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Novel functions for Rab GTPases in multiple aspects of tumour progression

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Abstract

Rab GTPases are master regulators of intracellular trafficking and, in recent years, their role in the control of different aspects of tumour progression has emerged. In the present review, we show that Rab GTPases are disregulated in many cancers and have central roles in tumour cell migration, invasion, proliferation, communication with stromal cells and the development of drug resistance. As a consequence, Rab proteins may be novel potential candidates for the development of anticancer drugs and, in this context, the preliminary results obtained with an inhibitor of Rab function are also discussed.

Rab proteins as key regulators of intracellular trafficking

Rab proteins are part of the large Ras superfamily of small GTPases. There are more than 60 members in humans and each of them is specifically localized to a subcellular membrane compartment, of which it controls the intracellular traffic [1]. Rab proteins cycle between an inactive cytosolic GDP-bound form and an active membrane-associated GTP-bound form. When in their GTP-bound form, Rabs recruit effector proteins that mediate vesicle budding from donor organelles, transport along microtublules or actin filaments, and tethering and fusion to acceptor compartments [2]. In this way, Rab proteins control protein secretion, endocytosis, recycling and degradation, and are thus widely recognized as master regulators of intracellular trafficking. The complexity of combinations between the different Rabs and their myriad effectors is modulated further by two families of regulators: the GEFs (guanine-nucleotide-exchange factors), that promote GTP binding by Rabs, and the GAPs (GTPase-activating proteins), that trigger Rab GTPase activity and thus GTP hydrolysis to GDP. The specific localization of GEFs and GAPs regulate in a precise space- and time-specific manner the interaction between Rabs and their effectors and, as a consequence, they control Rab activity.

In recent years, a new role has been emerging for Rab proteins in the control of tumour progression. Several Rabs have been found to be deregulated in cancers and many have been described as central in tumour cell migration, invasion of the ECM (extracellular matrix), proliferation, signalling to and from stromal cells, and drug resistance. In the present review, we will summarize the current knowledge on the role that some of these Rabs play in the aforementioned processes.

Key words: cancer, exosome, invasion, migration, Rab GTPase, tumour microenvironment.

Abbreviations used: CAF, cancer-associated fibroblast; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; GAP, GTPase-activating protein; GEF, guanine-nucleotide-exchange factor; MDR, multidrug resistance; miRNA, microRNA; MMP, matrix metalloproteinase; MT1-MMP, membrane-type 1 MMP; P-gp, P-glycoprotein; RabGGTase, Rab geranylgeranyltransferase; RCP, Rab-coupling protein; Shh, Sonic Hedgehog.

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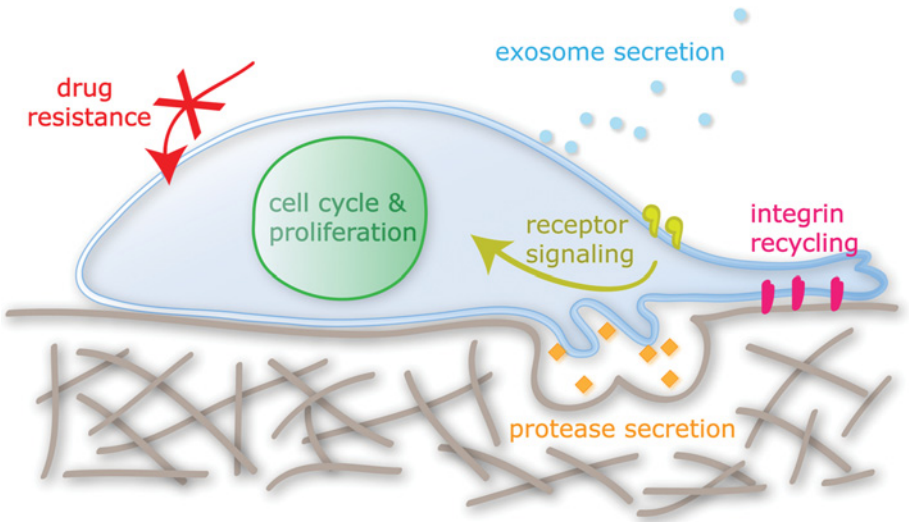
Rabs are aberrantly expressed in tumours

