The Phosphatase PRL-3 Is Involved in Key Steps of Cancer Metastasis

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Abstract

PRL-3 belongs to the PRL phosphatase family. Its physiological role remains unclear, but many studies have identified that PRL-3 is a marker of cancer progression and shown it to be associated with metastasis. Evidence implicating PRL-3 in various elements of the metastatic process, such as the cell cycle, survival, angiogenesis, adhesion, cytoskeleton remodeling, EMT, motility and invasion, has been reported. Furthermore, several molecules acting as direct or indirect substrates have been identified. However, this information was obtained in many different studies, and it remains difficult to see the larger picture. We therefore systematically collected the published information together and used it to develop a comprehensive signaling network map. By analyzing this network map, we were able to retrieve the signaling pathways via which PRL-3 governs the key steps of the metastatic process in cancer. In this review, we summarize current knowledge of the role of PRL-3 in cancer and the molecular mechanisms involved. We also provide the web-based open-source PRL-3 signaling network map, for use in further studies.

Introduction

Tumorigenesis is a gradual multistep process, by which cells acquire new biological capacities that facilitate tumor formation and dissemination, eventually resulting in metastasis [1,2]. The first step in this process is cell transformation and tumor growth due to uncontrolled proliferation. This proliferative capacity results from the acquisition of resistance to apoptosis, cell cycle deregulation and cell survival pathways. The deregulation of angiogenic pathways leads to neovascularisation of the tumor, which is important for tumor growth, but also for metastatic colonization. Finally, tumor cells must acquire the capacity to migrate, through the epithelial-to-mesenchymal transition (EMT), supported by cytoskeleton reorganization and changes to cell adhesion, if they are to invade distant organs [3].

Multiple signaling pathways are involved in this sequence of events, promoting the transition from a normal cell to an invasive cancer cell. Protein tyrosine phosphatases (PTPs) constitute a large family of enzymes playing crucial roles in the regulation of many key signaling pathways involved in the control of cell proliferation, adhesion, migration, differentiation, survival and apoptosis, for

example [4]. The deregulation of PTP activity, resulting in aberrant tyrosine phosphorylation, has been implicated in the progression of various diseases, including cancer [5].

Phosphatases of regenerating liver (PRLs) belong to the dual-specificity phosphatase subgroup of PTPs. PRLs are small (22 kDa), closely related proteins, with amino-acid sequences displaying at least 75% identity [6]. PRLs have been conserved during evolution and are expressed during embryonic development [7], particularly in the skeletal muscle of vertebrates [8]. PRLs have an N-terminal catalytic domain containing the PTP active-site sequence CX5R, in which cysteine is the catalytic residue [9], and a C-terminal CAAX prenylation sequence important for membrane association and intracellular localization [9]. Prenylated PRLs are associated with plasma membrane localization in early endosomes and autophagosomes, whereas non-prenylated PRLs are redistributed to the nucleus [10–13].

The phosphatase of regenerating liver-3 [encoded by *PRL-3*, and also known as tyrosine phosphatase 4A3 (PTP4A3)], belongs to the PRL phosphatase family, which has three members: PRL-1, PRL-2 and PRL-3. The gene encoding PRL-3 is located on chromosome 8q24.3. In human adult tissues, PRL-3 is present principally in the skeletal muscle and heart, with lower levels in other tissues, such as the retina, liver and pancreas [14].

Little is known about the physiological roles of PRLs, but they have been implicated in cell proliferation, migration, invasion, tumor growth and metastasis [6]. Interestingly, the inhibition of prenylation, leading to the translocaltion of PRLs to the nucleus, abolishes the pro-migratory and pro-metastatic effects of these enzymes in cancer [15–18]. PRL-3 was the first member of the PRLs found to be more strongly expressed in liver metastases of colon cancers than in healthy colon tissue or primary tumors [19]. PRL-3 is also the most widely studied PRL, due to its involvement in various types of cancer. PRL-3 is known to be involved in the metastatic processes of many different human cancers, including gastric cancers [20], ovarian cancers [21,22], cervical cancer [23], non-small cell lung cancer [24], liver cancer [25,26], human gliomas [27], nasopharyngeal carcinoma [28], oesophageal cancer [29], metastatic colorectal carcinomas [30,31], breast cancer [32], uveal melanoma [33], cervical cancer [34], salivary adenoid cystic carcinoma [35] myeloid leukemia [36] and multiple myeloma [37].

