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Driving cancer: Motor and adaptor protein dysregulation in endocytic receptor signalling

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Receptor tyrosine kinases and other cell surface receptors are tightly regulated by endocytosis, which controls both the duration and spatial organisation of their downstream signalling. In cancers, altered internalisation and trafficking lead to sustained or misrouted signalling that promotes uncontrolled cell growth and survival. Motor proteins and their cargo adaptors are central to receptor signalling since they determine intracellular endosome positioning, recycling, and degradation. While their roles in intracellular transport have long been studied, the dysfunction of motors and adaptors in the context of aberrant receptor signalling and cancer progression has only recently begun to emerge. In this review, we highlight recent advances in understanding motor and adaptor function in healthy cells, discuss evidence implicating these proteins in oncogenic signalling, and consider how these insights may guide future directions in the field.

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Motor protein expression is dysregulated in cancers and is implicated in uncontrolled cell proliferation and metastasis

Cytoplasmic dynein 1 (dynein henceforth), and several kinesin families (predominantly 1, 2 and 3) are microtubule-based motor proteins that drive long-range transport of cargo towards the cell centre (towards the minus ends of microtubules) and away from the cell centre (towards the plus ends of microtubules), respectively [1,2]. Dynein and other kinesins also play a key role in cell division, by enabling the formation and orientation of the mitotic spindle, and the production of forces required for the separation of the sister chromosomes [3].

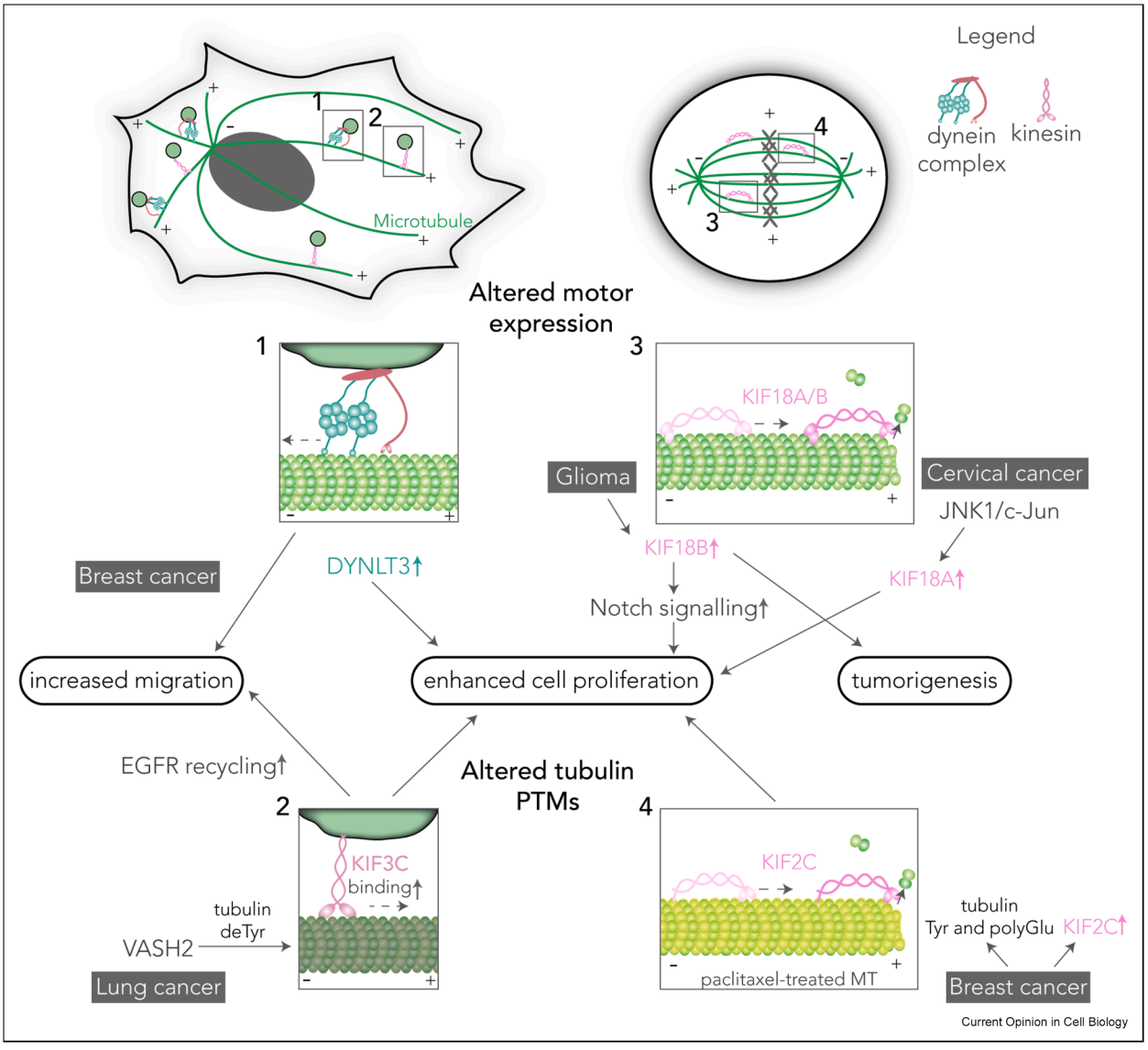
Motor proteins have been found to be overexpressed in several cancers, which in turn are linked to enhanced cell growth and migration. In a recent study, bioinformatic analysis of the Human Protein Atlas revealed that high expression of dynein and its regulator dynactin predicted a low survival rate for breast cancer patients [4]. Migration of MDA-MB-231 cells on biomimetic collagen grids was found to depend on dynein activity, which was inhibited when upregulating kinesin-1 activity [4] (Figure 1). Similarly, dynein subunit light chain 3 (DYNLT3) was found to be upregulated in several breast cancer tissues, and further overexpression of DYNLT3 in breast cancer cell lines resulted in reduced apoptosis, increased migration and induction of epithelial-to-mesenchymal transition (EMT) [5] (Figure 1).

