Golgi Dynamics in Cancer Metastasis

Subjects: Oncology

Contributor: Rakhee Bajaj , Amanda Warner , Jared Fradette , Don L Gibbons

The Golgi apparatus is at the center of protein processing and trafficking in normal cells. Under pathological conditions, such as in cancer, aberrant Golgi dynamics alter the tumor microenvironment and the immune landscape, which enhances the invasive and metastatic potential of cancer cells. Among these changes in the Golgi in cancer include altered Golgi orientation and morphology that contribute to atypical Golgi function in protein trafficking, post-translational modification, and exocytosis. Golgi-associated gene mutations are ubiquitous across most cancers and are responsible for modifying Golgi function to become pro-metastatic. The pharmacological targeting of the Golgi or its associated genes has been difficult in the clinic; thus, studying the Golgi and its role in cancer is critical to developing novel therapeutic agents that limit cancer progression and metastasis.

Golgi secretion cancer secretome Metastasis Therapeutics and biomarkers

1. Golgi-Mediated Vesicular Trafficking and Exocytosis

Vesicular trafficking was described as the “intracellular highway to carcinogenesis” [1]. Proper Golgi-mediated trafficking in cells maintains the steady flow of proteins from the Golgi to other organelles, the cell surface, and the EC space. Cancer cells hijack this process to exocytose proteins that eventually remodel cancer cells and their TME for metastasis [1]. RAB and ARF GTPases, which are frequently mutated in cancers, denote the vesicle and organelle identity and are required for the correct delivery of vesicles to their target organelle. Specifically, the activity of the small GTPases RAB and ARF are regulated by guanine exchange factors (GEFs) and GTPase activating proteins (GAPs) to maintain their GTP-bound active or GDP-bound inactive states, respectively. Both RAB and ARF proteins function through their effectors to regulate various functions, such as cargo budding, vesicle fusion, and exocytosis [2]. Aberrant activity of GTPases or their effectors impairs vesicular trafficking in tumor cells through incorrect localization of vesicles and is associated with altered trafficking kinetics, tumorigenesis, and metastasis [1][3][4].

RAB proteins localize to specific organelles or vesicles and their GTPase activity is required for proper vesicular transport and fusion, while improper activation or expression of RAB proteins can help to promote cancer progression [2]. Localization of RAB40b on VAMP4-positive secretory vesicles mediates the secretion of MMP-2 and MMP-9 from the Golgi to the EC space and was shown to enhance the invasive potential of human breast cancer cells [5]. Additionally, the expression of RAB27b is correlated with lymph node metastasis in ER+ breast cancer patients as it promotes the secretion of HSP90α, where HSP90α acts as a chaperone that prompts MMP-2 cleavage and activation [6]. This suggests that the secretion of chaperone proteins by cancer cells could also enhance metastasis through stabilization and activation of ECM-degrading proteins. Moreover, RAB-GTPases also

interact with cytoskeletal proteins, such as the motor proteins myosin and kinesin, to coordinate the directed movement of the vesicles along actin filaments and microtubules, respectively, to the EC space [1]. Golgi-driven exocytosis is regulated by RAB11 vesicles interacting with MyosinVa and -Vb to promote vesicle transport [7][8]. RAB11 has oncogenic roles in a variety of cancer types through altering vesicular trafficking, receptor recycling, and signaling pathways that control proliferation and metastasis [9][10]. RAB6 regulates vesicle movement by interacting with the kinesin KIF20a [11]. Through its effector PKA, RAB13 prevents actin polymerization and tight junction integrity, thereby promoting prostate cancer [12][13]. However, RAB13 was also implicated in disrupting cancer cell growth as loss of the protein inhibited junction proteins, Claudin-1 and Occludin [12]. More detailed mechanistic studies are needed to determine how RAB proteins promote cancer progression to develop therapeutic strategies to inhibit the GTPases or their interacting partners.

Similar to RAB functions, ARFs, ARF-GEFs, and ARF-GAPs regulate retrograde and anterograde transport in cells; hence, alterations in these proteins during cancer lead to enhanced vesicular transport, exocytosis, cellular invasion, and metastasis [14][15]. For example, ARF1 regulates Golgi exocytosis by altering cytoskeletal proteins such as myosin and F-actin. ARF1 mediates RhoA and RhoC activity, which regulates myosin light-chain phosphorylation and detachment of membrane-derived vesicles [16]. It negatively correlates with breast cancer patient survival [17]. Additionally, ARF GTPases also regulate retrograde transport that eventually alters the cancer cell secretome via a feed-forward mechanism, whereby enhanced retrograde trafficking stimulates anterograde trafficking. For example, ARF4 functions with the COPBI protein involved in Golgi-to-ER retrograde trafficking to enhance anterograde trafficking and breast cancer metastasis in murine models [18]. Additionally, ARF4 and COPBI are necessary for the secretion of pro-metastatic factors, such as VEGF, CXCL1, CXCL10, and CCL20 [18][19]. One of the key players in modulating retrograde transport with GTPases is the KDELR family. When KDELR binds ER chaperone proteins that have escaped to the Golgi, it stimulates retrograde transport of these chaperones back to the ER. This interaction of KDELR at the Golgi membrane activates Src-mediated anterograde vesicular transport, although in an unclear way. Thus, KDELR enhances Src-mediated anterograde transport, exocytosis of MMPs, ECM degradation, and invasion into melanoma cells [20][21]. These studies prompt future research to examine the molecular mechanism behind how retrograde trafficking stimulates anterograde transport and its implications in cancer biology.

