p120-catenin in cancer – mechanisms, models and opportunities for intervention

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Summary

The epithelial adherens junction is an E-cadherin-based complex that controls tissue integrity and is stabilized at the plasma membrane by p120-catenin (p120, also known as CTNND1). Mutational and epigenetic inactivation of E-cadherin has been strongly implicated in the development and progression of cancer. In this setting, p120 translocates to the cytosol where it exerts oncogenic properties through aberrant regulation of Rho GTPases, growth factor receptor signaling and derepression of Kaiso (also known as ZBTB33) target genes. In contrast, indirect inactivation of the adherens junction through conditional knockout of p120 in mice was recently linked to tumor formation, indicating that p120 can also function as a tumor suppressor. Supporting these opposing functions are findings in human cancer, which show that either loss or cytoplasmic localization of p120 is a common feature in the progression of several types of carcinoma. Underlying this dual biological phenomenon might be the context-dependent regulation of Rho GTPases in the cytosol and the derepression of Kaiso target genes. Here, we discuss past and present findings that implicate p120 in the regulation of cancer progression and highlight opportunities for clinical intervention.

Key words: p120, Tumor suppressor, Oncogene, Kaiso, Cancer, Metastasis, Mouse models

Introduction

Epithelial cells line the cavities and subsurfaces of most organs where they function as physical barriers and regulate the uptake and excretion of multiple substances. To facilitate these functions, cells need to interact with one another and the extracellular matrix. Cell–cell contact is initiated and maintained by the adherens junction (AJ). AJs are complexes located at the basolateral membrane and composed of classical cadherins (cadherins), transmembrane proteins that form Ca^{2+}-dependent homotypic interactions (Yoshida-Noro et al., 1984; Nagafuchi et al., 1987). The cadherin cytoplasmic domain directly interacts with p120-catenin (p120; also known as CTNND1) and β-catenin (CTNNB1). Together with α-catenin (CTNNA1), which binds to β-catenin and links the AJ to the actin cytoskeleton, they form the core AJ complex (Yamada et al., 2005).

p120 is best known for its ability to bind and stabilize cadherins (Reynolds et al., 1994; Shibamoto et al., 1995). Loss or functional inactivation of E-cadherin (also known as CDH1) is a seminal event in the acquisition of epithelial cell migration and invasion (Vleminckx et al., 1991), which has been strongly linked to progression towards metastatic disease (reviewed by Jeanes et al., 2008). Loss of E-cadherin leads to the induction of the epithelial-to-mesenchymal transition (EMT), a phenomenon where epithelial cells de-differentiate towards a mesenchymal cell type that is characterized by a more motile and invasive phenotype (reviewed by Kalluri and Weinberg, 2009). Because of its stabilizing function in the AJ, p120 has caught much attention in the context of tumor development and progression. Like β-catenin, p120 also controls many aspects of cytoskeletal organization, cell signaling and transcriptional regulation, thereby advocating itself as a key player in cancer. Here we outline the diverse general models and molecular mechanisms, and discuss the established oncogenic and tumor suppressor functions of p120 with an emphasis on breast cancer. On the basis of these diverse roles, we will point towards possible opportunities for p120-based clinical intervention strategies.

p120 – form and function

Family members, isoforms and splice variants

p120 is a member of a subfamily of armadillo (ARM) repeat-containing proteins (Riggleman et al., 1990), which consists of δ-catenin (CTNND2), p0071 (PKP4) and ARVCF (armadillo repeat gene deleted in Velo-Cardio-Facial syndrome) (Carnahan et al., 2010). ARM domain repeats are found in a large variety of proteins and facilitate protein–protein interactions (Hatzfeld, 1999).

p120, the protein encoded by *CTNND1*, consists of 21 exons encoding 968 amino acids (Keirsebilck et al., 1998). Alternative splicing occurs for exons 18 (exon A), the nuclear export signal (NES)-containing exon 20 (exon B) and exon 11 (exon C). The presence of the alternatively spliced exon C results in the disruption of a nuclear localization signal (NLS), the inhibition of binding to RHOA and decreased endothelial growth factor (EGF)-induced phosphorylation (Mo and Reynolds, 1996; Keirsebilck et al., 1998; van Hengel et al., 1999; Anastasiadis et al., 2000; Keilhack et al., 2000). Although mRNA containing exon A is abundantly expressed, exons B and C are often not expressed at all or are only expressed at low copy numbers with the exception of neural tissues, in which exon C is abundantly expressed (Keirsebilck et al., 1998). Four start codons located at amino acid residues 1, 55, 102 and 324 initiate expression of isoforms 1, 2, 3 and 4 (Fig. 1). Isoforms 1 and 3 are the most

