consistent with the idea that ECM components can be alternative nutrient sources, hyaluronic acid (HA) has been shown to be a source of sugar in PDAC (Figure 2e) by fuelling the hexosamine biosynthetic pathway (HBP). HBP is crucial to control cell structure, signalling, and survival through the modulation of glycosylation [44]. Interestingly, while HBP is required for cell growth *in vitro*, it is bypassed *in vivo*, where MP-dependent internalisation and subsequent metabolism of low molecular weight HA restored the glycosylation pool [45]. The details of the molecular mechanisms contributing to HA macropinocytosis await elucidation, but this seems to be conserved across multiple cancer types, as it has also been observed in melanoma [46].

Interestingly, ECM internalisation is not an exclusive feature of cancer cells, and it has been described in different cell types. For instance, the removal of excessive collagen I by macrophages is important for inflammation resolution, wound healing, and embryonic development [47]. Although the molecular mechanisms behind this uptake are not entirely clear, it has been suggested that glucose metabolism [47] and the vATPase subunit B2 [48] are required for this. It would be interesting to extend these studies in the context of macrophages within the TME to elucidate whether ECM internalisation contributes to macrophage differentiation and metabolism and, if so, how this might contribute to cancer progression.

Conclusions

MP plays a key role in supporting tumour cell growth by sustaining nutrient scavenging. This is particularly

important in the context of a harsh TME, such as in hypoxic regions or in response to anti-cancer treatments. In addition to albumin, several MP cargos have been described, including amino acids, lipids, and ECM components. Importantly, different ECM receptors were shown to either be endocytosed through MP or be involved in MP regulation, raising the intriguing hypothesis of a receptor-dependent MP subtype, whereby ECM receptors are concentrated in macropinocytic cups and drive MP-dependent nutrient scavenging. It would therefore be interesting to elucidate how cell/ECM interactions and/or ECM uptake impinge on the scavenging of other MP cargos. Finally, MP is not limited to cancer cells, and it will be important to determine the impact of MP on shaping the tumour-promoting functions of other TME components, such as macrophages.

Credit author statement

ER conceptualised, wrote the review and prepared the illustrations.

Funding

ER is funded by Cancer Research UK (C52879/A29144).