The mitotic kinesin-8 members KIF18A and KIF18B are often overexpressed in multiple cancers. KIF18A was found to be upregulated downstream of the mitogen-activated protein kinase JNK1, and the transcription factor/oncogene c-Jun in HeLa cells [6] (Figure 1). KIF18B was overexpressed in glioma, with reduced expression attenuating proliferation and metastasis by inhibiting the Notch signalling pathway [7]. Hyperactivation of Notch signalling by overexpressed KIF18B ultimately leads to tumorigenesis (Figure 1). However, the mechanisms underlying DYNLT3 and KIF18A overexpression-dependent tumor growth, and KIF18B-dependent Notch activation, remain elusive.

Tubulin decoration with post-translational modifications and microtubule associated proteins dictates motor binding and cargo transport in cancers

Post-translational modifications (PTMs) of microtubules mark subsets of microtubules with differing properties (e.g., stability) and alter the binding and

Figure 1



Altered motor protein expression is a common feature in several cancers, with overexpression of DYNLT3, KIF18A and KIF18B observed in breast cancer, glioma and cervical cancer [1,3]. In lung and breast cancers, altered tubulin PTMs (detyrosination and polyglutamylation respectively) change the motor protein KIF3C's association with microtubules to enhance EGFR recycling [2], or induce chemoresistance to paclitaxel by KIF2C-mediated microtubule depolymerisation [4] and contribute to cancer progression.