Several Rabs have been found in transcriptomic studies to present a deregulated expression in cancer cells compared with normal tissues, but for many of them a clear function in the context of cancer progression awaits characterization. For example, some Rabs such as Rab1b, Rab4b, Rab10, Rab22a and Rab24 are overexpressed in hepatocellular carcinoma [3]. Rab1a is overexpressed in tongue squamous cell carcinoma [4], whereas Rab2 is overexpressed in peripheral blood mononuclear cells from patients with solid tumours [5] and is associated with lung tumour progression in mouse [6]. Rab3B is up-regulated in prostate cancer, where it promotes cancer cell survival [7]. Rab20 is overexpressed in exocrine pancreatic carcinoma [8] and high levels of Rab31 are associated with worse outcome in breast cancer patients [9]. Interestingly, recent studies have analysed the expression profile of miRNAs (microRNAs) in cancer samples and have found that down-regulation of several miRNAs is associated with high levels of expression of various Rabs: this is the case for *miR-9* and Rab34 [10] and *let-7a* and Rab40c [11] in gastric carcinoma, *miR-451* and Rab14 in non-small lung carcinoma [12], and *has-miR-373* and Rab22a in colon cancer [13]. Conversely, some Rab genes are hypermethylated and thus down-regulated in tumours, such as those encoding Rab32 in colon [14] and gastric [15] cancer, and Rab37 in metastatic lung cancer [16]. Furthermore, Rab38 is down-regulated in melanoma primary tumours and metastasis compared with melanocytes [17]. Interestingly, a recent study in bladder cancer describes aberrant expression of not only several Rabs but also some Rab effectors, GAPs and GEFs [18], thus extending the analysis to Rab-related genes.

The picture emerging from these studies highlights the possibility that Rab GTPases may play an important role in cancer progression. Indeed, the contribution of some Rabs

Figure 1 | **Rab proteins have multiple functions in tumour cells**

The functions of Rab proteins in tumour cells include delivery and recycling of integrins at the front during cell migration, secretion of proteases to degrade the ECM and invade the surrounding tissues, secretion of exosomes that mediate the communication with stromal cells, trafficking of receptors and control of their signalling, impact on cell cycle and survival, and resistance to anticancer drugs.



to tumour progression has been investigated more in detail and is described in the following sections.

Rabs direct integrin trafficking and cell migration

A fundamental characteristic of metastatic cells is their ability to migrate and invade through the ECM to form metastases in other organs. In a series of well-documented studies, the family of Rab11 proteins (Rab11a, Rab11b and Rab25) and their effectors have been demonstrated to play a key role in the migration of cancer cells through the modulation of integrin recycling at the migration front (Figure 1). Rab11a had been described to regulate $\alpha 6\beta 4$ integrin transport at the cell surface during hypoxia-stimulated migration in breast cancer cells [19]. Rab25 is overexpressed in human ovarian cancers, where it correlates with poor prognosis, and increases cell survival *in vitro* and tumorigenesis *in vivo* [20]. In seminal works from Jim Norman's group, Rab25 has been shown to associate with $\alpha 5\beta 1$ integrin and promote its delivery at the pseudopodial tip of invading cells, thus driving cell migration in a three-dimensional environment [21]. Also, Rab25 collaborates with CLIC3 (chloride intracellular channel protein 3) to recycle integrins from late compartment to the back of migrating cells, a process necessary for the release of the cell rear during invasion [22]. Interestingly, the same group has also shown that the recycling of $\alpha 5\beta 1$ integrin is coupled to the recycling of EGFR (epidermal growth factor receptor) via the interaction with RCP (Rab-coupling protein), and this results in an increase in EGFR signalling to the survival factor Akt [23]. RCP is an effector of Rab11 and has been described as an oncogene that promotes breast cancer transformation [24]. Furthermore, RCP-mediated recycling and signalling of both integrin and EGFR are located downstream of a mutant form of p53 that drives an increase in cancer cell invasiveness [25]. In this way, metastatic cells integrate and co-ordinate signalling pathways important for migration and proliferation through Rab-mediated vesicular trafficking. Of note, although Rab25 has been described clearly as an oncogene in certain types of cancer, it has also been shown to act as a tumour suppressor in others, such as colorectal cancers [26,27] and triple-negative breast cancers [28,29]. So the exact function of Rab25 in tumour progression is likely to be context-dependent. Another Rab involved in the control of integrin trafficking is Rab21. Rab21 binds to α integrins in a GTP-dependent fashion and its level of expression correlates with integrin-mediated adhesion and motility in breast cancer cells [30]. Integrin internalization is also mediated by Rab5 and depletion of Rab5 reduces migration *in vitro* and tumour metastasis in neuroblastoma, downstream of caspase 8 signalling [31]. Furthermore, Rab5a expression is associated with higher-grade and lymph node metastasis in breast cancer patients [32], and it is overexpressed in cervical cancer, where again it promotes cell motility and invasion [33], and in hepatocellular carcinoma, where a dominant-negative mutant decreases cell migration [34].