The mechanism of action and intracellular substrates of PRL-3 remain largely unknown, which has led to many studies of the substrates of PRL-3 substrates, and the pathways and mechanisms in which this phosphatase is involved. We used a systems biology approach to integrate published evidence about the molecular mechanisms of action of PRL-3 into a comprehensive map of molecular interactions. The resulting comprehensive PRL-3 signaling map summarizes current knowledge on this topic. We also performed a structural network analysis to identify the main players in various key steps in the metastatic transformation of cancer cells governed by PRL3. We extracted minimal reduces models for the key pathways to major phenotypes during invasion. These diagrams can be used for the modeling of cell metastasis in cancer. This work makes it possible summarize, systematically and visually, what is known about PRL_3 in tumorigenesis and the multifaceted process of metastasis, as discussed in this review. We describe the action of PRL-3 in enabling cells to acquire the biological capabilities required for tumor development and invasion.

Construction and Annotation of the Signaling Network Map

We manually retrieved scientific discoveries concerning the molecular mechanisms of action of PRL-3 from previous publications and systematically gathered them together into a comprehensive signaling map, according to a well-established procedure [38] (Supplementary Fig. 1). We performed a literature search to identify studies of PRL-3, using the keywords “PRL-3” and “PTP4A3,” and we selected the references linking this phosphatase to cancer and invasion. We then depicted the molecular mechanisms described in these references graphically, in the form of a biochemical reaction network, with the Cell Designer tool [39] and Systems Biology Graphical Notation [40] syntax. The software creates a structured network representation in Systems Biology Markup Language [41], which can then be used for further computational analyses.

All entities depicted in the map are assigned common identifiers converted into links to the corresponding entity descriptions in the HGNC, UniProt, Entrez, GeneCards, Reactome, and Kegg databases, and the corresponding literature references are provided (Supplementary Fig. 2). The entities on the map are annotated in NaviCell format (https://navicell.curie.fr/doc/NaviCellMapperAdminGuide.pdf).

Structural analysis of the network and model reduction

For identification of the mechanisms by which PRL-3 regulates various phenotypes during invasion, we reduced the complexity of the map through a path analysis of the map with the OCSANA algorithm [42] in the BiNoM [43] plugin of Cytoscape