movement of motor proteins [8]. The prognostic marker for lung squamous-cell carcinoma, vasohibin-2 (VASH2) was found to promote microtubule detyrosination as a result of its tubulin carboxypeptidase activity, which in turn enhanced the binding of the kinesin-2 member KIF3C [9]. Increased KIF3C binding ameliorated recycling and thus sustained signalling of the epidermal growth factor receptor (EGFR) [9] (Figure 1). In recent work, triple negative breast cancer exhibited increased expression of the mitotic kinesin-13 microtubule depolymerase KIF2C, and the tubulin PTMs tyrosination and polyglutamylation [10]. These cells also exhibited chemoresistance to treatment with paclitaxel, which arrests cell division by stabilising microtubules. Pao et al. demonstrated that KIF2C continued to depolymerise polyglutamylated microtubules, even while paclitaxel was present. This resulted in the resumption of cell division and thus successful mitosis, negating the activity of paclitaxel (Figure 1).

Microtubule-associated proteins (MAPs) not only regulate microtubule dynamics, but also motor dynamics

by competing with motors for microtubule-binding, facilitating or preventing motor protein binding and dissociation [11]. MAP4 is a tau-related MAP whose phosphorylation was found to be enhanced in mouse embryonic fibroblasts lacking the kinase GSK3β [12]. This suggested that MAP4 is the substrate of a different kinase downstream of and inhibited by GSK3β. MAP4 phosphorylation resulted in detachment of MAP4 from microtubules, enhanced interaction of MAP4 with the cargo—dynein complex, and thus clustering of organelles near the minus-end of microtubules [12]. This study highlighted a possible mechanism underlying organelle mislocalisation that is seen in A549 lung carcinoma cells.

Motor adaptors alter receptor signalling in cancers

Motor adaptor proteins provide specificity to the interaction between receptor cargoes and dynein/kinesin motors [13,14]. Motor adaptors typically contain coiled-coil domains which facilitate interaction of the adaptor with the motor, and other protein interaction motifs that facilitate interaction with the receptor or other accessory proteins [15,16]. Many adaptors are also capable of activating the motor, stimulating receptor transport upon binding, and some interact with both dynein and kinesin, stimulating bi-directional transport of receptor cargoes [17]. Here, we focus on the dynein adaptors Hook1, Hook3, RILP and Rab11FIP3 (see Table 1). Recent studies have identified dysregulation of dynein motor adaptor expression in cancers, which impacts growth factor receptor signalling or immune cell cytotoxicity. In each case, the motor adaptor is likely to exert its effects by modulating the trafficking of the related receptors.

Hook1 and Hook3 are activating dynein adaptors that via interaction with their accessory protein FTS, associate with early and late endosomes along the endolysosomal pathway. FTS is predicted to interact directly with the epidermal growth factor receptor (EGFR) based on *in silico* modelling, with FTS expression positively correlated with EGFR expression [23] (Figure 2). This identifies the FTS-EGFR interaction as a potential druggable target for the treatment of cervical cancer to reduce EGFR signalling.

In clear cell renal cell carcinoma, Hook1 deletion was recently found to be predictive of carcinoma progression, and over-expression of Hook1 in cell line models reduced cell migration and proliferation [24]. Reduction in proliferation by Hook1 overexpression was attributed to a decrease in transforming growth factor-β (TGF-β) signalling [24] (Figure 2). While Hook1 can interact with regulators of both receptor recycling and degradation [15], it is likely in this case, that Hook1 regulates delivery of TGF-β to lysosomal pathways to reduce signalling, although this has not been directly investigated.

Hook3 predominantly associates with late endosomal/endolysosomal compartments [18]. Hook3 regulates the endosomal trafficking of activated EGFR which results in its delivery to the lysosome for degradation [25]. Low Hook3 expression has been recently described to be associated with a poor prognosis in patients with gastric cancer, with Hook3 knockdown in cell line models increasing cell proliferation, migration and invasion, and Hook3 over-expression inducing the opposite [26]. These effects of Hook3 were attributed to its regulation of vascular endothelial growth factor-A (VEGF-A) signalling (Figure 2), although how this signalling could be regulated by potential Hook3 lysosomal delivery of VEGF-A to reduce this signalling was not determined.