Rabs promote protease secretion and cell invasion

Tumour cells secrete a variety of proteases, including MMPs (matrix metalloproteinases), which help the cells to breach the basal membrane and the ECM and migrate to distant organs. Some Rabs have been described to play a role in the context of MMP secretion or activation (Figure 1). In breast

cancer cells, for instance, Rab8 contributes to cell invasiveness by promoting the secretion of MT1-MMP (membrane-type 1 MMP) at peripheral invasive structures [35]. Rab7 has also been recently described as contributing to MT1-MMP secretion and a dominant-negative mutant of Rab7 impairs both cell migration and invasion [36]. Rab27b, which is associated with lymph node metastasis and differentiation grade in ER (oestrogen receptor)-positive human breast cancer patients, induces invasive growth of breast cancer cells via the secretion of Hsp90α (heat-shock protein 90α), which is required for the extracellular activation of MMP2 [37]. Rab27a is overexpressed in lymph node metastases in breast cancer cells [38] and in primary hepatocellular carcinoma [39], it has been suggested to promote cell invasiveness [40] and we recently observed that it is required for secretion of MMP9 by mouse mammary carcinoma cells [41]. Another protease important for the modification of the tumour microenvironment is procathepsin-L and its secretion is controlled by Rab4 [42]. Indeed, overexpression of Rab4 in melanoma causes an increase in tumour mass, whereas depletion of Rab4 induces a reduction in tumour volume [42].

Rabs contribute to tumour–stromal cell communication and the modification of the tumour microenvironment

In recent years, the rising importance of stromal cells in the creation of a tumour microenvironment favourable to cancer cell growth and metastasis has emerged. Important actors in this process are CAFs (cancer-associated fibroblasts) [43], which, among other functions, remodel the ECM. In this context, Rab21 has been shown to promote integrin accumulation at the plasma membrane and actomyosin contractility in CAFs, which results in collagen contraction and allows the invasion of squamous cell carcinoma through the CAF-modified matrix [44]. Other important mediators in intercellular communication between cancerous and stromal cells are tumour-derived microvescicles and exosomes [45] (Figure 1). In this context, Rab27a was shown to be required for secretion of exosomes by HeLa cells [46]. *In vivo*, Rab27a inhibition in melanoma cell lines reduced primary tumour growth and formation of lung metastases: this anti-tumour effect was due to a combination of impaired secretion of pro-angiogenic factors such as PlGF (placental growth factor), and decreased secretion of exosomes that 'educate' and recruit bone-marrow-derived cells to create a pro-metastatic niche [47]. Of note, Rab27a had been identified previously as a driver gene in melanoma [48]. In a similar manner, combined Rab27a-dependent secretion of MMP9 and exosomes contributes to the mobilization of a pro-tumoral neutrophil population and supports growth of a mouse mammary tumour and its metastasis to lungs [41].

Rabs affect cell-cycle progression

The aberrant expression of some Rabs has been shown to affect cell-cycle progression. One example is Rab27b: its overexpression promotes cell-cycle progression and proliferation in the breast cancer cell line MCF-7 and this is dependent on its GTP-loaded active state [37]. Another Rab described in this context is Rab6c, which is localized to the centrosome and whose overexpression results in G_1-phase arrest and whose depletion generates tetraploid cells [49]. Furthermore, Rab21-mediated trafficking of integrins at the cleavage furrow is required for cytokinesis and, as a consequence, cells depleted of Rab21 present multinuclei and genomic instability [50].

Rab23 antagonizes the Shh (Sonic Hedgehog) pathway

The morphogenic Shh pathway is essential in the embryonic dorsoventral development and is deregulated in many cancers. Rab23 was first identified as an antagonist of the Shh signalling pathway [51] and recently it has been shown to interact in its GTP-bound form with Su(Fu) and thus inhibit the Gli transcription factor that is normally activated downstream of Shh signalling [52]. However, Rab23 is overexpressed in diffuse-type gastric cancer, where it promotes cell invasion [53], and in hepatocellular carcinoma, where it supports cell growth [54], so its role in tumour progression might also be Shh-independent.

Rabs are involved in resistance to anticancer drugs

MDR (multidrug resistance) in human cancers is often associated with the overexpression of P-gp (P-glycoprotein), a large transmembrane protein localized at the plasma membrane that extrudes anticancer drugs and thus decreases their concentration, and toxicity, inside the cells [55]. The recycling protein Rab4 interacts with P-gp, but it is underexpressed in MDR cells [56]. However, when Rab4 is overexpressed, it decreases P-gp levels at the plasma membrane, thus increasing drug sensitivity in MDR cells [56] (Figure 1). Similarly, Rab6c is underexpressed in MDR cells and its overexpression induces the intracellular accumulation of several anticancer drugs, although the mechanism underlying this phenotype has not yet been established [57]. Another Rab involved in resistance to a chemotherapeutic drug is the secretory Rab8: cancer cells resistant to the platinum compound cisplatin have high levels of Rab8 and overexpression of Rab8 in sensitive cells enhances resistance to cisplatin, possibly by increasing the secretion of the cisplatin-resistance-associated protein TMEM205 (transmembrane protein 205), with which it co-localizes [58].

