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Rab25 in Cancer: A brief update

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1.0 Introduction

Rab25 (Rab11c, Catx8) identified by Goldenring et al., in 1993¹ as a member of the Rab family of GTPases, shares 63% homology with the ubiquitous Rab11a. Rab25 contains a different GTP-binding sequence, WDTAGLE, compared to other Rab members, making it a constitutively active Rab GTPase, although this remains to be confirmed biochemically. At the cellular level, Rab25 function is thought to mirror that of Rab11a. Both of them are spatially and functionally associated with apical recycling and transcytosis pathways in polarized epithelial cells^{2,3}. Loss of cell polarity being an essential hallmark of cancer implicates Rab25 related trafficking and its impact on epithelial cell polarity program^{4,5} in cancer progression.

Till date about the seventy existing publications on Rab25 build our understanding regarding the localization, trafficking and other functions of this epithelial specific GTPase. Most importantly, by uncovering the role of Rab25 in solid tumors, we are beginning to understand how abnormal vesicular trafficking impacts cancer progression. Recently, several reviews were published updating the role of Rab25 and vesicular trafficking in cancer^{6–9}. More recently, global interest in Rab25 surged due to repeated appearance of Rab25 in multiple cancer screens across diverse studies in different parts of the world.

Here we are summarizing the past and more recent literature on Rab25 and its role in cancer, highlighting the mechanical insights that we have gained in the last few years.

2.0 Context dependent role of Rab25 in Cancer: Oncogene or Tumor Suppressor?

2.1 Rab25 as an Oncogene

The first reported association of Rab25 with epithelial cancers came from a study by He et al, where they characterized nine human GTPases showing variable gene expression in liver cancer. Rab25 was one of the six Rab proteins that were upregulated in hepatocellular carcinoma¹⁰. However, the most exhaustive evidence for Rab25 as an oncogene came from a pioneering study by Cheng et al, from our lab where Rab25 was identified as the driver of the 1q22 amplicon, a region frequently amplified in ovarian cancers^{11,12}. Rab25 was upregulated at DNA copy number, RNA and protein levels and associated with poor outcome in clinical studies. Overexpression of Rab25 in ovarian cancer cell lines increased quintessential hallmarks of cancer namely, anchorage independent growth, cell proliferation, and reduced apoptosis and anoikis, mostly in a PI3K dependent manner. Overall both *in vitro* and *in vivo* evidences showed that Rab25 contributed to aggressiveness of ovarian and breast cancers^{11,12}. Subsequently, others reported similar findings in ovarian cancer models¹³, making Rab25, not only a key oncogene for ovarian cancers but also an important biomarker. Rab25 expression varied based on cellular lineage and facilitated differential diagnosis in cases presenting a highly heterogeneous disease¹⁴. Specifically, Rab25 gene was a part of a signature that was upregulated in primary peritoneal serous carcinoma but not in highly metastatic diffused peritoneal malignant mesothelioma^{15,16}. The broad range

of Rab25 expression in ovarian cancers was also detectable in bioinformatics analysis of copy number variation and DNA methylation across primary serous ovarian tumors samples from the Cancer Genome Atlas Project suggesting that Rab25 is a sensitive biomarker in addition to a potential therapeutic target for ovarian cancers¹⁷.

In another study, utilizing the fact that androgens are implicated in the etiology of ovarian cancer, Sheach, et al., subjected androgen receptor expressing ovarian cancer cell lines to androgen treatment and tested for changes in global gene expression profiles. Surprisingly, Rab25 and Rab35 were the most prominent hits both at gene and protein level amongst the 121-upregulated genes panel.

Rab25 expression also correlated with histological grade in patients and emerged as an androgen responsive gene in ovarian cancer, identifying Rab25 as a clinical biomarker for AR function in ovarian cancers¹⁸.

2.2 Rab25 as a Tumor Suppressor

Unlike ovarian cancers, the role of Rab25 is far more ambiguous in breast, colon and intestinal carcinomas, although it still remains a major player in disease progression.

