The role of the oncogenic Rab35 in cancer invasion, metastasis, and immune evasion, especially in leukemia

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ABSTRACT
The study of cancer has allowed researchers to describe some biological characteristics that tumor cells acquire during their development, known as the "hallmarks of cancer" but more research is needed to expand our knowledge about cancer biology and to generate new strategies of treatment. The role that RabGTPases might play in some hallmarks of cancer represents interesting areas of study since these proteins are frequently altered in cancer. However, their participation is not well known. Recently, Ras35 was recognized as an oncogenic RabGTPase and because of its association with different cellular functions, distinctly important in immune cells, a possible role of Rab35 in leukemia can be suggested. Nevertheless, the involvement of Rab35 in cancer remains poorly understood and its possible specific role in leukemia remains unknown. In this review, we analyze general aspects of the participation of RabGTPases in cancer, and especially, the plausible role of Rab35 in leukemia.

Introduction
Cancer and small GTPases
The first reference of cancer dates back to the Egyptians (1500–1600 BCE), who identified pathological conditions, tentatively, as cancer. Later, Hippocrates (c.460–360 BC) described a disease characterized by masses (onkos), with benign or malignant properties, for which, he coined the terms karkinos and karkinomas, respectively. Initial studies by Fibiger (1867–1928), Yamagawi, and Ichikawa (1915) contributed to the identification of microorganisms and chemicals as causes of cancer. Harvey’s study of Ras in 1964 constituted a major breakthrough in cancer research [1,2]. Ras was initially identified in rodents and human cancer cell lines as a viral gene with highly oncogenic properties. Subsequent studies observed frequent mutations in Ras in a wide spectrum of human cancers [1,3]. This prompted intensive research on the Ras structure, biochemistry, and biology. Ras was characterized as a small (molecular weight) GTP-binding protein and as a component of different signaling networks, such as Akt, epidermal growth factor receptor (EGFR), and phosphatidylinositol 3-kinase (PI3K). The focus on Ras allowed the discovery of the Ras superfamily, a group of related proteins comprising different subfamilies: RhoGTPases, ArfGTPases, RasGTPases, and RabGTPases [1,3].

RabGTPases constitute the largest subfamily of the Ras superfamily of proteins. They are considered master regulators of vesicular trafficking, whose alteration is frequently associated with several complex aspects of cancer [4,5]. Despite cancer’s complexity, several common biological characteristics associated with tumor development have been defined as the hallmarks of cancer. These include: limitless replicative potential, apoptosis and immune destruction evasion, sustained angiogenesis, self-sufficiency in growth signals, insensitivity to anti-growth signals, reprogramming of energy metabolism, tissue invasion and metastasis. (For more details, see refs [6,7]). These hallmarks of cancer address the complexity of cancer and highlight the role of many important players, as well as providing new targets of study, as is the case with the RabGTPases.

Cancer and RabGTPases
RabGTPases are frequently altered in cancer [4,5] and many times such alterations are associated with the
hallmarks of cancer, invasion and metastasis, and are the main causes of death related to cancer [8] (see Table 1). Invasion and metastasis allow tumor cells to develop a motile and invasive phenotype required to escape from the primary tumor. In this process, migrating tumor cells use similar mechanisms to those in normal physiological functions, such as embryonic morphogenesis, wound healing, and immune-cell trafficking [9,10], which require actin cytoskeletal dynamics, vesicular transport, and recycling of adhesion molecules to modify the cellular shape and stiffness in the interaction with the surrounding tissue structures [6,7,11]. Also, endocytic pathway abnormalities are common in tumors [11] and accumulating evidence has suggested a link among endosome dynamics, cell migration, and invasion [12,13]. The RabGTPase Rab35 is of interest in these processes because of its implication in vesicular trafficking, its close link to actin dynamics, and its recent description as an oncogenic protein [14–17].

**The RabGTPase Rab35**

Rab35 was originally discovered in a search for new RabGTPases in skeletal muscle and was described in 1994 [18]. Since then, Rab35 has been determined to be located mainly on the plasma membrane and on endosomes of different cell types. Multiple regulators of its activation and the description of many of its functions have also been found.