Vesicular trafficking requires membrane fusion events, such as movement through the Golgi or upon vesicle fusion with the PM. Membranes contain proteins, termed SNARES, that can either be on the vesicle (v-SNARE) or the target membrane (t-SNARE). Once the v- and t-SNARES have fused, ATP is hydrolyzed by N-ethylmaleimide sensitive factor (NSF), which interacts with soluble NSF attachment factors (SNAPs) to release the SNARE proteins from the newly synthesized membrane [22][23]. SNARE and SNAP proteins are altered in cancer cells to promote invasion. VAMP7, which is a v-SNARE residing in the ER–Golgi membranes, co-localizes with SNAP23 and Bet1, which is an ER–Golgi SNARE, to aid in MT1-MMP translocation to invadopodia in invasive breast cancer cell lines [24][25]. Various SNARE proteins are expressed at early or later cancer stages and were proposed for use as biomarkers [26]. Syntaxin-6 is a t-SNARE on the trans-Golgi membrane that is highly expressed in renal cell carcinoma [27]. Here, it interacts with microtubules to direct EGFR to the Golgi, which is required for its nuclear translocation and activation [28]. Syntaxin-6 also co-localizes with VAMP4 and ATP11B to secrete cisplatin from the

Golgi to be released into the extracellular space in ovarian cancer cell lines [29]. In synovial sarcoma cells, SNAP23 and VAMP-3 aid in the secretion of IL-6 and TNF-α, which are known to have pro-tumorigenic roles [30]. Additionally, αSNAP negatively regulates AMPK, which is a known factor in tumor progression [31], and promotes disassociation of cellular junctions, which was suggested to promote invasion [32]. SNARE and SNAP proteins mediate many functions of Golgi vesicular transport to promote cancer invasion, progression, and drug resistance.

Beyond proteins involved in vesicular trafficking, Golgi-specific proteins can act as oncoproteins that have global implications on Golgi dynamics, function, and secretion. Golgi phosphoprotein 3 (GOLPH3) is involved in regulating directed vesicle exocytosis, cell migration, Golgi morphology and orientation, and protein glycosylation. Upon interacting with various Golgi membrane and structural proteins, GOLPH3 forms the PI(4)P/GOLPH3/MYO18A/F-actin complex that provides the force required for proper vesicle budding and Golgi-to-PM trafficking, whereas loss of the complex interrupts transport. As GOLPH3 binds to both a Golgi protein, namely, PI(4)P, and a myosin family member, namely, MYO18A, it allows for trafficking of the Golgi vesicles along actin filaments to aid secretion from the Golgi. Hence, increased GOLPH3 expression, as observed in various cancers, including melanoma and NSCLC, enhances anterograde trafficking from the Golgi and leads to increased exocytosis of pro-metastatic factors, such as cytokines, growth factors, and Wnt molecules [33][34]. Additionally, Rizzo et al. showed that GOLPH3 can also control the trafficking and recycling of enzymes that enhance glycosphingolipid synthesis and abundance [35]. A GOLPH3-mediated increase in these enzymes upregulates cellular growth and proliferation via mitogenic signals [35]. Thus, this data indicates that, in addition to mediating trafficking, Golgi proteins might also modulate cellular signaling. Furthermore, it can be demonstrated that two Golgi-associated proteins, namely, inositol monophosphatase domain containing 1 (IMPAD1) and KDELR2, also enhance Golgi-mediated exocytosis of MMPs to drive lung cancer metastasis. Both IMPAD1 and KDELR2 negatively correlate with NSCLC patient survival [21]. These studies imply that other proteins with functions related to increased vesicular trafficking in both the anterograde and retrograde directions can enhance Golgi exocytosis to drive a malignant TME during metastasis.

Furthermore, cellular conditions, such as hypoxia and nitric oxide (NO) abundance, can also regulate trafficking in malignant cells [36][37]. Hypoxia, which is the depletion of oxygen, is a key hallmark of metastasic cells [38]. Arsenault et al. showed that under hypoxic conditions the proprotein convertase, namely, Furin, was translocated from the trans-Golgi to the endosome and PM by RAB4 [39]. At the PM, Furin processed proproteins that were involved in tumorigenesis. Interrupting this re-localization suppressed hypoxia-induced invasion of fibrosarcoma cancer cells. Hypoxia was also shown to promote an adaptive unfolded protein response (UPR) and a suppression of coatomer protein complex genes (COPA, COPE, and COPG), thereby hampering ER-to-Golgi trafficking via the JNK pathway [40]. Additionally, oxygen levels can affect NO availability in the Golgi by modulating NO synthase expression. NO is a critical regulator with dual functions in metastasis. It was implicated in cytotoxic death of liver, breast, and skin tumors, but can also promote angiogenesis and intravasation in a context-dependent manner [41]. NO affects the nitrosylation of Golgi proteins, such as NSF, which is involved in fusion events; thus, delaying ER–Golgi vesicular trafficking [42]. Hence, cellular homeostasis is required to maintain normal trafficking and prevent tumorigenesis.