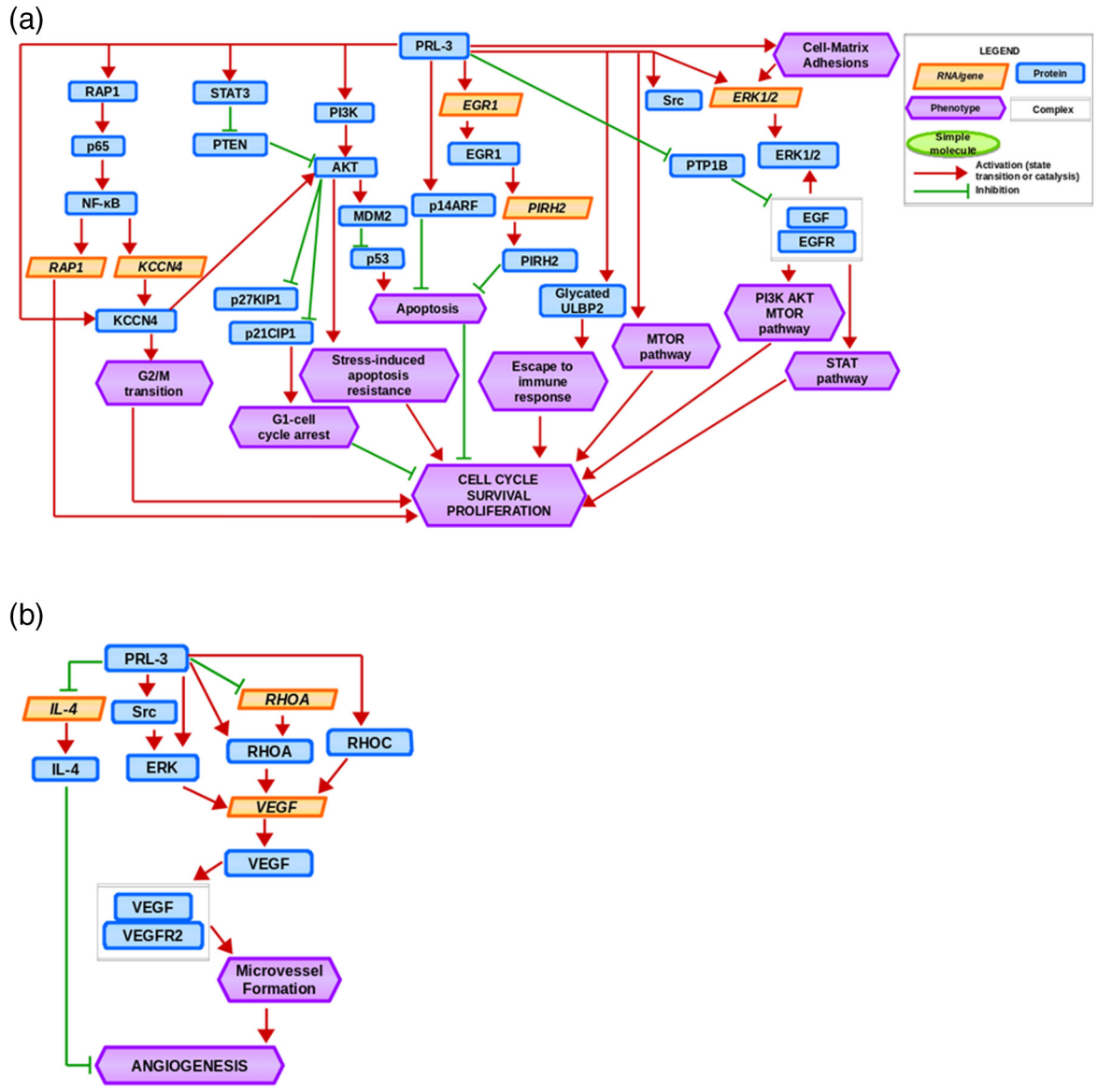

Fig. 1. (A) Molecular mechanisms induced by PRL-3 leading to cell cycle progression, survival and proliferation in cancer. (B) Molecular mechanisms leading to angiogenesis induced by PRL-3 in cancer.

[44]. Subnetworks containing major paths and players connecting PRL-3 and the six major phenotypes of interest (cell cycle; survival; angiogenesis; adhesion; cytoskeleton remodeling; and EMT, motility and invasion) were retrieved. These phenotype-specific subnetworks of the PRL-3 map were annotated with module tags (as further explained) and used to create functional module maps accessible from the NaviCell page. The RPL-3 map thus has a hierarchical structure, and each module can be visualized in the context of the global map or individually (Supplementary Fig. 3).

We used the paths identified on the map to guide the further reduction of complexity of the subnetworks, by maintaining first-order connections, but removing unrelated processes from the subnetwork. This reduction made it easier to understand the principles underlying the organization of the map and to identify the key paths. Diagrams of the reduced models relating to the regulation of the six aforementioned phenotypes were generated and are represented in Figs. 1–3.

Module tagging

Each entity in the map can participate in one or several functional modules. The corresponding module tags are systematically assigned in the