### Regulation of Rab35s activation

Rab35, similar to other small GTPases, cycles between a state of activation and inactivation regulated by different proteins (see Table 2). It is activated (bound to GTP) by the binding of GEF proteins (guanine-nucleotide exchange factor). This causes a conformational change in the GTPase structure increasing its affinity for GTP and reducing its affinity for GDP and GEF, followed by the

| RabGTPase alterations in cancer are frequently associated with the hallmarks of cancer invasion and metastasis. |
| --- |
| **Brain** | **Lung** | **Bladder** |
| Organs/RabGTPases | Organs/RabGTPases | Organs/RabGTPases |
| Rab3 [101], Rab27 [102], Rab35 [32], Rab1 [108], Rab4 [109], Rab5 [110–112], Rab6 [113,114], Rab27 [116–118], Rab35 [32,39,74], Rab40 [124], | Rab6 [103], Rab11 [104], Rab35 [78], Rab37 [105], Rab11, Rab20, Rab23, Rab27 [106], Rab25 [107], | Rab1 [110], Rab11 [104], Rab35 [78], Rab37 [105], Rab11, Rab20, Rab23, Rab27 [106], Rab25 [107], |
| **Colon/rectus** | **Stomach** | **Liver** |
| Rab25 [125], | Rab1 [126], Rab3 [127], Rab5 [128], Rab25 [129], | Rab23 [130], Rab40 [131], |
| **Pancreas** | **Skin** | **Blood** |
| Rab2 [142], Rab11 [132], Rab35 [32], | Rab7 [142], Rab7 [143,144], Rab4 [145], | Rab7 [138] |
| **Tongue** | **Head, neck and oral squamous cell carcinoma** | **Mesothelioma** |
| Rab1 [146] | Rab5, Rab7, Rab11 [147], Rab25 [148,149], | Rab7 [138] |

Superscripts refer to reference. The table shows reports of RabGTPase alterations in different organs and tissues, many of which were reported to be related with metastasis.
release of both. Rab35’s new conformational state, together with higher levels of GTP over GDP, favors the union of GTP. Once activated, Rab35 can interact temporarily with both effector proteins that associate with other elements. It can activate specific functional pathways and GAP proteins (GTPase-activating protein) that bind and increase the Rab35 GTPase activity and hence, the hydrolysis of GTP to GDP. Thus, Rab35 switches to the inactive state (bound to GDP). In turn, according to the cellular state, GEF proteins can either re-induce the activation of Rab35 or be maintained in the inactive state [14,19].

**Rab35’s functions**

Figure 1 schematically summarizes many functions and models of study so far related to Rab35, among which are cytokinesis, and apico-basal polarity (Fig. 1a) Rab35 participates in different processes required for cytokinesis in HeLa cells. This GTPase regulates the PIP2 (Phosphatidylinositol 4,5-bisphosphate) and SEPT2 localization for bridge stability [20], as well as endocytic recycling for proper completion of cytokinesis [21]. A mechanism has even been proposed for daughter cell separation by involving the Rab35’s participation over the localization of OCRL and MICAL1 (effector proteins for Rab35) in the intercellular bridge, which promoted the hydrolysis of PIP2 [22] and actin depolymerization by oxidoreduction [23], respectively. Also, this GTPase is capable of linking cytokinesis to the initiation of apico-basal polarity (in MDCK cells), by controlling the localization of intracellular vesicles containing apical determinants (aPKC, Cdc42, Crumbs3, and podocalyxin) [24]. Recycling of plasma membrane components (Fig. 1b). Rab35 participates in recycling of many membrane components, among them, RME-2 yolk receptors [27], KCa2.3 (Ca2+-activated K+ Channel) [25], TFR, transferrin receptor (in different cell types, such as HeLa [20], HTB-9 [28], and Jurkat cells [26]), GLUT4 [29], M-cadherins [30], β1-integrin, EGF receptors, and N-cadherin [32]. Also, this GTPase is related to the recycling of plasma membrane components of the immune response, such as Major Histocompatibility Complex Class I (MHC I) [31], peptide-Major Histocompatibility Complex Class II (pMHC II) [33], and the zeta (ζ) chain [26], part of the TCR (T cell receptor) and Endocytosis (Fig. 1c). Rab35 participates in different types of endocytosis, in clathrin-mediated
endocytosis (CME) and clathrin-independent endocytosis (CIE) [34], and in Phagocytosis of several particles: for example, *E. coli* by *Drosophila* [35], erythrocytes, by *Entamoeba histolytica* [36] and by Raw 264.7 cells [38], Raw cells also internalize zymosan [37]. Specifically, it is reported that Rab35 participates in different aspects of phagocytosis, such as phagosome formation (in *E. histolytica* [36] and in Raw 264.7 cells [37,38]), filopodia and lamellipodia generation [35], ROS production [39], as well as phagolysosome fusion (HeLa, Raw 264.7 cells [40] and in *E. histolytica* [36]). In addition, Rab35 participates in Autophagy [41], Exocytosis of Willebrand factor and P-selectin by Weibel-Palade bodies (WPB) [42], and Exosome release [43]. Rab35 is functionally altered by different microorganisms (Fig. 1d) such as *Anaplasmaphagocytophilum* [44], *Uropathogenic E. coli* [28], *Enterohaemorrhagic E. coli* [45], and *Legionella pneumophila* [46,47]. In Neurite outgrowth [48–53] (Fig. 1e) Rab35 is capable of promoting the formation of a complex between ACAP2 and MICAL-L1 (effector proteins for Rab35) to promote the recruitment of EHD1, which facilitates vesicle formation, to favor neurite outgrowth, bristle formation (in *Drosophila S2* cells) [54], cell morphology (in BHK cells) [48], oligodendrocyte differentiation (in FBD-102b cells) [55], axon elongation (in rat primary neurons) [56], and trafficking of synaptic vesicles (in *Drosophila*) [57].