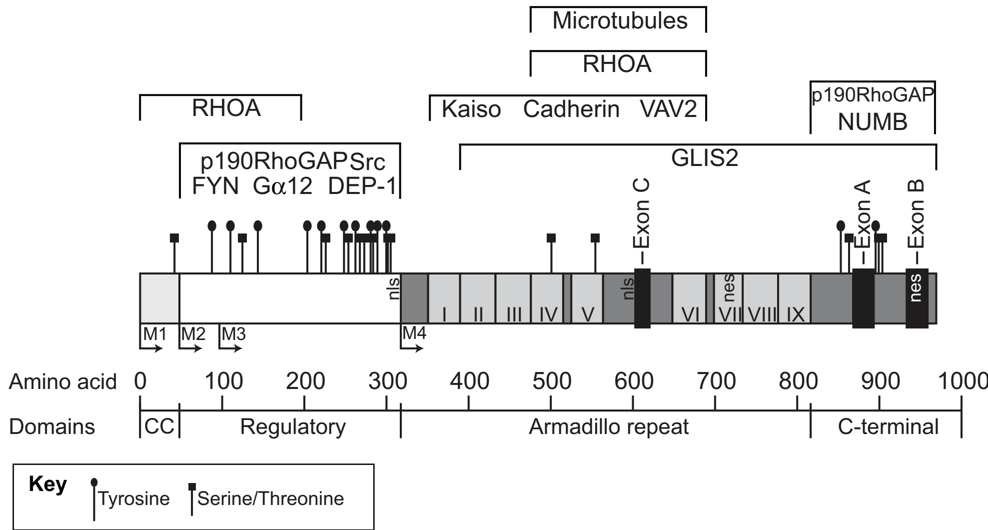

Fig. 1. Schematic representation of p120 protein structure. Illustrated here is the domain structure of p120. M1-4 denotes the transcription start sites for the p120 isoforms 1 to 4. Alternatively spliced exons A-C are indicated. Roman numbers indicate the nine Armadillo (ARM) repeats. Location of the identified Serine/Threonine and Tyrosine phosphorylation sites are depicted. Binding partners and their binding sites are also shown. NLS: nuclear localization signal; NES: nuclear export signal; CC: coiled coil.

widely and abundantly expressed isoforms. Isoform 1 is preferentially expressed in more motile mesenchymal-type cells, whereas isoform 3 characterizes epithelial cells. However, different p120 isoforms are often co-expressed in a balanced manner (Montonen et al., 2001; Aho et al., 2002). The p120 isoform 1 contains an N-terminal coiled-coil domain, which is absent in the other isoforms. A regulatory region harboring most of the tyrosine and serine/threonine phosphorylation sites in p120 follows the N-terminal domain (Alemà and Salvatore, 2007). Isoform 4 immediately precedes the central ARM domain, which consists of nine imperfect ARM repeats that harbor the rarely expressed exon C (Anastasiadis et al., 2000; Choi and Weis, 2005). Finally, the C-terminal tail of p120 contains several serine/threonine phosphorylation sites as well as the alternatively spliced exon A and exon B (Fig. 1).

p120 – a regulator of AJ formation, stability and function

p120 is thought to be transported to the plasma membrane along microtubules through interaction with the microtubule motor protein kinesin (Chen et al., 2003; Franz and Ridley, 2004; Yanagisawa et al., 2004). Once localized to the plasma membrane, the p120 ARM domain associates with the E-cadherin juxtamembrane region, resulting in stabilization and maturation of the AJ. Removal of p120 by genetic means or weakening of the p120–E-cadherin interaction, for instance through SRC-mediated phosphorylation of E-cadherin, exposes the E-cadherin dileucine motif (LL 743–744), resulting in its endocytosis (Miyashita and Ozawa, 2007; Nanes et al., 2012). Association of the Cbl-like protein Hakai to E-cadherin subsequently ubiquitylates E-cadherin either at the membrane or rapidly after endocytosis. This process determines whether E-cadherin is recycled to the membrane or targeted for lysosomal destruction (Fujita et al., 2002; Palacios et al., 2005; Hartsock and Nelson, 2012). Alternatively, p120 can recruit the γ-secretase complex member presenilin (PSEN1) to the AJ (Baki et al., 2001; Marambaud et al., 2002; Spasic and Annaert, 2008). Subsequent recruitment of the other members of the complex [Nicastrin (NCSTN), APH1 and Pen2 (PSENEN)] facilitates cleavage of several transmembrane receptors, including Notch, ERBB4, CD44 and E-cadherin (Fortini, 2002; Kiss et al., 2008; Kouchi et al., 2009). This secretase-mediated cleavage of E-cadherin results in the disassembly of AJs and a cytosolic pool of C-terminal fragments of E-cadherin that is capable of transporting p120 to the nucleus, thus affecting canonical WNT signaling, as discussed in more detail below (Sadot et al., 1998; Baki et al., 2001; Marambaud et al., 2002).