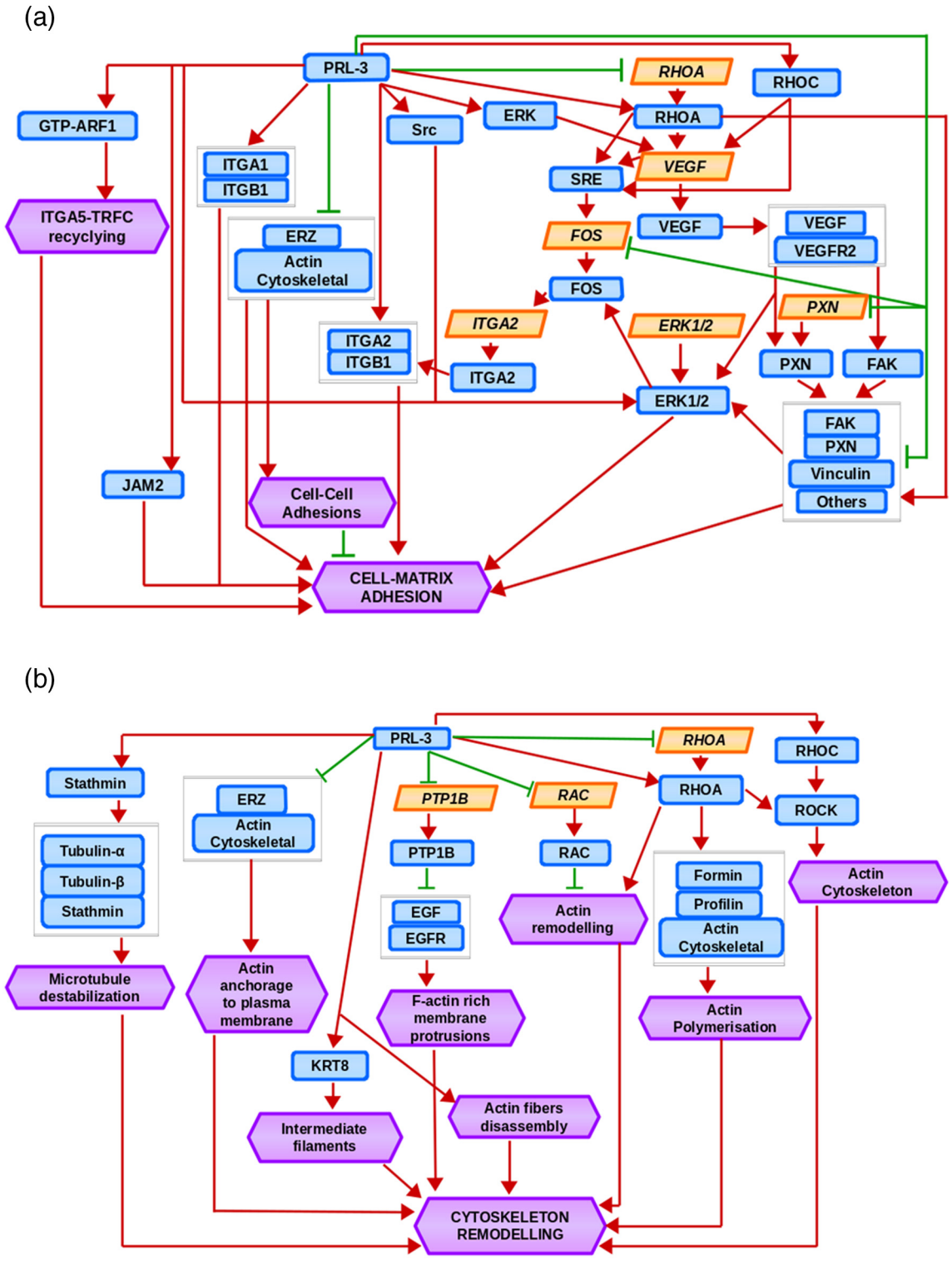

Fig. 2. (A) Molecular mechanisms of cell matrix adhesion induced by PRL-3 in cancer. (B) Molecular mechanism of cytoskeleton remodeling induced by PRL-3 in cancer. For the annotations, please see the legend to Fig. 1.

annotation of the map entities and converted into links by the NaviCell factory during the process of online map generation (Supplementary Fig. 2). The links can be used to trace the participation of entities in the different modules of the map and to facilitate shuttling between the module maps and the general

map. The list of module tags corresponds to the list of functional modules and to the model diagrams in Figs. 1–3.

Map availability and navigation

The comprehensive modular map is an open-source map accessible via several web-based platforms, such as NaviCell [45], MINERVA [46] and NDeX [47], facilitating map navigation and curation by the community. The resource is accessible via https://navicell.curie.fr/pages/maps_PRL3.html. Each module map can be accessed separately, to facilitate use of the map. We also provide downloadable materials, such as PPI networks extracted from the map, lists of references annotating the map and module content lists in a format suitable for enrichment analysis studies.

PRL-3 Signaling in Cell Cycle, Survival and Apoptosis

PRL-3 is involved in tumor development through control of cell cycle, apoptosis and survival processes. p53 is known to affect the transcription of the PRL-3 gene [48], but PRL-3 can also downregulate p53 expression in cancer cells by inducing the transcription of gene encoding PIRH2 and increasing the phosphorylation of MDM2, both of which downregulate p53 [49], or by downregulating expression of the alternative reading frame of p14 ($p14^{ARF}$) [50].

PRL-3 interacts with the telomere-related protein RAP1, which is responsible for telomere lengthening, thereby regulating the NF-κB signaling pathway, by upregulating the expression and phosphorylation of p65 [51]. PRL-3 also promotes cell proliferation by upregulating KCNN4 channels, in an NF-κB dependent manner, hence facilitating G2/M transition [52]. A study on triple-negative breast cancer demonstrated that PRL-3 knockdown results in G1 cell arrest, inducing a TNFα response, which leads to cell senescence through the TNF-R1-mediated activation of NF-κB, followed by apoptosis, due to an increase in TNF-R1 signaling through the TNFα-associated extrinsic death pathway, shunting signaling away from the NF-κB cascade [53].

In mouse embryonic fibroblasts (MEFs), Prl-3 overexpression induces G1 arrest downstream p53, by triggering a PI3K-Akt-activated negative feedback loop [48]. PRL-3 has also been shown to promote proliferation by activating the Akt/mTOR pathway [54]. Akt/mTOR signaling regulates apoptosis, cell growth, cell cycle and angiogenesis. PRL-3 can induce mTOR phosphorylation, leading to downstream signaling activation via mTOR substrates, such as p70S6K and 4E-BP1 [55]. A recent study also highlighted cooperation between the AKT/mTOR and WNT/β-catenin signaling cascades in PRL-3-high acute myeloid leukemia [56].

The downregulation of PRL-3 also inhibits proliferation and apoptosis induced by emodin in the SGC-7901 human gastric carcinoma cell line [57]. PRL-3 has been shown to induce hyperactivation of EGFR and its downstream signaling cascades in multiple human cancer cell lines [58]. Finally, PRL-3 overexpression in multiple myeloma increases survival, STAT3 phosphorylation and the number of cells in G2/M and decreases the number of cells in the S and G1 phases [59]. Remarkably, in colon cancer, the increase in STAT3 phosphorylation induced by PRL-3 triggers the expression of miR-21, miR-17 and miR-19a, which directly target PTEN [60].