RILP is a key regulator of growth factor receptor degradation by driving late endosome fusion with lysosomes [20,21]. RILP expression levels correlate with a favourable prognosis in osteosarcoma, with RILP over-expression inhibiting proliferation, migration and invasion in cell models, and RILP knockdown inducing the opposite [27]. RILP was found to directly interact with growth factor receptor-bound protein 10 (GRB10), which in turn negatively regulates the PI3K/AKT/mTOR signalling pathway (Figure 2). It is tempting to speculate that RILP-GRB10 regulates this signalling by directing the degradation of growth factor receptors, although this has not been experimentally demonstrated.

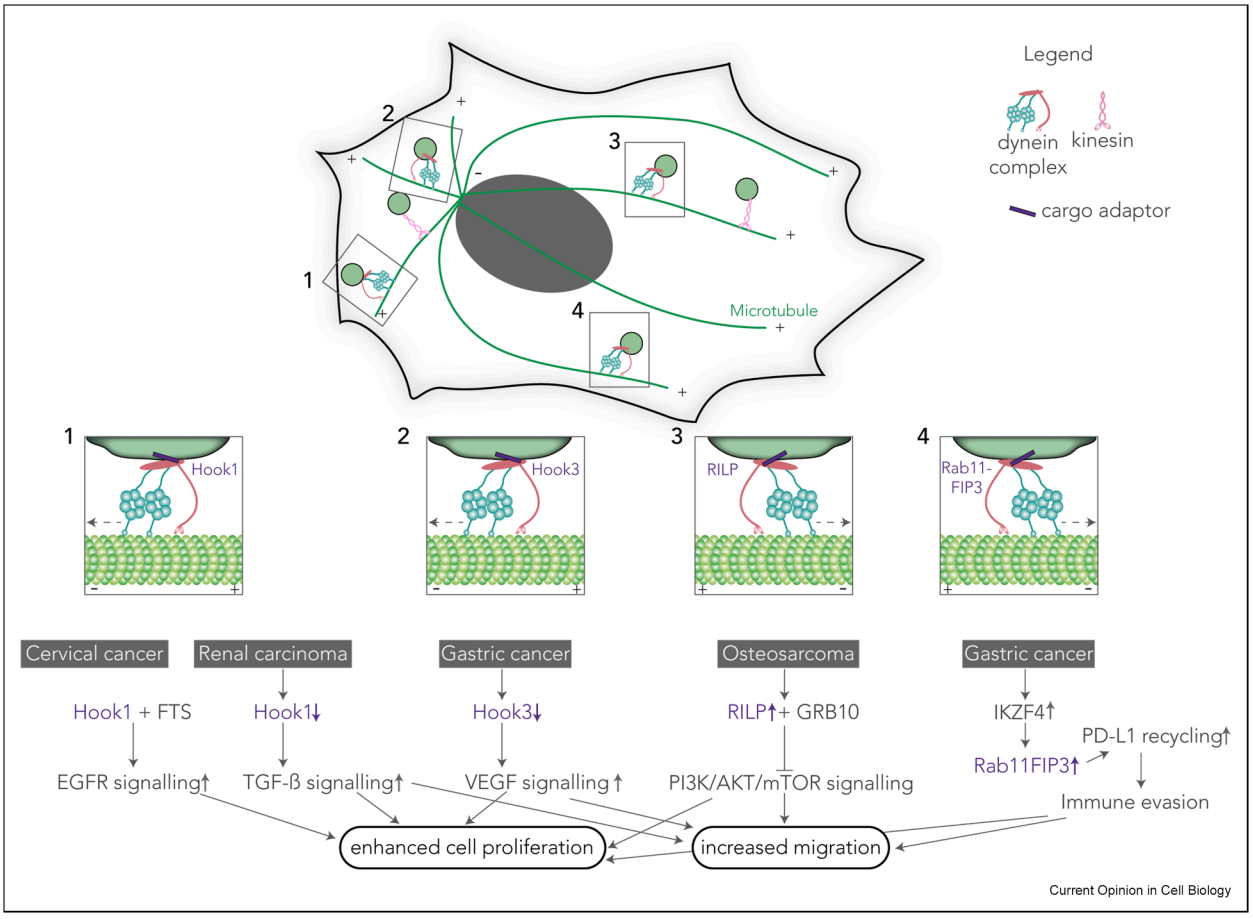
Rab11FIP3 mediates trafficking of receptors and cargoes into recycling endosomal compartments [22]. In gastric cancer, expression of the zinc finger protein IKZF4 is