Declaration of competing interest

The author declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest

** of outstanding interest

- Banushi B, *et al.*: **Endocytosis in cancer and cancer therapy.** *Nat Rev Cancer* 2023, **23**:450–473.
 - Gilleron J, Zeigerer A: **Endosomal trafficking in metabolic homeostasis and diseases.** *Nat Rev Endocrinol* 2023, **19**: 28–45.
 - Lyssiotis CA, Kimmelman AC: **Metabolic interactions in the tumor microenvironment.** *Trends Cell Biol* 2017, **27**:863–875.
 - Salloum G, Bresnick AR, Backer JM: **Macropinocytosis: mechanisms and regulation.** *Biochem J* 2023, **480**:335–362.
 - Puccini J, Badgley MA, Bar-Sagi D: **Exploiting cancer's drinking problem: regulation and therapeutic potential of macropinocytosis.** *Trends Cancer* 2022, **8**:54–64.
 - Le AH, Machesky LM: **Image-based quantification of macropinocytosis using dextran uptake into cultured cells.** *Bio Protoc* 2022, **12**:e4367.
 - Chen Z, *et al.*: **Hypoxic microenvironment in cancer: molecular mechanisms and therapeutic interventions.** *Signal Transduct Targeted Ther* 2023, **8**:70.
 - Garcia-Bermudez J, *et al.*: **Adaptive stimulation of macropinocytosis overcomes aspartate limitation in cancer cells under hypoxia.** *Nat Metab* 2022, **4**:724–738.
 - Ramirez C, *et al.*: **Plasma membrane V-ATPase controls oncogenic RAS-induced macropinocytosis.** *Nature* 2019, **576**: 477–481.
 - Su H, *et al.*: **Cancer cells escape autophagy inhibition via NRF2-induced macropinocytosis.** *Cancer Cell* 2021, **39**: 678–693.e11.
 - Wang X, *et al.*: **The phospholipid flippase ATP9A enhances macropinocytosis to promote nutrient starvation tolerance in hepatocellular carcinoma.** *J Pathol* 2023, **260**: 17–31.
 - Zhang MS, *et al.*: **Hypoxia-induced macropinocytosis represents a metabolic route for liver cancer.** *Nat Commun* 2022, **13**:954.
 - Hobbs GA, Der CJ: **Kras.** *Subcell Biochem* 2022, **98**:205–221.
 - Hou P, *et al.*: **USP21 deubiquitinase elevates macropinocytosis to enable oncogenic KRAS bypass in pancreatic cancer.** *Genes Dev* 2021, **35**:1327–1332.
 - Mylvaganam S, Freeman SA, Grinstein S: **The cytoskeleton in phagocytosis and macropinocytosis.** *Curr Biol* 2021, **31**: R619–R632.
 - Williamson CD, Donaldson JG: **Arf6, JIP3, and dynein shape and mediate macropinocytosis.** *Mol Biol Cell* 2019, **30**: 1477–1489.
 - Peng WX, *et al.*: **Hypoxia stabilizes microtubule networks and decreases tumor cell chemosensitivity to anticancer drugs through Egr-1.** *Anat Rec* 2010, **293**:414–420.
 - Carbonaro M, *et al.*: **Microtubules regulate hypoxia-inducible factor-1 α protein trafficking and activity: implications for taxane therapy.** *J Biol Chem* 2012, **287**:11859–11869.
 - Guertin DA, Wellen KE: **Acetyl-CoA metabolism in cancer.** *Nat Rev Cancer* 2023, **23**:156–172.
 - Puccini J, *et al.*: **Cytoskeletal association of ATP citrate lyase controls the mechanodynamics of macropinocytosis.** *Proc Natl Acad Sci U S A* 2023, **120**, e2213272120.
- This work links acetyl-CoA metabolism, mitochondrial localisation at the cell periphery, and actin cytoskeleton dynamics, elucidating a novel molecular mechanism underpinning the metabolic regulation of MP.
- Zhou Z, *et al.*: **Acetyl-coenzyme A synthetase 2 potentiates macropinocytosis and muscle wasting through metabolic reprogramming in pancreatic cancer.** *Gastroenterology* 2022, **163**:1281–1293.e1.
 - Byun JK, *et al.*: **Macropinocytosis is an alternative pathway of cysteine acquisition and mitigates sorafenib-induced ferroptosis in hepatocellular carcinoma.** *J Exp Clin Cancer Res* 2022, **41**:98.
- This work characterised the role of MP-mediated extracellular protein uptake in driving sorafenib resistance in HCC, providing both *in vitro* and *in vivo* evidence.
- Armenta DA, *et al.*: **Ferroptosis inhibition by lysosome-dependent catabolism of extracellular protein.** *Cell Chem Biol* 2022, **29**:1588–1600.e7.
 - Jayashankar V, Edinger AL: **Macropinocytosis confers resistance to therapies targeting cancer anabolism.** *Nat Commun* 2020, **11**:1121.
 - Michalopoulou E, *et al.*: **Macropinocytosis renders a subset of pancreatic tumor cells resistant to mTOR inhibition.** *Cell Rep* 2020, **30**:2729–2742.e4.
 - Finicle BT, Jayashankar V, Edinger AL: **Nutrient scavenging in cancer.** *Nat Rev Cancer* 2018, **18**:619–633.
 - Nofal M, *et al.*: **GCN2 adapts protein synthesis to scavenging-dependent growth.** *Cell Syst* 2022, **13**:158–172.e9.
 - Pechincha C, *et al.*: **Lysosomal enzyme trafficking factor LYSET enables nutritional usage of extracellular proteins.** *Science* 2022, **378**:eabn5637.