2. Golgi Orientation Governs Cell Polarity and Directional Migration

One of the hallmarks of metastatic cells is their ability to transition from an apico-basal polarity to a front–rear/migratory polarity, allowing them to spread from the primary tumor to secondary locations [43]. Similarly, the Golgi regulates its orientation to alter its function, where the orientation of the Golgi, with respect to the centrosome and microtubules, establishes the leading edge of a cell in the front–rear polarity model [34]. The secretome can be altered based on intracellular localization of the Golgi. For example, if the Golgi is closer to the cell membrane, such as in some cancer cells, it can enhance the frequency of secretion [34]. Additionally, Golgi orientation not only controls exocytosis but also guides vesicular flow to the leading edge of the cell to prompt directional migration [44]. The Golgi reorients to the leading edge of a cell, where migration of a cell begins, under stimuli, such as wounding or a chemotactic gradient in normal conditions [45]. It could be expected that these signals would stimulate Golgi reorientation in cancer cells as well; however, the stimuli and mechanisms for Golgi reorientation are diverse depending on the cancer type. For example, the small, secreted molecule gastrin, which aids in regulating gastric acid secretion, is abnormally expressed in pancreatic cancer. Gastrin stimulates phosphorylation of paxillin, which is a focal-adhesion-associated kinase protein, prompting Golgi reorientation to the leading edge to promote migration of pancreatic cancer cells [46]. Mutant LKB1, which is a tumor suppressor, disrupts Golgi reorientation to the leading edge through loss of interaction with CDC42, which is a Rho GTPase, affecting polarity in NSCLC cells [47]. Enhanced trafficking and cell motility at the leading edge of a cancer cell aids in the beginning of the metastasis process.

Several Golgi proteins are involved in altering cell polarity through their ability to regulate Golgi orientation. For example, Xing et al. showed that not only does GOLPH3 regulate exocytosis, as previously described, but also applies a tensile force through its interaction with PI(4)P/MYO18A/F-actin to promote a front–rear polarization by relocating the Golgi and trafficking toward the leading edge [48]. They also elucidated that this reorientation promotes directional cell migration, invasion, and metastasis through enhanced exocytosis. Thus, GOLPH3 is a key Golgi protein that has a multi-faceted role in regulating Golgi dynamics, further demonstrating that Golgi functions are complex and intertwined. Another Golgi matrix protein, namely, GM130, leads to a loss of polarity proteins, such as CDC42 and E-cadherin, when inhibited [49]. Additionally, they demonstrated that GM130 is necessary for the invasion of breast cancer cells [50][51]; thus, indicating an association between Golgi proteins, cell polarity, and cancerous behavior. Furthermore, paxillin also reorients the Golgi toward the leading edge to direct trafficking and cell migration through interactions with the centriole and is necessary for proper anterograde vesicular trafficking [52]. In melanoma, the interaction between paxillin, focal adhesion kinase (FAK), and histone deacetylase 6 enhanced the acetylated microtubule landscape, leading to the formation of invadopodia that promote cell migration, invasion, and metastasis [53]. The authors also showed that inhibiting this interaction may be a possible treatment for metastatic melanoma and it suggests that Golgi orientation is regulated by proteins with diverse functions [53]. Golgi positioning is dependent on cytoskeletal proteins, as Hela cells with knockdown of golgin proteins, namely, GMAP210 and golgin-160, that link the Golgi to motor proteins had altered directional secretion and migration due to random Golgi orientation despite intact microtubule and actin filaments [54]. Overall,

Golgi localization within the cell, assisted by cytoskeletal factors, can alter the direction of Golgi-mediated secretion and promote cancer metastasis.

3. Morphology of the Golgi Apparatus

It is not only the orientation of the Golgi but also the structural morphology of the organelle that governs protein secretion during metastasis. The Golgi is a dynamic organelle that alters its structure to accommodate the physiological state of the cell. There are three main states of the Golgi—condensed, elongated, and fragmented—between which, the organelle oscillates in a context-dependent manner in different cancers (**Figure 1**).