In a novel breast cancer cell line generated from human mammary epithelial cells by Rao's group (by transducing the Q61L mutant Ras in these cells and immortalizing with the catalytic subunit of telomerase), mutations in chromosome 1q22-23 locus resulted in the loss of Rab25, leading to oncogenic transformation. This was the first report of Rab25 as a tumor suppressor¹⁹. The same group followed up their earlier work by showing that Rab25 is lost in triple negative breast cancer, represented by MDA MB231 cell line and introduction of Rab25 in these cells partially reverses oncogenic progression²⁰. In their model, ectopic Rab25, in addition to enhancing apoptosis, also suppressed angiogenesis and invasion by regulating VEGF-A and VEGFR1 expression²⁰. However, this observation is contradictory to what our lab has observed in various broad spectrum analysis of breast cancer patients expression profiles as well as in cell lines where Rab25 is up regulated and is associated increased tumorigenicity and poor clinical outcome^{11,12}. Recently, increased levels of Rab25mRNA (real-time PCR) and protein (immunohistochemistry) were reported in tissues from invasive ductal carcinoma patients with lymphatic metastasis compared to those without lymph metastasis²¹, again implicating Rab25 as an oncogene in breast cancer.

It is important to note that breast cancer is a highly heterogeneous disease, populated by diverse cells types^{22,23}. Each molecular subtype has distinct gene expression profiles and overall outcome. Reconciling the conflicting evidence, it can be speculated that Rab25 is associated with specific cell lineage in breast cancer. Our unpublished data also strongly supports the notion that Rab25 is indeed an oncogene in hormone receptor positive, luminal B subtype of breast cancers whereas in subsets of basal subtypes (lacking hormone receptors) Rab25 is mostly lost, possibly playing a tumor suppressive role. In fact recently, patient data from the cancer genome atlas project (TCGA) presented the differential methylation status of Rab25 between luminal and basal subtypes of breast cancer with significant increase in methylation in the latter group (unpublished). Furthermore, with the reevaluation of molecular features of intrinsic subtypes of breast cancer and emergence of the new "claudin low" group within the basal category (exemplified by the MDA MB231 cell line), we find that Rab25 levels are concomitantly undetectable along with low claudin levels in these mesenchymal breast cancer subtypes, clinically closest to metaplastic breast cancers^{22,23}. So it is safe to conclude that in breast cancers, the oncogenic role of Rab25 is context dependent. In fact Yin et al, provide evidence that the level of Rab25 is significantly higher in ER/PR+ve patient samples than the ER/PR-ve ones, although the correlation of Rab25 with lymph metastasis holds true in both cases²¹.

Interestingly, probing further into the molecular heterogeneity of breast cancers, Leth-Larsen et al, performed an elegant study segregating the tumor initiating cells from the CD44+ high population in triple negative breast cancer cell lines. Many of the triple negative cell lines are composed at least two distinct phenotypic cell lineages. They found that the CD44 high population was a mixture of mesenchymal/basal B type cells and epithelial or luminal/basal A type cells. Unexpectedly they found that the CD44 high/CD24 low -luminal/basal A type retained stem cell like tumor initiating, mammosphere forming and chemo-resistant properties, instead of the mesenchymal subpopulation. In their study, Rab25 along with Muc1 and few other candidate genes were positively correlated with tumor initiating features and could potentially be utilized to predict distant metastasis in these estrogen receptor negative tumors²⁴.

Our lab is currently studying the context dependent role of Rab25 in luminal vs. basal subtypes to gain mechanistic insights how this trafficking protein serves both as tumor suppressor and tumor promoter. This dichotomy was addressed by Tang⁸, and earlier by Mills et al.⁷, offering insightful explanations. Ongoing work in our lab supports that the interaction of Rab25 with its effector, Rab Coupling Protein (RCP or Rab11Fip1), which itself is a potent oncogene driving the 8p11–12 amplicon, with high frequency of amplification in breast cancer²⁵, is of critical importance in understanding the clinical role of Rab25 in breast cancer.

In another instance of ambiguity, Rab25 previously reported to be present in colon carcinoma cell lines¹ was then shown to be lost in human colonic neoplasia^{26,27} as well as in intestinal neoplasia in mice and humans²⁷ in two recent works. Colorectal adenocarcinomas with low Rab25 correlated with shorter patient survival. Since Rab25 is essential for polarized trafficking to cell surface, the authors suggest that loss of Rab25 alters cell polarity and induces transformation.

Thus, based on the cases mentioned above, it is imperative for us to evaluate the role of Rab25 in case specific manner rather than view it as a global oncogene or a tumor suppressor. Instead of using Rab25 alone as a biomarker, it will be invaluable to generate a Rab25 signature with more powerful prognostic and predictive value.

2.3 Frequent appearance of Rab25 in various cancer screening studies

As highlighted in the previous section, the role of Rab25 has been studied in greater detail in a handful of cancers gaining significant mechanistic insights. However, Rab25 is gaining global prominence, as it is repeatedly features in gene signatures of a wide variety of cancers. However, these studies did not analyze the functional role of Rab25 in the respective diseases but they do open up the opportunity for groups focusing on Rab GTPases to gain more insights into the role of trafficking in various cancers.