Because many of these functions of Rab35 play prominent roles in actin dynamics and vesicular trafficking, and we know that Rab35 is altered in some cancers and now is recognized as an oncogenic protein, similar behavior to Ras leads us to infer that alteration of Rab35 might be involved in cancer development in an important way. In this paper we discuss the possible implication of Rab35 in some hallmarks of cancer, such as invasion and metastasis, with particular emphasis on immune evasion and leukemia.

### Rab35 and cancer: Invasion and metastasis

Several Rab35 associated functions cited in this review have been related to different aspects of cancer development but direct implications have not been shown, such as the alterations for clathrin-mediated/independent endocytosis [59], apical-basal polarity [60], and cytokinesis [61]. Major histocompatibility complex class I (MHC I) [62] and II (MHC II) [63] molecules are downregulated in cancer [62,63]. Zeta chain expression (in the T cell receptor) is modified in T lymphocytes taken from cancer patients [64]. Different aspects of phagocytosis, such as filopodia, lamellipodia, and ROS generation (reactive oxygen species) [66–68] have been related to increased cell motility and aggressiveness. Because phagocytosis is altered in cancer [68] and is key in the elimination of tumor cells [69] and in the intake of exosomes [70], this can contribute to changes in tumor microenvironment and metastasis [71]. These studies, in addition to the prominent roles that Rab35 play in actin dynamics and vesicular trafficking, support the hypothesis that functional abnormalities in this GTPase could contribute to different aspects of cancer development, perhaps in part, through membrane trafficking dysregulation. For more details see ref [16].

On the other hand, few reports directly associate Rab35 alteration in cancer. In 2009, it was shown that the expression of Rab35 (mRNA) was upregulated in ovarian cancer OVCAR3, OSEC2 cells, and in epithelial ovarian cancer tissue under androgen treatment, which then correlates Rab35 with androgen receptor (AR) expression [72]. Interestingly, androgens are related to changes in actin remodeling [73]. In 2013, a functional interplay between Rab35 and Arf6 was suggested in cell migration and cell–cell adhesion by a mechanism whereby Rab35 negatively regulated Arf6 activity and β1-integrin recycling by promoting cadherin recycling and cell adherence. Also Rab35 was reported to be downregulated in other human tumors (gliomas and squamous cancers) where Arf6 showed hyperactivity [32]. Also in 2013, Rab35 was associated to migration of tumor cells (breast cancer) by a different mechanism, one that included the Dvl2/Rab35/Rac1 signaling pathway promoted by Wnt5a [74] (the protein involved in cancer progression) [75]. In 2015, Rab35 was identified in ovarian cancer as a direct target of miR-720 (HeLa cells), suggesting that miR-720 promoted cell migration by downregulating Rab35 [76], and we know that this microRNA, miR-720, is implicated in cancer aggressiveness [77]. Although these reports associated Rab35 alteration to different types of cancer cells, it was in 2015 when Rab35 was described as an oncogenic protein, with oncogenic potential comparable to Ras in human cancer. Some mutations found on Rab35 were similar to those in Ras (S22N, A151T and F161L). Likewise, some of those mutations (A151T and F161L) were capable of activating the PI3K/AKT pathway and were shown to be oncogenic in the NIH-3T3 cell focus-formation assay, which is used to evaluate Ras transformation capability. In addition, it was shown that the Q67L mutation on Rab35, that turns the GTPase into a constitutively activated state, was oncogenic too [17].