All of these results indicate that PRL-3 is involved in control of cell cycle phases transition via the regulation of the major player p53, thus promoting proliferation and inhibiting apoptosis (Fig. 1A).

PRL-3 signaling in angiogenesis

Guo *et al*. [61] provided the first evidence for the role of PRL-3 in tumor angiogenesis in 2006. They reported that the expression of PRL-3 in fetal heart, developing blood vessels and immature erythrocytes, but not in their mature counterparts, suggesting an essential role for PRL-3 in early angiogenic events. They then investigated the functions of PRL-3 in tumor angiogenesis, demonstrating that Chinese hamster ovary (CHO) cells and DLD-1 human colon cancer cells expressing PRL-3 could attract migrating human umbilical vascular endothelial cells (HUVECs), and that DLD-1 cells could enhance vessel formation by HUVEC. Furthermore, after injecting CHO cells expressing PRL-3 into nude mice, the authors observed the recruitment of host endothelial cells to the tumors and the initiation of angiogenesis. Interestingly, PRL-3-expressing cells decreased interleukin (IL)-4 levels, thus attenuating the inhibitory effects of IL-4 on the HUVEC vasculature [61]. VEGF can also promote PRL-3 gene transcription, by inducing expression of the transcription factor MEF2C [62].

Another study showed that PRL-3 participates in VEGF signaling, potentially via Src activation, promoting angiogenesis in primary cultures of murine and human endothelium [63]. Finally, in endometrial adenocarcinoma, PRL-3 induces microvascular vessel formation by promoting VEGF expression via the upregulation of phosphorylated extracellular signal-regulated kinase [64]. Similar findings have also been reported for lung cancer cells [24] (Fig. 1B).