In Wilm's tumors, gain in the 1q22 region housing Rab25 segregated histologically favorable tumors that eventually relapsed from those that remained relapse free. RT-PCT validation of a recurring region of 1q, namely 1q22-q23.1, identified 5 candidate genes including Rab25²⁸.

Another group studying frequent amplification and overexpression of PPMD1 (protein phosphatase magnesium D-delta 1) in cancers with poor prognosis, measured global gene expression changes in several ER+ve breast cancer cell lines with RNAi mediated down-regulation of PPMD. Rab25 was noted in the shortlisted genes with maximum differential expression^{29,30}, supporting its key regulatory role in ER+ve breast cancers.

One group assayed the role of TIMP1 in tumor progression using triple negative MDAMB231 cells overexpressing TIMP1³¹. TIMP1, known to inhibit matrix metalloproteases-induced invasion, is often upregulated in breast cancers and is associated with poor prognosis. The authors testing the effect of TIMP1 overexpression both *in vitro* and *in vivo* found different sets of gene networks altered under each setting. Notably, Rab25 featured only in the *in vivo* xenograft panel comparing control vs. over expressing cells³¹. Questions such as, if TIMP1 is a regulator of Rab25 transcription and/or protein expression arise from this study. Since MDAMB231 cell line itself comprises of heterogeneous cell populations, it raises the question if TIMP1 is affecting the epithelial/basal A cell population or other populations.

Considering that Rab25 is reportedly a tumor suppressor in MDAMB231 cells, TIMP1 could be changing the context dependent function of Rab25. Further studies are essential to explain how Rab25 levels are manipulated by TIMP1 in a cell line that has very low endogenous levels of Rab25.

In endometrial cancers, Kruppel-like factor 9(KLF9), which transcriptionally regulates uterine cell proliferation, differentiation and adhesion during pregnancy, is deregulated. Suppression of KLF9 in a endometrial cancer cell line induced a gene network comprising of 24 genes with wide functional diversity including those involved in aldehyde metabolism, cell motility, cell signaling as well transcription regulation. Once again, Rab25 emerged a prominent part of this signature, implicating it in endometrial cancer progression³².

Lung cancer is another instance of a clinically heterogeneous disease with at least 4 histopathological subtypes. Molecular stratification of this subtypes using principal component analysis of DNA microarrays and RT PCR data from 12 representative lung cancer lines identified 12 genes including Rab25 and CDH-1³³, underscoring association of Rab25 with cell lineage and possibly polarization status.

Multiple studies so far including those conducted in our laboratory imply an association of Rab25 with cell lineage and differentiation state. Although not much is known about Rab25 in context of stem cells or cancer stem cells, a recent study encourages a closer look. In order to improve stem cell therapy, it is essential to identify tumorigenic genes within induced pluripotent stem cells (iPSC) that could lead to the feared oncogenic onslaught. Recently, a group utilizing bioinformatics analysis of a compilation of all available datasets on iPSCs and 11 differentiated cells lines identified a consensus gene list with over 500 genes, half of which were found in cancer tissues and cell lines. They found five of these genes to be overexpressed in iPSCs³⁴. Interestingly, only Rab25 was found in the iPSC differentiated cells, opening a huge opportunity to study the role of Rab25 in stem cell and differentiation, which would have a deep impact in our understanding its complex role in cancers, especially in breast cancer.

3.0 Mechanistic insights into the cellular function of Rab25 and its regulation

One of the most powerful oncogenic effects of Rab25 is driving metastatic progression following loss of cell polarity. Rab25 is implicated in cancer cell migration and invasion in multiple studies published from our lab and others^{11, 35}. The remarkable work of Jim Norman and his group pioneered our understanding of the molecular mechanisms of Rab25, especially how it affects metastasis. First in a seminal piece of work they showed a direct interaction between cytoplasmic end of beta1 integrin and Rab25, promoting cell migration, involving long pseudopodia in a 3D matrix. Basically, Rab25 decorated vesicles transport alpha5-beta1 integrins to the plasma membrane at the pseudopodia tip during fibronectin

stimulated cell migration and simultaneously maintain a readily available pool of the same at cell front³⁶.

A potential link between integrin recycling by Rab25 and the differential expression of Rab25 in TIMP1 overexpressing breast cancer cells growing as xenografts, as reported in the previous section³¹ remains to be tested, but may provide important clues to Rab25 function in triple negative breast cancer.