Other studies continued reporting the association of Rab35 with cancer. In 2016, it was shown that the silencing of this GTPase correlated to decreased cell migration in non-small cell lung cancer, NSCLC [78]. Also, Rab35 was capable of enhancing breast cancer cell invasion, through the activation of MICAL1 and ROS generation [39].
Despite several lines of evidence that relate Rab35 to cancer, many questions remain unanswered about its implication in cancer development, particularly in invasion and metastasis. It is possible that the Rab35’s close link to actin dynamics, vesicular trafficking [15,16,35,48,54,79,80], and its close functional relationship with Rac1, Cdc42 as well as Arf6 [21,32,34,35,37,38,48,50,52,53,55] could be playing important roles in those hallmarks of cancer. Alteration of Rab35 could impact tumor establishment and the tumor microenvironment in different ways. To begin with, actin dynamics dysfunction could cause cellular morphological changes, which could affect mechano-transduction signaling and how cells sense and interact with the microenvironment and perhaps influence invasion by means of actin protrusions [35,48,80]. In turn, those protrusions could be favoring the release of exosomes and metastasis [71,81]. Additionally, altered vesicular trafficking could support the release of tumor cells from the primary tumor and aid their survival during migration, perhaps by modulating the recycling of particular membrane proteins (β1-integrin, EGF receptors and cadherins), according to cellular needs. Specifically, the altered vesicular trafficking of β1-integrin, EGF receptors and cadherins has also been suggested recently. For more details see Ref [16]. The crosstalk between Rab35 and other small GTPases, such as Rac1, Cdc42 and Arf6 could also be contributing to developing and potentially altering actin dynamics and vesicular trafficking. Altered vesicular trafficking associated to Rab35 or Rac1, Cdc42 and Arf6 could cause mutual functional abnormalities, thus potentiating important biological changes, among them; proteome membrane composition and dysregulated cellular signaling events. Dysregulation of CME and CIE could affect the normal trafficking of proteins [34] giving rise to increased receptor signaling through internalized vesicles and improper recycling of proteins. Additionally, those defects could be affecting local physical membrane properties such as membrane tension, which is also associated to invasion [82].

Alterations in the phagocytic capabilities of tumor and/or tumor related cells could be associated with modifications in exosome intake [68,70], constituting another way to promote transformation and malignity [83,84], in addition to immune evasion [85]. Thus, Rab35 alteration could contribute to cancer development and aggressiveness (Fig. 2a). On the other hand, the presence of Rab35 in released exosomes [86,87], its participation in the regulation of exosome release [43], its participation in TCR recycling [26], as well as in TCR modulation [58] suggests that Rab35 could be playing an important role in leukemia as well as in immune evasion.

Rab35: An outlook in leukemia and immune evasion

In our work, we point out different lines of evidence that support the hypothesis that Rab35 could be implicated in leukemia.