An alternative mechanism of AJ degradation is facilitated by NUMB, which can interact with the C-terminal region of p120 resulting in stimulation of clathrin-dependent endocytosis of AJ complex components (Wang et al., 2009; Wang and Li, 2010; Sato et al., 2011). In conclusion, whereas several diverse mechanisms control AJ recycling, p120 takes center stage as the key regulator of AJ formation, stability, turnover, and connection to the microtubule cytoskeleton.

Regulation of Rho GTPase activity by p120

The Rho GTPases, of which RHOA, RAC1 and CDC42 are the most well-studied members, are the master regulators of actin dynamics. Their highly localized activity is required to induce proper cell polarity, migration and AJ formation and maturation (Etienne-Manneville and Hall, 2002). Here, p120 has a crucial function by acting as a scaffolding protein for RHOA and several Rho regulatory proteins. For instance, fibronectin-induced integrin activation or stimulation by growth factors can lead to the activation of RAC1 and the subsequent membrane targeting of p190Rho GTPase activating protein (GAP) (also known as ARHGAP35) (Arthur and Burridge, 2001; Wildenberg et al., 2006; Balanis et al., 2011). p190RhoGAP then associates with p120 and drives the local inhibition of RHOA-Rho associated protein (ROCK) signaling, which in turn destabilizes actin and reduces the contractile forces that are generated along actin filaments (Wildenberg et al., 2006; Bustos et al., 2008). In addition, p120 can interact with the Rho guanine nucleotide exchange factor (GEF) VAV2, which results in activation of the Rho GTPases RAC1 and CDC42, and a strong decrease in RHOA activity, causing actin polymerization (Noren et al., 2000; Yanagisawa and Anastasiadis, 2006). Furthermore, FYN-mediated phosphorylation of p120 on tyrosine 112 (Y112) prevents the binding of RHOA to membrane-localized p120 and is proposed to render RHOA cytosolic and loaded with GDP (Castaño et al., 2007). Alternatively, the G-protein Gα12 (Galpha12) can bind p120 and simultaneously recruit several

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Rho GEFs [p115RhoGEF (ARHGEF1), PDZ-RhoGEF (ARHGEF11) and LARG (ARHGEF12)] that are capable of activating RHOA (Fukuhara et al., 2001).

Overexpression of p120 in the fibroblast cell line NIH3T3 leads to its cytosolic localization and the direct inhibition of RHOA owing to the Rho GDP dissociation inhibitor (GDI) function of p120. Here, cells are characterized by the formation of a neuron-like protrusion known as a 'branching' phenotype, which is probably caused by the robust inhibition of RHOA-GTP loading by p120 (Anastasiadis and Reynolds, 2000; reviewed by Anastasiadis, 2007).

In contrast to its Rho GDI function, cytosolic p120 can also activate RHOA. In primary keratinocytes and MDCK cells, p120 overexpression results in cytosolic p120, which facilitates growth factor-induced activation of RHOA, leading to the induction of stress fiber formation and increasing migration (Cozzolino et al., 2003). Interestingly, we found that loss of E-cadherin induces cytosolic translocation of p120 and subsequent binding to myosin phosphatase Rho interacting protein (MRIP, also known as MPRIP), which prevents inhibition of RHOA by p120 (Schackmann et al., 2011).

Taken together, several studies have shown that p120 is a main regulator of Rho GTPase activity. Depending on the cellular state and biochemical context, RHOA and RAC1 will be coordinately regulated by a plethora of regulatory proteins (Fig. 2) (for comprehensive reviews on the regulation of Rho GTPases by p120 see Menke and Giehl, 2012; Anastasiadis, 2007).