Although Rab25 and Rab11 were originally identified in apical recycling compartment and thought to be associated with long loop recycling (as opposed to short loop recycling via Rab4) a recent study using Hela cells and MDA MB231 cells, found that ectopic Rab25 acts predominantly in the short distance rapid recycling within cellular tips while Rab11 propelled a rear to front long distance transport in migrating cells³⁵. This study also noted that overexpression of Rab25 and Rab11 increased the overall speed of cell migration³⁵.

Another fascinating discovery from Norman's lab further elucidated Rab25 mediated integrin trafficking. Using photo-activation and biochemical approaches the group showed that Rab25 rescues lysosomally targeted integrins from degradation by transporting them back to the plasma membrane³⁷. The molecule that collaborates with Rab25 in achieving this retrograde transport is CLIC3, which, not surprisingly, is upregulated in Rab25 expressing cells³⁷. CLIC3, itself is an independent marker of lymph node metastasis and poor prognosis in pancreatic cancers, suggesting that Rab25 and its effectors create potent oncogenic network by deregulating vesicular trafficking of key signaling molecules that increases the aggressiveness of these cancers.

There is also an argument that Rab25 associated invasive phenotype is not caused only by actin based cytoskeletal changes, but also profoundly impacts microtubules, as observed during Rab25 induced transformation of rat intestinal epithelial cells³⁸.

The literature so far shows direct or indirect involvement of Rab25 in virtually all the classic hallmarks of cancer proposed by Hanahan and Weinberg, including proliferation, survival, evading apoptotic signals, angiogenesis, invasion and migration³⁹. In the last few years the field of oncology developed renewed interest in cancer cell metabolism reviving Otto Warburg's findings that cancer cells prefer aerobic glycolysis. In fact the increased glucose uptake of cancer cells facilitated the development of develop 18F-FD glucose PET as a standard diagnostic tool in various solid tumors^{40,41}, enlisting altered metabolism as a new hallmark of cancer⁴².

Recently, our laboratory showed for the very first time, the profound effect of Rab25 on cellular energetics. This is of immense importance because rapidly growing tumors frequently undergo metabolic stress arising from limited growth factors, nutrients and oxygen. The intercellular trafficking system is geared to rewire circulation of cellular resources to allow stressed cancer cells to survive. By conserving reserves, recycling glucose transporters and growth factors rather than degrading them, endosomal trafficking imparts a huge survival advantage. Rab25, as we showed our recent work, regulates cellular bioenergetics and autophagy⁴³ in cancer cells undergoing stress. It does so by activating AKT, leading to increased glucose uptake. Unexpectedly, Rab25 also facilitates accumulation of glycogen, an additional energy reserve for cells. We found that Rab25 overexpressing ovarian cells maintained higher levels of basal cellular ATP under metabolic stress conditions, once again protecting them from energy catastrophe that would otherwise trigger apoptosis. Importantly, a wide array of bioenergetic targets were enriched in 'Rab25-dependent' patient profiles and this combined signature significantly improved identification of patients with poor prognosis¹⁴. Moreover, recently another group also showed that loss of

Rab25 in ovarian cancer cells inhibit cell proliferation and induce autophagy¹⁴ suggesting a pivotal role for Rab25 in cellular energetics.

The big question remains how a gene like Rab25 with many critical pleiotropic effects is regulated. Till date there is little understanding of it. But a recent breakthrough by Xue et al., lays the foundation for future structural studies⁴⁴. By characterizing the human Rab25 promoter the authors found a CRE binding CREB that binds to the Rab25 core promoter region and activates it. They also found that certain PKA activators could induce phosphorylation of the CREB by exposing the CRE. CREB phosphorylation recruits cofactors and further opens up chromatic configuration, strengthening promoter activity and Rab25 expression⁴⁴.

4.0 Conclusions

Rab25 is a relatively new entrant in the field of Rab GTPases and we are only beginning to understand its role in disease progression, its various trafficking routes, the cargo it carries, its effectors and interactions and how it is regulated. So far its role as an oncogene is most convincing in ovarian cancers. Therefore its value as a clinical biomarker is also associated best with ovarian cancers⁴⁵. In case of breast cancers, Rab25 function is highly context dependent. We believe this is also true for colon and intestinal carcinomas and other cancers with heterogeneous lineage. What will greatly benefit the field is identification of Rab25 'interactomes' in different cancers and also within specific subtypes in each cancer.

Lastly, development of a robust Rab25 activity assay is absolutely essential to improve functional studies involving is important trafficking protein.

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