Table 1

List of known motor adaptors that participate in endosomal transport and receptor signalling.

Adaptor	Motor	Accessory Proteins	Compartments	Reference
Hook1	Dynein	FTS-FHIP2A/1A/1B, Hook3	Early/sorting endosomes.	[15]
Hook3	Dynein, KIF1C	FTS-FHIP1A/1B, Hook1	Early-late endosomes, lysosomes.	[15,18]
RILP	Dynein	VPS41	Late endosomes, lysosomes.	[19–21]
Rab11FIP3	Dynein	Not yet identified.	Rab11 recycling endosomes.	[22]

Figure 2



Altered motor adaptor expression is a common feature across multiple cancer types. Decreased expression of adaptors driving growth factor receptor degradation (Hook1, Hook3) increases receptor signalling to drive cell proliferation and migration [1,2]. Increased expression of degradative adaptors (RILP) inhibits signalling, driving cell proliferation and migration, likely by driving growth factor receptor degradation [3]. Increased expression of a recycling associated adaptor (Rab11FIP3) increases immune related receptor recycling, facilitating immune evasion of cancer cells [4].

associated with poor prognostic outcomes [28]. IKZF14 upregulates expression of Rab11FIP3 in patient gastric cancer biopsies compared to paired tissue, and in cell models, Rab11FIP3 re-routes programmed death-ligand 1 (PD-L1) from lysosomal degradation to Rab11 recycling endosomes. Increased recycling leads to upregulation of PD-L1 at the cell surface and facilitates immune evasion of cancer cells, and knockdown of Rab11FIP3 in cell lines enhances T cell mediated cytotoxicity [28] (Figure 2).

By establishing precisely how motor adaptors interact with and regulate trafficking of growth factor and immunological receptors, these adaptors could represent promising targets for developing novel cancer treatments. Binding of accessory proteins for motor adaptors such as the FHIP proteins, and motor adaptor heterodimerisation, are likely central to conferring specificity of the motor adaptor with its designated cargo (Table 1). Compared to Hook motor adaptors, no accessory proteins have been identified for Rab11FIP3 that may confer specific interaction with receptors such as PD-L1. Identification of these accessory proteins that mediate specific receptor-motor adaptor interactions for each motor adaptor would be advantageous for specific targeting of receptors in the development of cancer treatments.

EGFR provides an example of the importance of understanding receptor transport in cancer