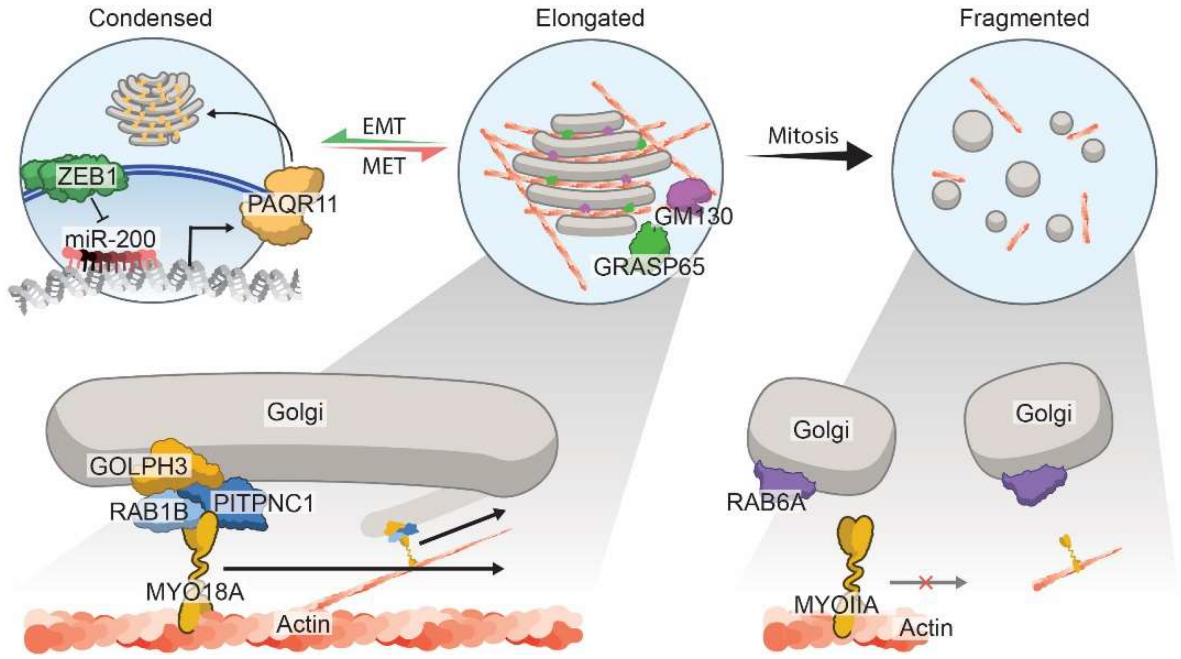

Figure 1. Regulation of Golgi morphology states in cancer. The Golgi oscillates dynamically between three main defined morphological states: the condensed (left Golgi), the elongated (middle Golgi), or the fragmented (right Golgi). Zeb1-mediated EMT orchestrates Golgi condensation by repressing the epithelial miRNA, namely, miR-200, and upregulating PAQR11. PAQR11 is a Golgi scaffold protein that mediates Golgi organization and secretion of pro-metastatic factors. The elongated Golgi morphology is maintained via the PITPNC1–RAB1B–GOLPH3–MYO18A complex, where GOLPH3 links vesicles to myosin motors and facilitates movement along actin filaments. Additionally, other Golgi matrix proteins, namely, GM130 and GRASP65, also interact with various Golgi factors to promote the elongated ribbon-like structures, which is necessary for cancer cell invasion and vesicular trafficking. Loss of these matrix proteins prevents organelle stacking, thereby leading to a fragmented Golgi architecture, which is commonly seen during mitosis. Moreover, in prostate cancer, a disrupted Golgi promotes invasion through dysregulated vesicle interaction with RAB6A, which results in diminished interactions with myosin, MYOIIA, and fewer fusion events.

The epithelial-to-mesenchymal transition (EMT) is one of the cellular phenomena that repositions and restructures the Golgi to redirect traffic toward the leading edge of cells, enabling migratory and invasive behavior [55]. EMT is

hypothesized to allow cancer cells to gain the ability to disseminate from primary tumors and metastasize to secondary locations [56][57]. A lab and others showed that metastasis-prone cells tend to be more plastic as they transition between epithelial and mesenchymal states [58]. Using NSCLC models, it can be demonstrated that this transition is highly dependent on the negative-feedback loop between key regulators of a mesenchymal or epithelial state—namely, ZEB1 and miRNA-200 family (miR-200)—where they promote and inhibit EMT, respectively [58][59]. ZEB1-induced EMT leads to compaction and polarization of the Golgi with improved ribbon linking and cisternal stacking [55]. This organization is orchestrated by progestin and adipoQ receptor family member 11 (PAQR11), which is a scaffold for multiple Golgi-associated protein complexes that can then control organelle structure. The upregulation of PAQR11, which is correlated with shorter survival in cancer patients, directs and enhances protein exocytosis. In the same model, the authors show that PAQR11 also drives lung cancer metastasis, thus indicating a possible correlation between Zeb1-induced EMT, alterations in Golgi architecture, and the metastatic secretome [55]. Collagen deposition and crosslinking in the ECM are upregulated during EMT, which, in turn, enhances integrin/FAK/Src signaling in cancer cells to promote invasion and metastasis [57][60]. Additionally, enzymes such as lysyl hydroxylases that modify collagen to allow for its cross-linking and stabilization correlate with lung cancer metastasis and worse patient survival [61]. Moreover, increased collagen deposition also suppresses effective immune surveillance of the tumor immune microenvironment (TIME) by leading to an exhausted CD8+ T cell state [62]. Interestingly, the immune suppression was reversible upon inhibiting collagen interactions with the T cells, leading to an enhanced anti-tumor immune response. Hence, a feedback loop driven by EMT facilitates cellular secretion and ECM alterations that make cancer cells more malignant and resistant to therapy.

In contrast to the EMT-regulated Golgi compaction model that enhances exocytosis and malignancy, an elongated Golgi ribbon structure was also implicated in metastasis. GOLPH3 alters vesicular trafficking and Golgi orientation, as previously described, and regulates Golgi morphology, where its expression elongates the organelle ribbon structure [19][63][64][65][66]. Knockdown studies showed that GOLPH3 repression causes Golgi fragmentation and prevents cancer cell spreading. This indicates that a GOLPH3-mediated ribbon-like elongated Golgi structure may promote invasion and metastasis [67]. Additionally, Halberg et al. showed that the PITPNC1–RAB1B–GOLPH3 complex regulates Golgi elongation and enhances exocytosis of pro-invasive components, such as MMP1, FAM3C, and PDGFA, thereby driving metastatic breast, melanoma, and colon cancers [63][68]. Golgins are another family of Golgi membrane proteins that interact with Golgi-associated proteins to maintain organelle architecture [69]. Golgin-97 facilitates Golgi tethering and vesicle formation for cytokines, including IL-10 and IL-6, which alters the cancer secretome during metastasis [70].

The third morphology of the Golgi exists in a fragmented form, which is especially seen during mitosis in physiological conditions. Fragmentation of the Golgi first begins in the G2 phase of the cell cycle, where individual Golgi stacks are dissociated and then undergo fragmentation into small vesicles. These vesicles are then reformed into the Golgi in each new daughter cell during the telophase [71][72]. In advanced prostate cancer cells, the fragmented Golgi was also implicated in cancer metastasis (**Figure 1**). Decreased expression of the Golgi matrix proteins—Giantin, GM130, and GRASP65—as well as a disrupted interaction between RAB6a and Myosin IIA, promote Golgi fragmentation and carcinogenesis [73][74]. In addition to the previously described effects on

trafficking, hypoxia and NO can also mediate Golgi fragmentation and cancer malignancy. Using a high-throughput RNAi screen, previous work implicated dual-specificity phosphatase-2 (DUSP-2) in maintaining Golgi integrity, where the loss of the protein led to Golgi disruption [75]. Lin et al. further showed that hypoxia suppresses DUSP-2 expression, leading to chemoresistance and malignancy in many cancers, including colon, lung, and breast cancer [76]. Thus, DUSP-2 might be the link that connects hypoxia and Golgi fragmentation in cancer. Conversely, Lee et al. showed that compounds that scavenge NO can also promote Golgi fragmentation and a decrease in Golgi membrane proteins, such as SNAREs and SNAPs [77][78]. The ability of the Golgi to dynamically shift between different morphologies depending on the cellular context highlights the need for future studies focused on unraveling the regulation of complex Golgi morphology and understanding how best to target Golgi structural changes in cancer progression.