A role for GAPs in cancer

As mentioned above, the activity of Rab proteins is regulated by GEFs and GAPs, and some of them may well play a role in cancer. PRC17 (prostate cancer gene 17) (TBC1D3A) is a GAP for Rab5, it is overexpressed in metastatic

prostate cancer and its overexpression transforms NIH 3T3 fibroblasts [59]. Another GAP for Rab5 implicated in cell transformation is the regulatory subunit of class I PI3K (phosphoinositide 3-kinase) p85α: if p85α is impaired in its GAP function, it induces loss of contact inhibition, growth in soft agar and tumour formation in nude mice, owing to disrupted regulation of PDGFR (platelet-derived growth factor receptor) trafficking and increased downstream signalling to Akt [60]. Another GAP recently described in cancer is TBC1D7, a GAP for Rab17: it is overexpressed in lung cancer, where it is associated with poor prognosis, and promotes cell growth [61]. Also, TBC1D16 has been identified using a bioinformatic approach as a driver gene for melanoma and its depletion reduces melanoma cell growth [48]. However, its substrate Rab is not yet known.

Rabs as therapeutic targets

Since Rab proteins are implicated in multiple aspects of tumour progression, they might represent new targets for anticancer therapies. Although no Rab-specific drug has been developed to date, it is important to mention encouraging results obtained with inhibitors of RabGGTase (Rab geranylgeranyltransferase). All Rabs are post-translationally modified mostly by the addition of two geranylgeranyl groups at their C-termini by RabGGTase and this modification is essential for the association of Rab proteins to membranes. The *gunmetal* mouse model, in which Rab prenylation is severely reduced owing to an 80% decrease in RabGGTase activity, presents only hypopigmentation and altered platelet biogenesis, showing that a decrease in Rab prenylation would be generally well tolerated [62]. RabGGTase is overexpressed in some tumours and some farnesyltransferase inhibitors that have a pro-apoptotic effect indeed target RabGGTase and can be mimicked by depletion of RabGGTase [63]. A biphosphonate derivative, 3-PEHPC [3-(3-pyridyl)-2-hydroxy-2-phosphonopropanoic acid], which is highly specific for RabGGTase, has an anti-resorptive activity in osteoclasts [64], induces apoptosis of human myeloma cells *in vitro* [65] and prevents bone disease *in vivo* in a mouse model [66]. Furthermore, it inhibits metastatic cell invasion *in vitro* [67] and reduces skeletal tumour growth *in vivo* [68]. These findings highlight the potentiality of Rab inhibition as a therapeutic approach.

Concluding remarks

Mutations in some Rabs or in regulators of the Rab GTP/GDP cycle had been identified as causative of some severe complex hereditary diseases [69]. However, the potential role of Rab proteins in the context of tumour progression has only begun to emerge in recent years. As presented above, some functions for Rab GTPases in cancer development have now been elucidated and the emerging picture points to the importance of intracellular trafficking as a co-ordinator of the cross-talk between signalling pathways promoting proliferation, migration and invasion. Also, Rabs have been shown to direct the communication between cancerous and stromal cells, and are thus able to modulate the creation of a metastatic niche favourable to tumour growth, an emerging concept that is attracting much interest as a therapeutic target. Although inhibitors of specific Rab proteins have not yet been developed, they could represent a potential tool as novel anticancer drugs in the years to come.