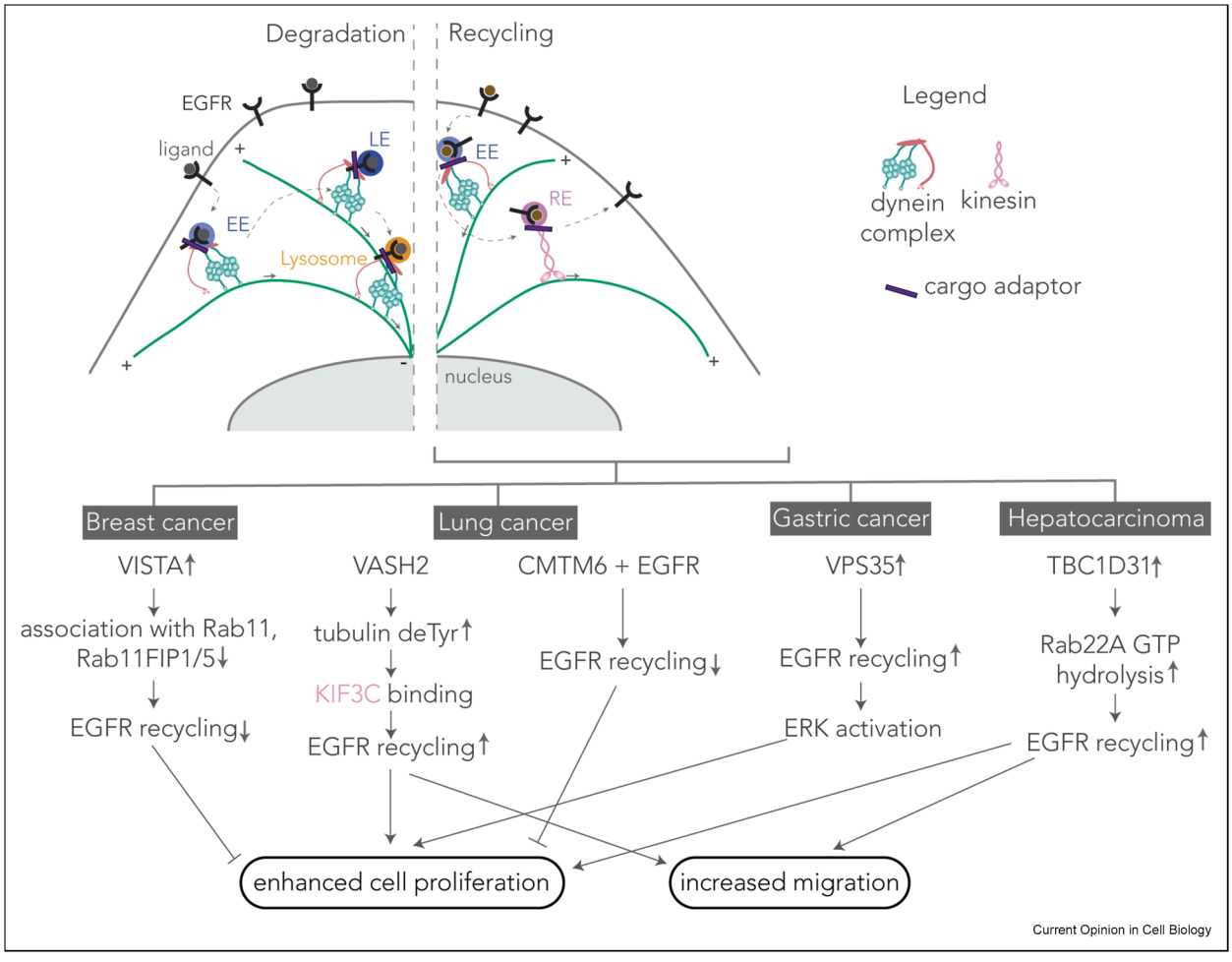
EGFR presents an excellent case study on how targeting receptor signalling by modulating its intracellular transport via motor and motor adaptor interactions could serve as a new route for developing cancer therapeutics. Recent publications have advanced our understanding

of the recycling pathways utilised by EGFR and how this impacts cancer development and treatment.