References

1. Goldenring, J.R. A central role for vesicle trafficking in epithelial neoplasia: Intracellular highways to carcinogenesis. Nat. Reviews. Cancer 2013, 13, 813–820.
2. Bhuin, T.; Roy, J.K. Rab proteins: The key regulators of intracellular vesicle transport. Exp. Cell Res. 2014, 328, 1–19.
3. Mughees, M.; Chugh, H.; Wajid, S. Vesicular trafficking-related proteins as the potential therapeutic target for breast cancer. Protoplasma 2020, 257, 345–352.
4. Tzeng, H.-T.; Wang, Y.-C. Rab-mediated vesicle trafficking in cancer. J. Biomed. Sci. 2016, 23, 70.
5. Acob, A.; Jing, J.; Lee, J.; Schedin, P.; Gilbert, S.M.; Peden, A.A.; Junutula, J.R.; Prekeris, R. Rab40b regulates trafficking of MMP2 and MMP9 during invadopodia formation and invasion of breast cancer cells. J. Cell Sci. 2013, 126 Pt 20, 4647–4658.
6. Hendrix, A.; Maynard, D.; Pauwels, P.; Braems, G.; Denys, H.; Van den Broecke, R.; Lambert, J.; Van Belle, S.; Cocquyt, V.; Gespach, C.; et al. Effect of the secretory small GTPase Rab27B on breast cancer growth, invasion, and metastasis. J. Natl. Cancer Inst. 2010, 102, 866–880.
7. Lapierre, L.A.; Kumar, R.; Hales, C.M.; Navarre, J.; Bhartur, S.G.; Burnette, J.O.; Provance, D.W., Jr.; Mercer, J.A.; Bähler, M.; Goldenring, J.R. Myosin vb is associated with plasma membrane recycling systems. Mol. Biol. Cell 2001, 12, 1843–1857.
8. Welz, T.; Kerkhoff, E. Exploring the iceberg: Prospects of coordinated myosin V and actin assembly functions in transport processes. Small GTPases 2019, 10, 111–121.
9. Howe, E.N.; Burnette, M.D.; Justice, M.E.; Schnepp, P.M.; Hedrick, V.; Clancy, J.W.; Guldner, I.H.; Lamere, A.T.; Li, J.; Aryal, U.K.; et al. Rab11b-mediated integrin recycling promotes brain metastatic adaptation and outgrowth. Nat. Commun. 2020, 11, 3017.

10. Ferro, E.; Bosia, C.; Campa, C.C. RAB11-mediated trafficking and human cancers: An updated review. Biology 2020, 10, 26.
11. Miserey-Lenkei, S.; Bousquet, H.; Pylypenko, O.; Bardin, S.; Dimitrov, A.; Bressanelli, G.; Bonifay, R.; Fraisier, V.; Guillou, C.; Bougeret, C.; et al. Coupling fission and exit of RAB6 vesicles at Golgi hotspots through kinesin-myosin interactions. Nat. Commun. 2017, 8, 1254.
12. Ioannou, M.S.; McPherson, P.S. Regulation of Cancer Cell Behavior by the Small GTPase Rab13. J. Biol. Chem. 2016, 291, 9929–9937.
13. Neary, C.L.; Nesterova, M.; Cho, Y.S.; Cheadle, C.; Becker, K.G.; Cho-Chung, Y.S. Protein kinase A isozyme switching: Eliciting differential cAMP signaling and tumor reversion. Oncogene 2004, 23, 8847–8856.
14. Casalou, C.; Faustino, A.; Barral, D.C. Arf proteins in cancer cell migration. Small GTPases 2016, 7, 270–282.
15. Casalou, C.; Ferreira, A.; Barral, D.C. The Role of ARF Family Proteins and Their Regulators and Effectors in Cancer Progression: A Therapeutic Perspective. Front. Cell Dev. Biol. 2020, 8, 217.
16. Schlienger, S.; Campbell, S.; Claing, A. ARF1 regulates the Rho/MLC pathway to control EGF-dependent breast cancer cell invasion. Mol. Biol. Cell 2014, 25, 17–29.
17. Xie, X.; Tang, S.; Cai, Y.; Pi, W.; Deng, L.; Wu, G.; Chavanieu, A.; Teng, Y. Suppression of breast cancer metastasis through the inactivation of ADP-ribosylation factor 1. Oncotarget 2016, 7, 58111–58120.
18. Howley, B.V.; Link, L.A.; Grelet, S.; El-Sabban, M.; Howe, P.H. A CREB3-regulated ER-Golgi trafficking signature promotes metastatic progression in breast cancer. Oncogene 2018, 37, 1308–1325.
19. Howley, B.V.; Howe, P.H. Metastasis-associated upregulation of ER-Golgi trafficking kinetics: Regulation of cancer progression via the Golgi apparatus. Oncoscience 2018, 5, 142–143.
20. Ruggiero, C.; Grossi, M.; Fragassi, G.; Di Campli, A.; Di Ilio, C.; Luini, A.; Sallese, M. The KDEL receptor signalling cascade targets focal adhesion kinase on focal adhesions and invadopodia. Oncotarget 2018, 9, 10228–10246.
21. Bajaj, R.; Kundu, S.T.; Grzeskowiak, C.L.; Fradette, J.J.; Scott, K.L.; Creighton, C.J.; Gibbons, D.L. IMPAD1 and KDELR2 drive invasion and metastasis by enhancing Golgi-mediated secretion. Oncogene 2020, 39, 5979–5994.
22. Malsam, J.; Söllner, T.H. Organization of SNAREs within the Golgi stack. Cold Spring Harb Perspect. Biol. 2011, 3, a005249.
23. Sehgal, P.B.; Mukhopadhyay, S.; Xu, F.; Patel, K.; Shah, M. Dysfunction of Golgi tethers, SNAREs, and SNAPs in monocrotaline-induced pulmonary hypertension. Am. J. Physiol. Lung