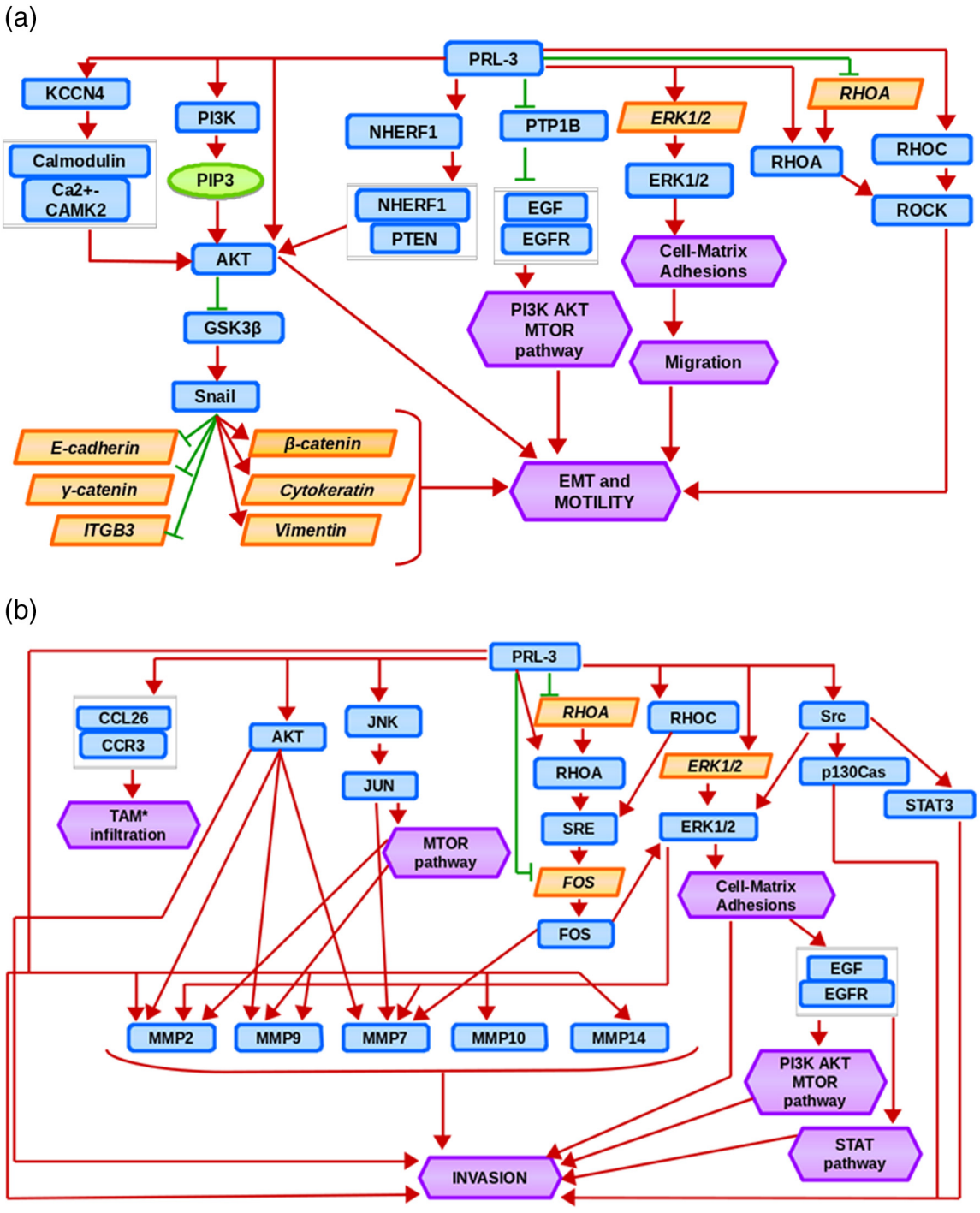

Fig. 3. (A) Molecular mechanisms leading to EMT and motility induced by PRL-3 in cancer. (B) Molecular mechanisms that promote invasion induced by PRL-3 in cancer. For the annotations, please see the legend to Fig. 1.

PRL-3 signaling in adhesion

Several studies have shown that PRL-3 promotes cancer invasion and metastasis by regulating cell adhesion. Peng *et al*. [65] were the first to identify integrin α1 as a protein interacting with PRL-3 by co-immunoprecipitation assays. PRL-3 was subsequently shown to interact with and downregulate the tyrosine phosphorylation of integrin β1 [18,66], particularly for Y783, a key residue for integrin β1 function [67]. PRL-3 also regulates integrin α2 by suppressing c-fos expression and decreases production and phosphorylation of paxillin in ovarian cancer cells [68]. The downregulation of paxillin by

PRL-3 has also been reported in HeLa cells [69]. In addition, PRL-3 regulates integrin α5 recycling through Arf1 activity [70]. JAM2, a junctional adhesion molecule, was recently shown to interact with PRL-3 in colon cancer [71]. Consistent with these observations, PRL-3 has been shown to mediate SDF-1α-stimulated calcium release in acute lymphoblastic leukemia, leading to the activation of focal adhesion kinase (FAK) and Src, important effectors for migration and adhesion [72]. Finally, PRL-3 can also dephosphorylate phosphatidylinositol [73] and increase the phosphorylation of Erk1/2 [74] (Fig. 2A).

PRL-3 signaling in cytoskeleton remodeling

PRL-3 substrates remain incompletely characterized, but three cytoskeletal proteins have been identified as PRL-3 targets, providing strong evidence of a role for PRL-3 in promoting migration and invasion by cytoskeleton remodeling.

The first substrate of PRL-3 to be identified was Ezrin. Ezrin belongs to the ERM protein family, which links cell surface receptors and the actin cytoskeleton. PRL-3 decreases Ezrin phosphorylation, and *in vitro* phosphatase assays suggested that PRL-3 affected Ezrin-pThr567 in endothelial cells, thereby promoting tumor progression [75].

The cytoskeletal intermediate filament keratin 8 (KRT8) was also identified as a PRL-3 substrate. PRL-3 and KRT8 interact physically and are colocalized at cellular lamellipodia and ruffles *in vivo*. PRL-3 expression decreases or abolishes KRT8 phosphorylation, particularly at the invasive front and in liver metastases, suggesting a possible role for PRL-3 in cell migration and metastasis in colon carcinoma via KRT8 dephosphorylation [76].

Finally, Stathmin, a key oncoprotein, is also a cytoskeletal PRL-3-associated protein. Stathmin is involved in controlling microtubule dynamics. It interacts with PRL-3 in colon cancer cells, leading to microtubule destabilization, thereby contributing to the progression and metastasis of colorectal carcinoma [77].

Other studies have shown that PRL-3 can modulate the cytoskeleton by regulating Rho family GTPases. In SW480 colorectal carcinoma cells expressing exogenous PRL-1 and PRL-3, the activation of Rho and, RhoC, and the and consequent PRL-mediated motility and invasion were blocked by inhibition of Rho kinase (ROCK), a key Rho effector. Furthermore, PRL PTPs decreased Rac activity without affecting Cdc42 activity [16]. PRL-3 also increases the activity of RhoA and mDia1 in lung cancer, promoting actin polymerization and increases in migration and invasion [65]. The activation of RhoC by PRL-3 was confirmed by additional studies [78,79], showing that in CHO cells expressing PRL-3, the levels of active RhoA and Rac1 were reduced, which coincided with a reduction of actin filaments [69]. The effects of PRL-3 on RhoA and probably on the other Rho GTPases might be cell type dependent or fluctuate according to the biological context (Fig. 2B).