Rab11 mediated recycling of EGFR is central to aberrant EGFR signalling in many cancer types, and in developing chemoresistance. In some triple negative breast cancers, a subset of cells has recently been identified that have low proliferative potential [29]. These cells express high levels of the VISTA immune checkpoint regulator, which sequesters the endocytic adaptor protein NUMB, which in turn sequesters Rab11 and reduces EGFR recycling and signalling in cell models. VISTA also sequesters Rab11FIP1 and Rab11FIP5 [29] (Figure 3), the latter of which is a putative kinesin adaptor (KIF3A/B) involved in regulating transport of recycling cargoes [30]. As detailed earlier, the protein VASH2 promotes malignant properties in lung squamous-cell carcinoma and contributes to the development of chemoresistance [9]. VASH2 leads to increased Rab11 recycling of EGFR by microtubule detyrosination, enhancing interaction of EGFR with the kinesin KIF3C (Figure 3). Interaction of the chemokine-like transmembrane protein CMTM6 with EGFR increases trafficking of EGFR into Rab11 recycling endosomes in cells, and CMTM6 is associated with aberrant EGFR signalling in receptor tyrosine kinase inhibitor resistant non-small cell lung cancer [31]. By targeting CMTM6 with a nanobody, EGFR trafficking into Rab11 recycling endosomes is reduced, and the growth of receptor tyrosine kinase inhibitor resistant cells is reduced in *in vivo* patient xenograft tumour models (Figure 3).

Beyond Rab11, retromer, retriever, and other undetermined recycling pathways also play a role in EGFR signalling in cancer development. In gastric cancer,

Figure 3



EGFR recycling is dysregulated across many cancer types. Increased recycling of EGFR is mediated by multiple cellular trafficking pathways, and leads to increased signalling that drives cell proliferation and migration in multiple classes of cancer. Conversely, reducing EGFR recycling (e.g., by increased VISTA expression, CMTM6 nanobody treatment) reduces the signalling driving cell proliferation and migration.

vacuolar protein sorting-associated protein 35 (VPS35) expression is correlated with reduced patient survival [32]. VPS35 is a core component of the retromer recycling complex, and in cell models it mediates recycling of EGFR directly from early endosomes, promoting ERK activation and proliferation [32] (Figure 3). In *Drosophila* models of tumour suppressing cell competition, EGFR recycling by the retriever recycling complex leads to increased EGFR activation, which in turn may also lead to increased retriever-dependent recycling of other receptor tyrosine kinases [33]. In hepatocellular carcinoma, expression of the GTPase activating factor TBC1D31 is amplified [34]. In cell models, TBC1D31 increases Rab22A GTP hydrolysis, reducing Rab22A mediated EGFR trafficking to the lysosome and leading to increased EGFR recycling via an undetermined pathway (Figure 3). This leads to ERK and AKT hyperactivation, contributing to receptor kinase tyrosine inhibitor resistance in *in vivo* tumour models [34].

This multitude of recycling pathways utilised by EGFR makes specific therapeutic targeting of EGFR recycling difficult. Interactions between EGFR and dynein [25,35] and EGFR and multiple *bona fide* and putative motor adaptor proteins have already been identified (Hook1, Hook3, BICD2, RUFY1, JIP4, Rab11FIP1, Rab11FIP5, 14-3-3ε) [36–38]. Similarly, the importance of microtubule PTMs and MAPs in enhancing or inhibiting motor association with microtubules and with cargo presents an attractive additional target to manipulate receptor transport [9,10]. EGFR is also subject to PTMs; notably, sialylation redirects the receptor from degradative to recycling pathways [39], thereby sustaining plasma membrane EGFR signalling and promoting an invasive cellular phenotype [40]. This indicates that receptor PTMs may influence interactions with motors or adaptors to regulate receptor trafficking and function. We posit that by working to identify the specific accessory proteins and tubulin and receptor PTMs that regulate these motor adaptor–receptor interactions, EGFR (*or any receptor for which increased signalling facilitated by receptor recycling causes cancer, such as HER2* [41]) could be specifically targeted for degradation by enhancing or disrupting these interactions *irrespective* of the cancer type or cellular context that leads to receptor recycling. Advances in quantitative cellular imaging, integrated with quantitative omics, will be essential to define precisely how trafficking processes regulate receptor signalling in healthy and cancer-derived cells, and how these pathways can be most effectively exploited for therapeutic benefit.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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Data availability

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

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