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References

1 Diekmann, Y., Seixas, E., Gouw, M., Tavares-Cadete, F., Seabra, M.C. and Pereira-Leal, J.B. (2011) Thousands of rab GTPases for the cell biologist. PLoS Comput. Biol. **7**, e1002217
2 Stenmark, H. (2009) Rab GTPases as coordinators of vesicle traffic. Nat. Rev. Mol. Cell Biol. **10**, 513–525
3 He, H., Dai, F., Yu, L., She, X., Zhao, Y., Jiang, J., Chen, X. and Zhao, S. (2002) Identification and characterization of nine novel human small GTPases showing variable expressions in liver cancer tissues. Gene Expression **10**, 231–242
4 Shimada, K., Uzawa, K., Kato, M., Endo, Y., Shiiba, M., Bukawa, H., Yokoe, H., Seki, N. and Tanzawa, H. (2005) Aberrant expression of RAB1A in human tongue cancer. Br. J. Cancer **92**, 1915–1921
5 Culine, S., Honore, N., Closson, V., Droz, J.P., Extra, J.M., Marty, M., Tavitian, A. and Olofsson, B. (1994) A small GTP-binding protein is frequently overexpressed in peripheral blood mononuclear cells from patients with solid tumours. Eur. J. Cancer **30A**, 670–674
6 Yao, R., Wang, Y., Lubet, R.A. and You, M. (2002) Differentially expressed genes associated with mouse lung tumor progression. Oncogene **21**, 5814–5821
7 Tan, P.Y., Chang, C.W., Chng, K.R., Wansa, K.D., Sung, W.K. and Cheung, E. (2012) Integration of regulatory networks by NKX3-1 promotes androgen-dependent prostate cancer survival. Mol. Cell. Biol. **32**, 399–414
8 Amillet, J.M., Ferbus, D., Real, F.X., Antony, C., Muleris, M., Gress, T.M. and Goubin, G. (2006) Characterization of human Rab20 overexpressed in exocrine pancreatic carcinoma. Hum. Pathol. **37**, 256–263
9 Kotzsch, M., Sieuwerts, A.M., Grosser, M., Meye, A., Fuessel, S., Meijer-van Gelder, M.E., Smid, M., Schmitt, M., Baretton, G., Luther, T. et al. (2008) Urokinase receptor splice variant uPAR-del4/5-associated gene expression in breast cancer: identification of rab31 as an independent prognostic factor. Breast Cancer Res. Treat. **111**, 229–240
10 Luo, H., Zhang, H., Zhang, Z., Zhang, X., Ning, B., Guo, J., Nie, N., Liu, B. and Wu, X. (2009) Down-regulated miR-9 and miR-433 in human gastric carcinoma. J. Exp. Clin. Cancer Res. **28**, 82
11 Yang, Q., Jie, Z., Cao, H., Greenlee, A.R., Yang, C., Zou, F. and Jiang, Y. (2011) Low-level expression of let-7a in gastric cancer and its involvement in tumorigenesis by targeting RAB40C. Carcinogenesis **32**, 713–722
12 Wang, R., Wang, Z.X., Yang, J.S., Pan, X., De, W. and Chen, L.B. (2011) MicroRNA-451 functions as a tumor suppressor in human non-small cell lung cancer by targeting ras-related protein 14 (RAB14). Oncogene **30**, 2644–2658
13 Tanaka, T., Arai, M., Wu, S., Kanda, T., Miyauchi, H., Imazeki, F., Matsubara, H. and Yokosuka, O. (2011) Epigenetic silencing of microRNA-373 plays an important role in regulating cell proliferation in colon cancer. Oncol. Rep. **26**, 1329–1335