First: we found that Rab35 seems to be overexpressed in leukemia according to our analysis in Oncomine [88]. The oncogenic mutation (A151T) on Rab35, capable of activating the PI3K/AKT pathway, has been identified in an acute lymphoblastic leukemia (ALL) sample and reported in the Cosmic database [89]. The PI3K/AKT pathway is critical for the biology of leukemia, as reported by different studies. One study described constitutive hyperactivation of that pathway in T-Acute lymphoblastic leukemia (T-ALL) specimens, even though those cells expressed higher levels of the main negative regulator PTEN (Phosphatase and tensin homolog) compared to normal T cell precursors. This effect was associated, in part, to the role of Casein Kinase 2 (CK2) in activating the PI3K/AKT pathway [90]. In another study, the expression and activity levels of CK2 were higher than their counterparts (in healthy thymocytes) in primary T-ALL (γδ T-ALL and αβ T-ALL) cells. Furthermore, it was shown that CK2 activity (modulated by stimulating the TCR, T cell receptor) was capable of promoting the AKT signaling in thymocytes (γδ), all of which suggested a link between the PI3K/AKT pathway and TCR in leukemia [91]. The importance of upstream regulators of the PI3K/AKT pathway in leukemia can be concluded from this evidence and that of CK2, in accordance with the last two articles cited. At the same time, it is feasible to think that Rab35, which is an upstream activator of the PI3K/AKT pathway, in some cells [17], with TCR modulating roles [26,58], could be contributing to leukemia development in this way.

Second: Rab35 participates in characteristic cellular functions associated to the immune response of lymphocytes, in zeta (ζ) chain recycling for immunological synapse formation [26], TCR modulation [58], and exosome release [43]. Specifically at the TCR level, in 1992 researchers reported alterations in TCR of lymphocytes from tumor-bearing mice. The alteration was related to the expression of an unusual TCR that lacked zeta chain. Notably, that phenotype was also documented in peripheral blood T cells in human cancer patients. It is possible to think that those abnormalities could have been associated to defective zeta chain recycling [64]. Later, several works described similar alterations in the TCR for different types of cancer, such as in infiltrating T-cells isolated from patients with colorectal carcinomas, which
expressed significantly less zeta chain than T-cells in the peripheral blood of the same patients, and even less than in the healthy controls [92]. Also, tumor-infiltrating lymphocytes from patients with renal cell carcinoma (in 10 of 11 cases) showed marked decrease in the expression of the same chain [93]. Later, a similar phenotype (decreased levels of zeta chain) in tumor-associated lymphocytes was reported in ascitic fluids of women with ovarian carcinoma (OvCA) [94]. All these reports have provided insights on the pathophysiology of leukemia, specifically at the TCR level, and have even allowed the suggestion that tumor growth may induce a functional state in T cells characterized by low zeta chain content in the TCR [95]. TCR alterations have also been described in cancer where lymphocytes per se are transformed. The zeta chain expression on T lymphocytes from patients with B cell chronic lymphocytic leukemia (CLL) was significantly reduced compared to normal controls [96], as were the peripheral blood T lymphocytes from patients with untreated Hodgkin’s disease [97]. The phenotype associated to TCR dysregulation in cancer has led to the suggestion that the downregulation of zeta chain in T cells in tumor-bearing patients might be a widespread phenomenon as an escape from the immune response against cancer [97]. In part, this suggestion came from the observation that this chain was expressed at very low levels in peripheral blood T cells of the patient at the time of diagnosis, but the expression of this molecule rose to almost normal levels after successful treatment [95, 97]. Remarkably, the phenotype described, the TCR defects in cancer, have also been reported in leukemic T lymphocytes (T-ALL samples), which showed marked reduction in zeta chain expression [98]. It seems that alteration in the TCR could be a mechanism that the transformed tumor lymphocytes use to evade immune destruction.

Third: it has been reported that Rab35 participates in TCR modulation. This alteration was related to
enhancement of TCR signaling in T\textsubscript{H}2 cell [58]. The participation of Rab35 in T\textsubscript{H}2 cells supposes that this GTPase could play different roles in different lymphocyte subpopulations.

Fourth: we found that in Jurkat cells, Rab35 regulates zeta chain recycling and the immunological synapse formation. These processes were altered by the S22N mutation on Rab35, which takes the GTPase to the inactive state. Those lymphocytes also showed defects at the vesicular level related to the development of big vacuoles, which supposed a role of such negative regulators for Rab35 activity as Epi64C [26] (a hematopoietic restricted Rab35 GAP) [99] that inactivates Rab35. We showed that Epi64C caused similar defects in the same cells. In lymphocytes, we also found that the oncogenic mutation on Rab35 (Rab35 Q67L) was associated with the generation of membrane protrusions in those cells. This highlights the capacity of Rab35 to influence actin dynamics [26], thus resembling morphological changes induced by the overexpression of Rac1 and Cdc42 [35]. These membrane protrusion could be a way to favor the release of exosomes and malignity [83,84], as well as another path for immune evasion [85].