PRL-3 signaling in EMT and motility

PRL-3 also plays a crucial role in EMT. EMT is an physiological process that occurs during embryonic development. In *Xenopus laevis*, PRL-3 is required for cephalic neural crest migration *in vivo,* which is essential for embryonic development [80]. The same EMT mechanism guides the transformation of epithelial cells into cells with a mesenchymal phenotype in cancer, facilitating their migration and the formation of metastases. PRL-3 is known to initiate EMT in cancer cells by activating the Akt pathway. Wang *et al*. [69] were the first to report, in 2007, that PRL-3 activates Akt by downregulating PTEN expression, inhibiting GSK-3β, and thereby causing an increase in mesenchymal markers, such as fibronectin and Snail, and a decrease in epithelial markers, as E-cadherin, γ-catenin and integrin β3. The activation of the Akt pathway by PRL-3 was subsequently confirmed in other studies [54,81–84]. PRL-3 has also been shown to promote EMT by directly downregulating E-cadherin and CDH22 expression [85,86]. Another study showed that PRL-3 downregulated PTEN by dephosphorylating NHERF1 in the nucleus, leading to the translocation of both PTEN and NHERF1 from the nucleus to the cytoplasm [87]. Moreover, in colon cancer cells, PRL-3 induces KCNN4 expression, resulting in Snail expression and a parallel decrease in E-cadherin levels [88].

Finally, a study on acute myelogenous leukemia showed that LEO1, a component of RNA polymerase II-associated factor, activates the expression of SOX2 and SOX4 genes, two potent oncogenes in myeloid transformation. This molecular regulation is positively correlated with PRL-3 levels [89], again confirming the role of PRL-3 in EMT and motility in cancer (Fig. 3A).

PRL-3 signaling in invasion

The link between PRL-3 and the tyrosine kinase Src, a well-known proto-oncogene, seems to be fundamental in the promotion of invasion and metastasis. PRL-3 can promote cell invasion by activating Src [90], and Src can promote invasion and motility by mediating PRL-3 phosphorylation [78], highlighting the mutual dependence of these two proteins. PRL-3 induces Src activation by increasing eIF2 phosphorylation, downregulating Csk, a negative Src regulator [91]. Furthermore, to clarify the PRL3-mediated signaling network, Walls *et al*. [92] showed that PRL-3 expressing cells

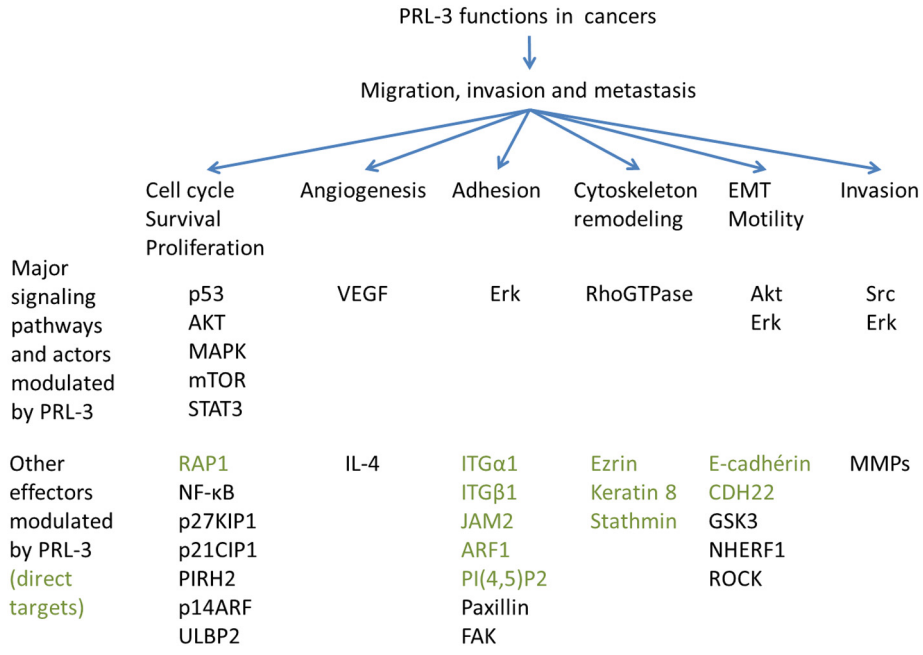

Fig. 4. Main players and signaling pathways regulated by PRL-3 in the key steps in the processes of tumorigenesis and metastasis.

display a general increase in protein tyrosine phosphorylation, but that this increase is particularly strong for multiple signaling effectors responsible for Rho-family GTPase, PI3K-Akt, STAT, and ERK activation, suggesting that Src is the primary signal transducer for PRL-3 effects.