Regulation of growth factor receptor signaling by p120

An additional layer of complexity regarding the functions of p120 might be provided by the crosstalk with growth factor receptor (GFR) signaling. It is generally accepted that membrane receptors can directly influence the activity of GFRs, integrins and other neighboring adhesion molecules (reviewed by Chen and Gumbiner, 2006). For example, E-cadherin expression can influence EGFR activation in a context-dependent manner (Takahashi and Suzuki, 1996; Qian et al., 2004; Reddy et al., 2005). Supporting this are studies in gastric cancer showing that germ-line and somatic (in-frame deleterious) mutations in the E-cadherin extracellular domain lead to increased activation of EGFR signaling (Mateus et al., 2007; Bremm et al., 2008). Furthermore, p120 was shown to interact with several protein phosphatases, such as RPTPμ (also known as PTPRM) and DEP-1 (also known as PTPRJ) (Zondag et al., 2000; Tarcic et al., 2009), which control GFR dephosphorylation at the plasma membrane. These findings put forth an additional mechanism by which p120 regulates GFR activity (Zondag et al., 2000; Holsinger et al., 2002; Palka et al., 2003).

Nuclear localization and regulation of transcriptional activity by p120

In addition to its membrane-related and cytosolic functions, the presence of an NLS, NES and ARM-domain render p120 capable of shuttling in and out of the nucleus (van Hengel et al., 1999; Roczniak-Ferguson and Reynolds, 2003; Kelly et al., 2004). There is some controversy with regards to how p120 translocates to the nucleus. Nuclear localization might be solely attributed to either of the two NLS (Kelly et al., 2004) or the ARM repeat domain (Roczniak-Ferguson and Reynolds, 2003) (Fig. 3). Alternatively, p120 might travel to the nuclear compartment through association and subsequent translocation with Gli-similar protein GLIS2 (Hosking et al., 2007; Vasanth et al., 2011) or a C-terminal fragment of E-cadherin (Ferber et al., 2008) (Fig. 3).

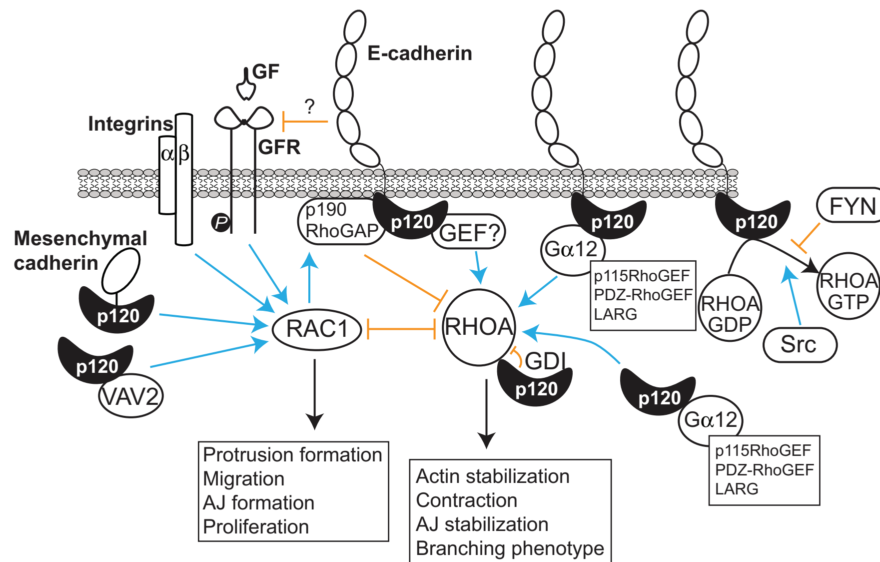

Fig. 2. p120-mediated regulation of Rho GTPase activity. A number of mechanisms, including growth factor signaling, integrin activation and binding of p120 to mesenchymal cadherins, or the Rho GEF VAV2 can facilitate activation of RAC1. In turn, RAC1 can inhibit RHOA activity. Furthermore, RAC1 promotes membrane recruitment of p190RhoGAP, leading to inhibition of RHOA activity. Alternatively, inhibition of RHOA can occur through cytosolic p120, which might act as a RhoGDI. FYN-induced phosphorylation of membrane-localized p120 prevents association of p120 with RHOA, resulting in cytosolic and inactive RHOA. By contrast, SRC-mediated phosphorylation of p120 stimulates rapid activation of RHOA. Furthermore, both membrane-localized and cytosolic p120 can associate with Gα12, which serves as a docking platform for several Rho GEFs (p115RhoGEF, PDZ-RhoGEF and LARG), resulting in activation of RHOA. Overall, p120 acts as key regulator of Rho GTPases downstream of adhesion and growth factor (GF) receptor (GFR) signaling. As such, p120 is at the center of epithelial homeostasis through its regulation of AJ assembly and cellular adhesion. Blue and orange arrows indicate activating and inhibitory signaling events, respectively. GAP, GTPase activating protein; GDI, guanosine nucleotide dissociation inhibitor; GEF, guanine nucleotide exchange factor.