Different reports relate Rab35 to exosomes. Rab35 was identified in secreted exosomes from colorectal adenocarcinoma (Human CRC cells, HT29) [86] and transformed B cells (human B-cell line RN; HLA-DR15) [87]. Rab35 is also reported as participating in the regulation of exosome release (Oli-neu cells), along with its GAP Epi64C [43], which was later related to the same process in adenocarcinoma cells [100]. Those suggest that Rab35 alteration could impact exosomes at different levels, such as cargo composition and rate of release. The alteration of Rab35 associated to abnormal rate of exosome release [43] could affect intercellular communication and perhaps favor the generation of bone marrow niches. Since Rab35 is part of the content of exosome release by different cell types [86,87], it is possible that alterations of Rab35 could affect the levels of Rab35 in exosomes. This is turn would alter Rab35 expression on recipient cells, and could unbalance many functions in which Rab35 participates. Given the intracellular localization of Rab35 (plasma membrane mainly), such abnormalities could be changing many physical plasma membrane properties, such as membrane tension and related functions [82].

Taken together, these studies suggest a possible link between leukemia and some Rab35 related functions, such as the PI3K/AKT pathway, TCR modulation, and exosomes, which could be contributing to leukemia development and/or immune evasion. Accordingly, some important and fundamental questions need to be answered in order to support or reject such a hypothesis about Rab35 and leukemia. Some of those questions are:

Is Rab35 activating the PI3K/AKT pathway in lymphocytes? Is there and association between Rab35 and TCR alteration in leukemic samples? Is Rab35 regulating exosome release in lymphocytes?

We hypothesize that Rab35 could be contributing to leukemia development through various mechanisms. For example, since Rab35 is capable of activating the PI3K/AKT pathway in different cell types [17], it is possible that the Rab35 participation in that pathway could be operating in lymphocytes too, which could be favoring leukemic cell survival. The TCR alteration observed in different types of cancer, including leukemia, and the roles of Rab35 on TCR modulation suppose Rab35 as a protein target of study in leukemia development by means of TCR alteration. Perhaps, the Rab35 alteration in its expression (with or without oncogenic mutations) might be altering proper TCR-dependent processes, such as lymphocyte selection (during lymphocyte development), TCR signaling associated with lymphocyte activation and clonal expansion (proliferation). Also, TCR defects could be related to immune evasion by an as yet unrecognized mechanism, as suggested above. In addition, improper Rab35 function could be altering the rate of exosome release on lymphocytes as well as their cargo content. Perhaps, more proteins that limit the anti-leukemic immune response could be present in those exosomes, which could contribute to the generation of bone marrow niches and immune evasion (Fig. 2b).

**Concluding remarks**

The frequent alterations of RabGTPases in cancer imply that these proteins can contribute importantly to cancer development. Specifically, the oncogenic potential of the RabGTPase Rab35 and its prominent roles in actin dynamics and vesicular trafficking in the endo/exocytic pathway, suggest that this protein might be playing important roles in some hallmarks of cancer, including invasion and metastasis, which are the main causes of death in cancer patients. The possible Rab35 participation in the PI3K/AKT pathway in lymphocytes, its role on TCR modulation, as well as its possible implication in exosome release, in the same cells, suppose that Rab35 might be acting in leukemia development and in immune evasion. As we proposed, Rab35 could be participating in the hallmarks of cancer invasion, metastasis, and immune evasion by different mechanisms, some of which could be related to its participation on vesicular trafficking, actin dynamics, as well as close functional relationship with Rac1, Cdc42 and Arf6.

In spite of the stated hypothesis about Rab35 and some hallmarks of cancer, it is necessary to investigate important basic questions about them, such as whether it
is known if Rab35 and its immune GAP regulator Epi64C regulate exosome release as well as regulating the PI3K/AKT pathway in lymphocytes. In summary, Rab35 research in the context of cancer is a novel and exciting field where Rab35 might become a possible therapeutic target.

**Disclosure potential conflicts of interest**

No potential conflicts of interest.

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