14 Mori, Y., Yin, J., Sato, F., Sterian, A., Simms, L.A., Selaru, F.M., Schulmann, K., Xu, Y., Olaru, A., Wang, S. et al. (2004) Identification of genes uniquely involved in frequent microsatellite instability colon carcinogenesis by expression profiling combined with epigenetic scanning. Cancer Res. **64**, 2434–2438
15 Shibata, D., Mori, Y., Cai, K., Zhang, L., Yin, J., Elahi, A., Hamelin, R., Wong, Y.F., Lo, W.K., Chung, T.K. et al. (2006) RAB32 hypermethylation and microsatellite instability in gastric and endometrial adenocarcinomas. Int. J. Cancer **119**, 801–806
16 Wu, C.Y., Tseng, R.C., Hsu, H.S., Wang, Y.C. and Hsu, M.T. (2009) Frequent down-regulation of hRAB37 in metastatic tumor by genetic and epigenetic mechanisms in lung cancer. Lung Cancer **63**, 360–367
17 Mueller, D.W., Rehli, M. and Bosserhoff, A.K. (2009) miRNA expression profiling in melanocytes and melanoma cell lines reveals miRNAs associated with formation and progression of malignant melanoma. J. Invest. Dermatol. **129**, 1740–1751
18 Ho, J.R., Chapeaublanc, E., Kirkwood, L., Nicolle, R., Benhamou, S., Lebret, T., Allory, Y., Southgate, J., Radvanyi, F. and Goud, B. (2012) Deregulation of rab and rab effector genes in bladder cancer. PLoS ONE **7**, e39469
19 Yoon, S.O., Shin, S. and Mercurio, A.M. (2005) Hypoxia stimulates carcinoma invasion by stabilizing microtubules and promoting the Rab11 trafficking of the $\alpha 6\beta 4$ integrin. Cancer Res. **65**, 2761–2769
20 Cheng, K.W., Lahad, J.P., Kuo, W.L., Lapuk, A., Yamada, K., Auersperg, N., Liu, J., Smith-McCune, K., Lu, K.H., Fishman, D. et al. (2004) The RAB25 small GTPase determines aggressiveness of ovarian and breast cancers. Nat. Med. **10**, 1251–1256
21 Caswell, P.T., Spence, H.J., Parsons, M., White, D.P., Clark, K., Cheng, K.W., Mills, G.B., Humphries, M.J., Messent, A.J., Anderson, K.I. et al. (2007) Rab25 associates with $\alpha 5\beta 1$ integrin to promote invasive migration in 3D microenvironments. Dev. Cell **13**, 496–510
22 Dozynkiewicz, M.A., Jamieson, N.B., Macpherson, I., Grindlay, J., van den Berghe, P.V., von Thun, A., Morton, J.P., Gourley, C., Timpson, P., Nixon, C. et al. (2012) Rab25 and CLIC3 collaborate to promote integrin recycling from late endosomes/lysosomes and drive cancer progression. Dev. Cell **22**, 131–145
23 Caswell, P.T., Chan, M., Lindsay, A.J., McCaffrey, M.W., Boettiger, D. and Norman, J.C. (2008) Rab-coupling protein coordinates recycling of $\alpha 5\beta 1$ integrin and EGFR1 to promote cell migration in 3D microenvironments. J. Cell Biol. **183**, 143–155
24 Zhang, J., Liu, X., Datta, A., Govindarajan, K., Tam, W.L., Han, J., George, J., Wong, C., Ramnarayanan, K., Phua, T.Y. et al. (2009) RCP is a human breast cancer-promoting gene with Ras-activating function. J. Clin. Invest. **119**, 2171–2183
25 Muller, P.A., Caswell, P.T., Doyle, B., Iwanicki, M.P., Tan, E.H., Karim, S., Lukashchuk, N., Gillespie, D.A., Ludwig, R.L., Gosselin, P. et al. (2009) Mutant p53 drives invasion by promoting integrin recycling. Cell **139**, 1327–1341
26 Goldenring, J.R. and Nam, K.T. (2011) Rab25 as a tumour suppressor in colon carcinogenesis. Br. J. Cancer **104**, 33–36
27 Nam, K.T., Lee, H.J., Smith, J.J., Lapierre, L.A., Kamath, V.P., Chen, X., Aronow, B.J., Yeatman, T.J., Bhartur, S.G., Calhoun, B.C. et al. (2011) Loss of Rab25 promotes the development of intestinal neoplasia in mice and is associated with human colorectal adenocarcinomas. J. Clin. Invest. **120**, 840–849
28 Cheng, J.M., Ding, M., Aribi, A., Shah, P. and Rao, K. (2006) Loss of RAB25 expression in breast cancer. Int. J. Cancer **118**, 2957–2964
29 Cheng, J.M., Volk, L., Janaki, D.K., Vyakaranam, S., Ran, S. and Rao, K.A. (2009) Tumor suppressor function of Rab25 in triple negative breast cancer. Int. J. Cancer **126**, 2799–2812
30 Pellinen, T., Arjonen, A., Vuoriluoto, K., Kallio, K., Fransen, J.A. and Ivaska, J. (2006) Small GTPase Rab21 regulates cell adhesion and controls endosomal traffic of $\beta 1$-integrins. J. Cell Biol. **173**, 767–780
31 Torres, V.A., Mielgo, A., Barbero, S., Hsiao, R., Wilkins, J.A. and Stupack, D.G. (2010) Rab5 mediates caspase-8-promoted cell motility and metastasis. Mol. Biol. Cell **21**, 369–376
32 Yang, P.S., Yin, P.H., Tseng, L.M., Yang, C.H., Hsu, C.Y., Lee, M.Y., Horng, C.F. and Chi, C.W. (2011) Rab5A is associated with axillary lymph node metastasis in breast cancer patients. Cancer Sci. **102**, 2172–2178
33 Liu, S.S., Chen, X.M., Zheng, H.X., Shi, S.L. and Li, Y. (2011) Knockdown of Rab5a expression decreases cancer cell motility and invasion through integrin-mediated signaling pathway. J. Biomed. Sci. **18**, 58