Cell Mol. Physiol. 2007, 292, L1526–L1542.

24. Miyagawa, T.; Hasegawa, K.; Aoki, Y.; Watanabe, T.; Otagiri, Y.; Arasaki, K.; Wakana, Y.; Asano, K.; Tanaka, M.; Yamaguchi, H.; et al. MT1-MMP recruits the ER-Golgi SNARE Bet1 for efficient MT1-MMP transport to the plasma membrane. Cancer Cell Biol. 2019, 218, 3355–3371.
25. Steffen, A.; Le Dez, G.; Poincloux, R.; Recchi, C.; Nassoy, P.; Rottner, K.; Galli, T.; Chavrier, P. MT1-MMP-Dependent Invasion Is Regulated by TI-VAMP/VAMP7. Curr. Biol. 2008, 18, 926–931.
26. Meng, J.; Wang, J. Role of SNARE proteins in tumourigenesis and their potential as targets for novel anti-cancer therapeutics. Biochim. Et Biophys. Acta (BBA) Rev. Cancer 2015, 1856, 1–12.
27. Peak, T.C.; Su, Y.; Chapple, A.G.; Chyr, J.; Deep, G. Syntaxin 6: A novel predictive and prognostic biomarker in papillary renal cell carcinoma. Sci. Rep. 2019, 9, 3146.
28. Du, Y.; Shen, J.; Hsu, J.L.; Han, Z.; Hsu, M.C.; Yang, C.C.; Kuo, H.P.; Wang, Y.N.; Yamaguchi, H.; Miller, S.A.; et al. Syntaxin 6-mediated Golgi translocation plays an important role in nuclear functions of EGFR through microtubule-dependent trafficking. Oncogene 2014, 33, 756–770.
29. Moreno-Smith, M.; Halder, J.B.; Meltzer, P.S.; Gonda, T.A.; Mangala, L.S.; Rupaimoole, R.; Lu, C.; Nagaraja, A.S.; Gharpure, K.M.; Kang, Y.; et al. ATP11B mediates platinum resistance in ovarian cancer. J. Clin. Investig. 2013, 123, 2119–2130.
30. Boddul, S.V.; Meng, J.; Dolly, J.O.; Wang, J. SNAP-23 and VAMP-3 contribute to the release of IL-6 and TNFα from a human synovial sarcoma cell line. FEBS J. 2014, 281, 750–765.
31. Wang, L.; Brautigan, D.L. α-SNAP inhibits AMPK signaling to reduce mitochondrial biogenesis and dephosphorylates Thr172 in AMPKα in vitro. Nat. Commun. 2013, 4, 1559.
32. Naydenov, N.G.; Brown, B.; Harris, G.; Dohn, M.R.; Morales, V.M.; Baranwal, S.; Reynolds, A.B.; Ivanov, A.I. A membrane fusion protein αSNAP is a novel regulator of epithelial apical junctions. PLoS ONE 2012, 7, e34320.
33. Song, J.W.; Zhu, J.; Wu, X.X.; Tu, T.; Huang, J.Q.; Chen, G.Z.; Liang, L.Y.; Zhou, C.H.; Xu, X.; Gong, L.Y. GOLPH3/CKAP4 promotes metastasis and tumorigenicity by enhancing the secretion of exosomal WNT3A in non-small-cell lung cancer. Cell Death Dis. 2021, 12, 976.
34. Ravichandran, Y.; Goud, B.; Manneville, J.B. The Golgi apparatus and cell polarity: Roles of the cytoskeleton, the Golgi matrix, and Golgi membranes. Curr. Opin. Cell Biol. 2020, 62, 104–113.
35. Rizzo, R.; Russo, D.; Kurokawa, K.; Sahu, P.; Lombardi, B.; Supino, D.; Zhukovsky, M.A.; Vocat, A.; Pothukuchi, P.; Kunnathully, V.; et al. Golgi maturation-dependent glycoenzyme recycling controls glycosphingolipid biosynthesis and cell growth via GOLPH3. EMBO J. 2021, 40, e107238.
36. Kellokumpu, S. Golgi pH, Ion and Redox Homeostasis: How Much Do They Really Matter? Front. Cell Dev. Biol. 2019, 7, 93.