Several studies have also highlighted that PRL-3 facilitates tumor cells invasiveness by regulating the extracellular matrix degradation, mediated by matrix metalloproteinases (MMPs). In particular, PRL-3 has been shown to promote invasion by upregulating MMP-10 [93] in triple-negative breast cancer cells, MMP-7 in human colorectal cancer [94] and in glioblastoma [95]. Likewise, PRL-3 upregulates MMP-7[74] and MMP-2/MMP-9 in gastric carcinoma [81]. In colon cancer cells, PRL-3 promotes MMP-2 activity by regulating the balance between MMP-2 and TIMP2 (an endogenous inhibitor of MMP-2) [66]. PRL-3 also increases cell membrane accumulation and activity of MMP-14 in uveal melanoma [96].

Finally, a recent study reported another mechanism by which PRL-3 can promote invasion in colorectal cancer. According to this study, PRL-3 upregulates CCL26, which binds to the CCR3 receptor and induces the mobilization of intracellular Ca^{2+} in tumor-associated macrophages (TAMs), resulting in an increase in the expression of IL-6 and IL-8 and, thus, an increase in TAM infiltration (see Fig. 3B) [97]. TAMs play a role in invasion, as they are present in inflammatory infiltrates in tumor tissues and can produce numerous lymphangiogenic growth factors, cytokines and proteases that promote tumor cell proliferation and metastasis [98].

Discussion

As described above, PRL-3 modulates the key processes implicated in metastasis, mostly by targeting major signaling pathways, such as the p53, MAPK, mTOR and STAT3 pathways, thereby promoting proliferation and survival. PRL-3 induces angiogenesis via VEGF activation (Fig. 4). A strong correlation was found between PRL-3 and Erk levels; Erk is well known to facilitate extracellular matrix adhesion. The effects of PRL-3 on RhoGTPase remain unclear, with some studies reporting that PRL-3 activates RhoA and others reporting that the phosphatase downregulates RhoA expression, and that PRL-3 modulates RhoGTPase to promote cytoskeleton remodeling, EMT and motility, invasion and angiogenesis. The activation of AKT by PRL-3 is also well established and promotes survival, EMT, motility, and invasion. Finally, one of the most important players activated by PRL-3 is the Src kinase, which promotes invasion and metastasis. PRL-3 also acts by regulating some effectors directly. Indeed, this phosphatase directly regulates integrins, FAK and paxillin in focal adhesions and MMPs involved in the degradation of extracellular matrix (Fig. 4). PRL-3 also modulates cytoskeleton proteins, such as Ezrin, stathmin and keratin 8, which regulate actin, microtubules and intermediate filaments, respectively.

The involvement of PRL-3 in many cancers suggests that this phosphatase may be a viable therapeutic target. Some PTP inhibitors are already the focus of research studies, but further efforts are

required to achieve sufficient selectivity for use in treatment. Numerous molecules have been shown to inhibit PRL-3 via different mechanisms. Some inhibit the phosphatase activity of PRL-3. However, it is also possible to inhibit the anchoring of this molecule to the plasma membrane by inhibiting farnesylation, and the localization of PRL-3 may regulate its function. For example, it has been shown that preventing PRL-3 anchorage to the plasma membrane with farnesyl transferase inhibitors abolishes PRL-3-induced cell migration [12]. Unfortunately, most of these studies did not mention the localization or post-translational modification state (phosphorylation, prenylation) of PRL-3, so it remains unclear whether these parameters are crucial for all of its functions.

Details of the signaling of PRL-3 in cancer invasion are now presented in the form of a comprehensive modular signaling map available online. The global map represents the state-of-the-art for knowledge concerning the regulation of metastasis by PRL-3. The modular maps show how each subpart of the multifaceted invasion process is executed. Finally, the simplified diagrams represent executable minimal models, with the main players governing each phenotype during the process.

The PRL-3 map is part of the Atlas of Cancer Signalling Network (ACSN, https://acsn.curie.fr) [99] and is entitled "The invasion and motility map." ACSN is a web-based resource that contains a collection of maps depicting molecular processes in cancer cells and the tumor microenvironment. This tool has many applications that have been reviewed elsewhere [100]. This systems biology approach to knowledge representation makes it possible to analyze -omics data in the context of the map, to understand the role of PRL-3-regulated processes in different cancer types. ACSN also forms part of the disease maps community (http://disease-maps.org), which aims to apply similar approaches to the study of different diseases. This partnership facilitates studies of disease comorbidities and treatment response prediction, for example [101,102]. This integration with other resources opens up additional opportunities for deciphering the role of PRL-3-related signaling in human diseases other than cancer.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmb.2019.06.008.

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PTP4A3, protein tyrosine phosphatase 4A3; PRL, phosphatase of regenerating liver; EMT, epithelial-to-mesenchymal transition; PTP, protein tyrosine phosphatase; MMPs, metalloproteinases.

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