34 Fukui, K., Tamura, S., Wada, A., Kamada, Y., Igura, T., Kiso, S. and Hayashi, N. (2007) Expression of Rab5a in hepatocellular carcinoma: possible involvement in epidermal growth factor signaling. Hepatol. Res. **37**, 957–965
35 Bravo-Cordero, J.J., Marrero-Diaz, R., Megias, D., Genis, L., Garcia-Grande, A., Garcia, M.A., Arroyo, A.G. and Montoya, M.C. (2007) MT1-MMP proinvasive activity is regulated by a novel Rab8-dependent exocytic pathway. EMBO J. **26**, 1499–1510
36 Williams, K.C. and Coppolino, M.G. (2011) Phosphorylation of membrane type 1-matrix metalloproteinase (MT1-MMP) and its vesicle-associated membrane protein 7 (VAMP7)-dependent trafficking facilitate cell invasion and migration. J. Biol. Chem. **286**, 43405–43416
37 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. (2010) The secretory small GTPase Rab27B regulates invasive tumor growth and metastasis through extracellular HSP90α. J. Natl. Cancer Inst. **102**, 866–880
38 Montel, V., Huang, T.Y., Mose, E., Pestonjamasp, K. and Tarin, D. (2005) Expression profiling of primary tumors and matched lymphatic and lung metastases in a xenogeneic breast cancer model. Am. J. Pathol. **166**, 1565–1579
39 Dong, W.W., Mou, Q., Chen, J., Cui, J.T., Li, W.M. and Xiao, W.H. (2012) Differential expression of Rab27A/B correlates with clinical outcome in hepatocellular carcinoma. World J. Gastroenterol. **18**, 1806–1813
40 Wang, J.S., Wang, F.B., Zhang, Q.G., Shen, Z.Z. and Shao, Z.M. (2008) Enhanced expression of Rab27A gene by breast cancer cells promoting invasiveness and the metastasis potential by secretion of insulin-like growth factor-II. Mol. Cancer Res. **6**, 372–382
41 Brobrie, A., Krumeich, S., Reyal, F., Recchi, C., Moita, L.F., Seabra, M.C., Ostrowski, M. and Thery, C. (2012) Rab27a supports exosome-dependent and -independent mechanisms that modify the tumor microenvironment and can promote tumor progression. Cancer Res. **72**, 4920–4930
42 Barbarin, A. and Frade, R. (2011) Procathepsin L secretion, which triggers tumour progression, is regulated by Rab4a in human melanoma cells. Biochem. J. **437**, 97–107
43 Cirri, P. and Chiarugi, P. (2012) Cancer-associated-fibroblasts and tumour cells: a diabolic liaison driving cancer progression. Cancer Metastasis Rev. **31**, 195–208
44 Hooper, S., Gaggioli, C. and Sahai, E. (2010) A chemical biology screen reveals a role for Rab21-mediated control of actomyosin contractility in fibroblast-driven cancer invasion. Br. J. Cancer **102**, 392–402
45 Iero, M., Valenti, R., Huber, V., Filipazzi, P., Parmiani, G., Fais, S. and Rivoltini, L. (2008) Tumour-released exosomes and their implications in cancer immunity. Cell Death Differ. **15**, 80–88
46 Ostrowski, M., Carmo, N.B., Krumeich, S., Fanget, I., Raposo, G., Savina, A., Moita, C.F., Schauer, K., Hume, A.N., Freitas, R.P. et al. (2009) Rab27a and Rab27b control different steps of the exosome secretion pathway. Nat. Cell Biol. **12**, 19–30
47 Peinado, H., Aleckovic, M., Lavotshkin, S., Matei, I., Costa-Silva, B., Moreno-Bueno, G., Hergueta-Redondo, M., Williams, C., Garcia-Santos, G., Ghajar, C.M. et al. (2012) Melanoma exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype through MET. Nat. Med. **18**, 883–891
48 Akavia, U.D., Litvin, O., Kim, J., Sanchez-Garcia, F., Kotliar, D., Causton, H.C., Pochanard, P., Mozes, E., Garraway, L.A. and Pe'er, D. (2010) An integrated approach to uncover drivers of cancer. Cell **143**, 1005–1017
49 Young, J., Menetrey, J. and Goud, B. (2010) RAB6C is a retrogene that encodes a centrosomal protein involved in cell cycle progression. J. Mol. Biol. **397**, 69–88
50 Pellinen, T., Tuomi, S., Arjonen, A., Wolf, M., Edgren, H., Meyer, H., Grosse, R., Kitzing, T., Rantala, J.K., Kallioniemi, O. et al. (2008) Integrin trafficking regulated by Rab21 is necessary for cytokinesis. Dev. Cell **15**, 371–385
51 Eggenschwiler, J.T., Espinoza, E. and Anderson, K.V. (2001) Rab23 is an essential negative regulator of the mouse Sonic hedgehog signalling pathway. Nature **412**, 194–198
52 Chi, S., Xie, G., Liu, H., Chen, K., Zhang, X., Li, C. and Xie, J. (2012) Rab23 negatively regulates Gli1 transcriptional factor in a Su(Fu)-dependent manner. Cell. Signalling **24**, 1222–1228
53 Hou, Q., Wu, Y.H., Grabsch, H., Zhu, Y., Leong, S.H., Ganesan, K., Cross, D., Tan, L.K., Tao, J., Gopalakrishnan, V. et al. (2008) Integrative genomics identifies RAB23 as an invasion mediator gene in diffuse-type gastric cancer. Cancer Res. **68**, 4623–4630
54 Liu, Y.J., Wang, Q., Li, W., Huang, X.H., Zhen, M.C., Huang, S.H., Chen, L.Z., Xue, L. and Zhang, H.W. (2007) Rab23 is a potential biological target for treating hepatocellular carcinoma. World J. Gastroenterol. **13**, 1010–1017
55 Fu, D. and Arias, I.M. (2012) Intracellular trafficking of P-glycoprotein. Int. J. Biochem. Cell Biol. **44**, 461–464