37. Mennerich, D.; Kellokumpu, S.; Kietzmann, T. Hypoxia and Reactive Oxygen Species as Modulators of Endoplasmic Reticulum and Golgi Homeostasis. Antioxid. Redox Signal. 2019, 30, 113–137.
38. Rankin, E.B.; Nam, J.M.; Giaccia, A.J. Hypoxia: Signaling the Metastatic Cascade. Trends Cancer 2016, 2, 295–304.
39. Arsenault, D.; Lucien, F.; Dubois, C.M. Hypoxia enhances cancer cell invasion through relocalization of the proprotein convertase furin from the trans-Golgi network to the cell surface. J. Cell. Physiol. 2012, 227, 789–800.
40. Bensellam, M.; Maxwell, E.L.; Chan, J.Y.; Luzuriaga, J.; West, P.K.; Jonas, J.-C.; Gunton, J.E.; Laybutt, D.R. Hypoxia reduces ER-to-Golgi protein trafficking and increases cell death by inhibiting the adaptive unfolded protein response in mouse beta cells. Diabetologia 2016, 59, 1492–1502.
41. Cheng, H.; Wang, L.; Mollica, M.; Re, A.T.; Wu, S.; Zuo, L. Nitric oxide in cancer metastasis. Cancer lett. 2014, 353, 1–7.
42. Iwakiri, Y.; Satoh, A.; Chatterjee, S.; Toomre, D.K.; Chalouni, C.M.; Fulton, D.; Groszmann, R.J.; Shah, V.H.; Sessa, W.C. Nitric oxide synthase generates nitric oxide locally to regulate compartmentalized protein S-nitrosylation and protein trafficking. Proc. Natl. Acad. Sci. USA 2006, 103, 19777–19782.
43. Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: The next generation. Cell 2011, 144, 646–674.
44. Wilson, B.J.; Allen, J.L.; Caswell, P.T. Vesicle trafficking pathways that direct cell migration in 3D matrices and in vivo. Traffic 2018, 19, 899–909.
45. Kupfer, A.; Louvard, D.; Singer, S.J. Polarization of the Golgi apparatus and the microtubule-organizing center in cultured fibroblasts at the edge of an experimental wound. Proc. Natl. Acad. Sci. USA 1982, 79, 2603–2607.
46. Mu, G.; Ding, Q.; Li, H.; Zhang, L.; Zhang, L.; He, K.; Wu, L.; Deng, Y.; Yang, D.; Wu, L.; et al. Gastrin stimulates pancreatic cancer cell directional migration by activating the Gz12/13-RhoA-ROCK signaling pathway. Exp. Mol. Med. 2018, 50, 1–14.
47. Zhang, S.; Schafer-Hales, K.; Khuri, F.R.; Zhou, W.; Vertino, P.M.; Marcus, A.I. The tumor suppressor LKB1 regulates lung cancer cell polarity by mediating cdc42 recruitment and activity. Cell Tumor Stem. Cell Biol. 2008, 68, 740–748.
48. Xing, M.; Peterman, M.C.; Davis, R.L.; Oegema, K.; Shiau, A.K.; Field, S.J. GOLPH3 drives cell migration by promoting Golgi reorientation and directional trafficking to the leading edge. Mol. Biol. Cell 2016, 27, 3828–3840.

49. Baschieri, F.; Confalonieri, S.; Bertalot, G.; Di Fiore, P.P.; Dietmaier, W.; Leist, M.; Crespo, P.; Macara, I.G.; Farhan, H. Spatial control of Cdc42 signalling by a GM130-RasGRF complex regulates polarity and tumorigenesis. Nat. Commun. 2014, 5, 4839.
50. Baschieri, F.; Farhan, H. Endomembrane control of cell polarity: Relevance to cancer. Small GTPases 2015, 6, 104–107.
51. Baschieri, F.; Uetz-von Allmen, E.; Legler, D.F.; Farhan, H. Loss of GM130 in breast cancer cells and its effects on cell migration, invasion and polarity. Cell Cycle 2015, 14, 1139–1147.
52. Dubois, F.; Alpha, K.; Turner, C.E. Paxillin regulates cell polarization and anterograde vesicle trafficking during cell migration. Mol. Biol. Cell 2017, 28, 3815–3831.
53. Mousson, A.; Legrand, M.; Steffan, T.; Vauchelles, R.; Carl, P.; Gies, J.P.; Lehmann, M.; Zuber, G.; De Mey, J.; Dujardin, D.; et al. Inhibiting FAK-Paxillin Interaction Reduces Migration and Invadopodia-Mediated Matrix Degradation in Metastatic Melanoma Cells. Cancers 2021, 13, 1871.
54. Yadav, S.; Puri, S.; Linstedt, A.D. A primary role for Golgi positioning in directed secretion, cell polarity and wound healing. Mol. Biol. Cell 2009, 20, 1728–1736.
55. Tan, X.; Banerjee, P.; Guo, H.F.; Ireland, S.; Pankova, D.; Ahn, Y.H.; Nikolaidis, I.M.; Liu, X.; Zhao, Y.; Xue, Y.; et al. Epithelial-to-mesenchymal transition drives a pro-metastatic Golgi compaction process through scaffolding protein PAQR11. J. Clin. investig. 2017, 127, 117–131.
56. Kalluri, R.; Weinberg, R.A. The basics of epithelial-mesenchymal transition. J. Clin. Investig. 2009, 119, 1420–1428.
57. Peng, D.H.; Ungewiss, C.; Tong, P.; Byers, L.A.; Wang, J.; Canales, J.R.; Villalobos, P.A.; Uraoka, N.; Mino, B.; Behrens, C.; et al. ZEB1 induces LOXL2-mediated collagen stabilization and deposition in the extracellular matrix to drive lung cancer invasion and metastasis. Oncogene 2017, 36, 1925–1938.
58. Gibbons, D.L.; Lin, W.; Creighton, C.J.; Rizvi, Z.H.; Gregory, P.A.; Goodall, G.J.; Thilaganathan, N.; Du, L.; Zhang, Y.; Pertsemlidis, A.; et al. Contextual extracellular cues promote tumor cell EMT and metastasis by regulating miR-200 family expression. Genes Dev. 2009, 23, 2140–2151.
59. Gregory, P.A.; Bert, A.G.; Paterson, E.L.; Barry, S.C.; Tsykin, A.; Farshid, G.; Vadas, M.A.; Khew-Goodall, Y.; Goodall, G.J. The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1. Nat. Cell Biol. 2008, 10, 593–601.
60. Ungewiss, C.; Rizvi, Z.H.; Roybal, J.D.; Peng, D.H.; Gold, K.A.; Shin, D.-H.; Creighton, C.J.; Gibbons, D.L. The microRNA-200/Zeb1 axis regulates ECM-dependent β1-integrin/FAK signaling, cancer cell invasion and metastasis through CRKL. Sci. Rep. 2016, 6, 18652.