29. Mollinedo F, Gajate C: **Lipid rafts as signaling hubs in cancer cell survival/death and invasion: implications in tumor progression and therapy: thematic Review Series: biology of Lipid Rafts.** *J Lipid Res* 2020, **61**:611–635.
30. Skorda A, *et al.*: **Activation of invasion by oncogenic reprogramming of cholesterol metabolism via increased NPC1 expression and macropinocytosis.** *Oncogene* 2023, **42**: 2495–2506.
31. Kim SH, *et al.*: **Novel regulators of macropinocytosis-dependent growth revealed by informer set library screening in pancreatic cancer cells.** *Metabolites* 2022, **12**.
32. * Huang Z, *et al.*: **ATM inhibition drives metabolic adaptation via induction of macropinocytosis.** *J Cell Biol* 2023, **222**.
- This work demonstrated that the inhibition of ATM promoted MP in ovarian cancer cells, resulting in amino acid uptake and cell growth. The combined inhibition of ATM and MP resulted in suppression of cell proliferation and induction of cell death both *in vitro* and *in vivo*.
33. ** Derby S, *et al.*: **Inhibition of ATR opposes glioblastoma invasion through disruption of cytoskeletal networks and integrin internalisation via macropinocytosis.** *Neuro Oncol* 2024 Apr 5, **26**:625–639.
- This work demonstrated the role of MP of ECM receptors of the integrin family in promoting cancer cell invasion.
34. Le AH, *et al.*: **CYRI-A limits invasive migration through macropinosome formation and integrin uptake regulation.** *J Cell Biol* 2021, **220**.
35. Llanses Martinez M, *et al.*: **Internalisation of integrin-bound extracellular matrix modulates invasive carcinoma cell migration.** bioRxiv; 2024.
36. Olivares O, *et al.*: **Collagen-derived proline promotes pancreatic ductal adenocarcinoma cell survival under nutrient limited conditions.** *Nat Commun* 2017, **8**, 16031.
37. Su H, *et al.*: **Collagenolysis-dependent DDR1 signalling dictates pancreatic cancer outcome.** *Nature* 2022, **610**:366–372.
38. Yao W, *et al.*: **Syndecan 1 is a critical mediator of macropinocytosis in pancreatic cancer.** *Nature* 2019, **568**:410–414.
39. Cui C, *et al.*: **Eltrombopag binds SDC4 directly and enhances MAPK signaling and macropinocytosis in cancer cells.** *Am J Cancer Res* 2022, **12**:2697–2710.
40. Onyeisi JOS, Lopes CC, Götte M: **Syndecan-4 as a pathogenesis factor and therapeutic target in cancer.** *Biomolecules* 2021, **11**.
41. Bass MD, *et al.*: **Syndecan-4-dependent Rac1 regulation determines directional migration in response to the extracellular matrix.** *J Cell Biol* 2007, **177**:527–538.
42. Nazemi M, *et al.*: **The extracellular matrix supports breast cancer cell growth under amino acid starvation by promoting tyrosine catabolism.** *PLoS Biol* 2024, **22**:e3002406.
43. Yamazaki S, *et al.*: **Uptake of collagen type I via macropinocytosis cause mTOR activation and anti-cancer drug resistance.** *Biochem Biophys Res Commun* 2020, **526**: 191–198.
44. Akella NM, Ciraku L, Reginato MJ: **Fueling the fire: emerging role of the hexosamine biosynthetic pathway in cancer.** *BMC Biol* 2019, **17**:52.
45. * Kim PK, *et al.*: **Hyaluronic acid fuels pancreatic cancer cell growth.** *Elife* 2021, **10**.
- This work demonstrated a role for MP-mediated hyaluronic acid uptake in controlling the glycosylation pool in pancreatic cancer cells.
46. Greyner HJ, *et al.*: **Inducible macropinocytosis of hyaluronan in B16-F10 melanoma cells.** *Matrix Biol* 2010, **29**:503–510.
47. Maassen S, *et al.*: **Mitochondrial interaction of fibrosis-protective 5-methoxy tryptophan enhances collagen uptake by macrophages.** *Free Radic Biol Med* 2022, **188**:287–297.
48. Lee JU, *et al.*: **Overexpression of V-ATPase B2 attenuates lung injury/fibrosis by stabilizing lysosomal membrane permeabilization and increasing collagen degradation.** *Exp Mol Med* 2022, **54**:662–672.