56 Ferrandiz-Huertas, C., Fernandez-Carvajal, A. and Ferrer-Montiel, A. (2011) Rab4 interacts with the human P-glycoprotein and modulates its surface expression in multidrug resistant K562 cells. Int. J. Cancer **128**, 192–205
57 Shan, J., Mason, J.M., Yuan, L., Barcia, M., Porti, D., Calabro, A., Budman, D., Vinciguerra, V. and Xu, H. (2000) Rab6c, a new member of the rab gene family, is involved in drug resistance in MCF7/AdrR cells. Gene **257**, 67–75
58 Shen, D.W. and Gottesman, M.M. (2012) RAB8 enhances TMEM205-mediated cisplatin resistance. Pharm. Res. **29**, 643–650
59 Pei, L., Peng, Y., Yang, Y., Ling, X.B., Van Eyndhoven, W.G., Nguyen, K.C., Rubin, M., Hoey, T., Powers, S. and Li, J. (2002) *PRC17*, a novel oncogene encoding a Rab GTPase-activating protein, is amplified in prostate cancer. Cancer Res. **62**, 5420–5424
60 Chamberlain, M.D., Chan, T., Oberg, J.C., Hawrysh, A.D., James, K.M., Saxena, A., Xiang, J. and Anderson, D.H. (2008) Disrupted RabGAP function of the p85 subunit of phosphatidylinositol 3-kinase results in cell transformation. J. Biol. Chem. **283**, 15861–15868
61 Sato, N., Koinuma, J., Ito, T., Tsuchiya, E., Kondo, S., Nakamura, Y. and Daigo, Y. (2010) Activation of an oncogenic TBC1D7 (TBC1 domain family, member 7) protein in pulmonary carcinogenesis. Genes Chromosomes Cancer **49**, 353–367
62 Detter, J.C., Zhang, Q., Mules, E.H., Novak, E.K., Mishra, V.S., Li, W., McMurtrie, E.B., Tchernev, V.T., Wallace, M.R., Seabra, M.C. et al. (2000) Rab geranylgeranyl transferase α mutation in the gunmetal mouse reduces Rab prenylation and platelet synthesis. Proc. Natl. Acad. Sci. U.S.A. **97**, 4144–4149
63 Lackner, M.R., Kindt, R.M., Carroll, P.M., Brown, K., Cancilla, M.R., Chen, C., de Silva, H., Franke, Y., Guan, B., Heuer, T. et al. (2005) Chemical genetics identifies Rab geranylgeranyl transferase as an apoptotic target of farnesyl transferase inhibitors. Cancer Cell **7**, 325–336
64 Coxon, F.P., Helfrich, M.H., Larijani, B., Muzylak, M., Dunford, J.E., Marshall, D., McKinnon, A.D., Nesbitt, S.A., Horton, M.A., Seabra, M.C. et al. (2001) Identification of a novel phosphonocarboxylate inhibitor of Rab geranylgeranyl transferase that specifically prevents Rab prenylation in osteoclasts and macrophages. J. Biol. Chem. **276**, 48213–48222
65 Roelofs, A.J., Hulley, P.A., Meijer, A., Ebetino, F.H., Russell, R.G. and Shipman, C.M. (2006) Selective inhibition of Rab prenylation by a phosphonocarboxylate analogue of risedronate induces apoptosis, but not S-phase arrest, in human myeloma cells. Int. J. Cancer **119**, 1254–1261
66 Lawson, M.A., Coulton, L., Ebetino, F.H., Vanderkerken, K. and Croucher, P.I. (2008) Geranylgeranyl transferase type II inhibition prevents myeloma bone disease. Biochem. Biophys. Res. Commun. **377**, 453–457
67 Boissier, S., Ferreras, M., Peyruchaud, O., Magnetto, S., Ebetino, F.H., Colombel, M., Delmas, P., Delaisse, J.M. and Clezardin, P. (2000) Bisphosphonates inhibit breast and prostate carcinoma cell invasion, an early event in the formation of bone metastases. Cancer Res. **60**, 2949–2954
68 Fournier, P.G., Daubine, F., Lundy, M.W., Rogers, M.J., Ebetino, F.H. and Clezardin, P. (2008) Lowering bone mineral affinity of bisphosphonates as a therapeutic strategy to optimize skeletal tumor growth inhibition *in vivo*. Cancer Res. **68**, 8945–8953
69 Seabra, M.C., Mules, E.H. and Hume, A.N. (2002) Rab GTPases, intracellular traffic and disease. Trends Mol. Med. **8**, 23–30

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