61. Guo, H.-F.; Bota-Rabassedas, N.; Terajima, M.; Leticia Rodriguez, B.; Gibbons, D.L.; Chen, Y.; Banerjee, P.; Tsai, C.-L.; Tan, X.; Liu, X.; et al. A collagen glucosyltransferase drives lung adenocarcinoma progression in mice. Commun. Biol. 2021, 4, 482.
62. Peng, D.H.; Rodriguez, B.L.; Diao, L.; Chen, L.; Wang, J.; Byers, L.A.; Wei, Y.; Chapman, H.A.; Yamauchi, M.; Behrens, C.; et al. Collagen promotes anti-PD-1/PD-L1 resistance in cancer through LAIR1-dependent CD8(+) T cell exhaustion. Nat. Commun. 2020, 11, 4520.
63. Sechi, S.; Frappaolo, A.; Karimpour-Ghahnavieh, A.; Piergentili, R.; Giansanti, M.G. Oncogenic Roles of GOLPH3 in the Physiopathology of Cancer. Int. J. Mol. Sci. 2020, 21, 933.
64. Rahajeng, J.; Kuna, R.S.; Makowski, S.L.; Tran, T.T.T.; Buschman, M.D.; Li, S.; Cheng, N.; Ng, M.M.; Field, S.J. Efficient Golgi Forward Trafficking Requires GOLPH3-Driven, PI4P-Dependent Membrane Curvature. Dev. Cell 2019, 50, 573–585.e575.
65. Scott, K.L.; Kabbarah, O.; Liang, M.C.; Ivanova, E.; Anagnostou, V.; Wu, J.; Dhakal, S.; Wu, M.; Chen, S.; Feinberg, T.; et al. GOLPH3 modulates mTOR signalling and rapamycin sensitivity in cancer. Nature 2009, 459, 1085–1090.
66. Kuna, R.S.; Field, S.J. GOLPH3: A Golgi phosphatidylinositol(4)phosphate effector that directs vesicle trafficking and drives cancer. J. Lipid Res. 2019, 60, 269–275.
67. Makhoul, C.; Gosavi, P.; Gleeson, P.A. Golgi Dynamics: The Morphology of the Mammalian Golgi Apparatus in Health and Disease. Front. Cell Dev. Biol. 2019, 7, 112.
68. Halberg, N.; Sengelaub, C.A.; Navrazhina, K.; Molina, H.; Uryu, K.; Tavazoie, S.F. PITPNC1 Recruits RAB1B to the Golgi Network to Drive Malignant Secretion. Cancer Cell 2016, 29, 339–353.
69. Saraste, J.; Prydz, K. A New Look at the Functional Organization of the Golgi Ribbon. Front. Cell Dev. Biol. 2019, 7, 171.
70. Stow, J.L.; Murray, R.Z. Intracellular trafficking and secretion of inflammatory cytokines. Cytokine Growth Factor Rev. 2013, 24, 227–239.
71. Robbins, E.; Gonatas, N.K. The Ultrastructure of a Mammalian Cell during the Mitotic Cycle. J. Cell Biol. 1964, 21, 429–463.
72. Valente, C.; Colanzi, A. Mechanisms and Regulation of the Mitotic Inheritance of the Golgi Complex. Front. Cell Dev. Biol. 2015, 3, 79.
73. Petrosyan, A. Unlocking Golgi: Why Does Morphology Matter? Biochemistry 2019, 84, 1490–1501.
74. Petrosyan, A. Onco-Golgi: Is Fragmentation a Gate to Cancer Progression? Biochem. Mol. Biol. J. 2015, 1, 16.

75. Chia, J.; Goh, G.; Racine, V.; Ng, S.; Kumar, P.; Bard, F. RNAi screening reveals a large signaling network controlling the Golgi apparatus in human cells. Mol. Syst. Biol. 2012, 8, 629.
76. Lin, S.C.; Chien, C.W.; Lee, J.C.; Yeh, Y.C.; Hsu, K.F.; Lai, Y.Y.; Lin, S.C.; Tsai, S.J. Suppression of dual-specificity phosphatase-2 by hypoxia increases chemoresistance and malignancy in human cancer cells. J. Clin. Investig. 2011, 121, 1905–1916.
77. Lee, J.E.; Patel, K.; Almodóvar, S.; Tuder, R.M.; Flores, S.C.; Sehgal, P.B. Dependence of Golgi apparatus integrity on nitric oxide in vascular cells: Implications in pulmonary arterial hypertension. Am. J. Physiology. Heart Circ. Physiol. 2011, 300, H1141–H1158.
78. Lee, J.E.; Yuan, H.; Liang, F.X.; Sehgal, P.B. Nitric oxide scavenging causes remodeling of the endoplasmic reticulum, Golgi apparatus and mitochondria in pulmonary arterial endothelial cells. Nitric Oxide Biol. Chem. 2013, 33, 64–73.