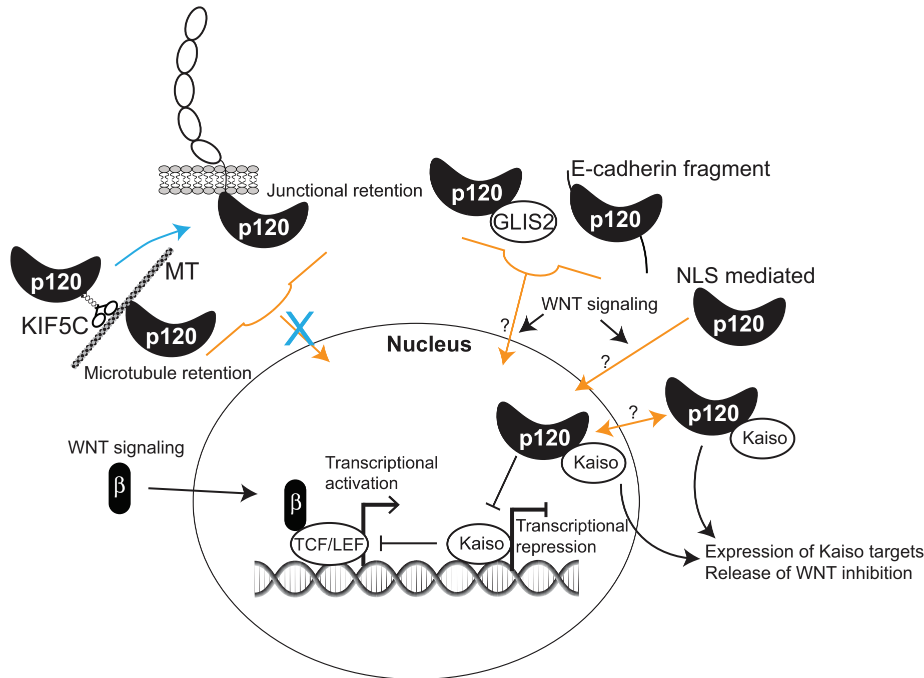

Fig. 3. Regulation of transcription by p120. Stimulation of WNT induces stabilization and nuclear import of β-catenin where it controls TCF-LEF mediated transcriptional activation (canonical WNT signaling). Nuclear localization of the transcription repressor Kaiso can inhibit WNT signaling by sequestering TCF factors, and competing with them for binding to promoter regions. Upon disruption of AJs, p120 can translocate to the nucleus, either directly through its NLS or by being shuttled by its binding partners, such as GLIS2, the cytosolic fragment of E-cadherin, or other yet unidentified mechanisms. In the nucleus, p120 binds to Kaiso and thus prevents the transcriptional repression of its target genes. In addition, this interaction might also prevent Kaiso from sequestering TCF-LEFs, thereby allowing canonical WNT signaling. Furthermore, the association of p120 with microtubules through the kinesin KIF5C or with E-cadherin at junctions might prevent its nuclear localization. Indicated in blue are mechanisms that result in Kaiso-mediated repression and in orange those that lead to the relief of Kaiso-mediated transcriptional repression. β, β-catenin; MT, microtubule.

p120 can modulate gene expression through its direct interaction with the transcriptional repressor Kaiso (ZTBT33) (Daniel and Reynolds, 1999). Kaiso is a member of the POZ-ZF or BTB family of transcription factors that can bind to methylated DNA and/or a specific Kaiso binding sequence (*TCCTGCNA*) (Prokhortchouk et al., 2001; Daniel et al., 2002; Daniel, 2007; Donaldson et al., 2012). Binding of p120 to Kaiso might inhibit its DNA binding and relieve the repression of its target genes, such as WNT11, CyclinD1 (CCND1) and MMP7, which have been linked to noncanonical and canonical WNT-dependent developmental processes (Daniel et al., 2002; Kim et al., 2004; Park et al., 2006; Hong et al., 2010). Nuclear Kaiso might also indirectly inhibit canonical WNT signaling by sequestering β-catenin and TCF/LEF transcription factors that act downstream from canonical WNT signaling (Ruzov et al., 2009; Del Valle-Pérez et al., 2011).

Overall, it appears that p120 is an important regulator of Kaiso-dependent repression of transcription. Furthermore, in a similar manner to β-catenin, p120 can control post-translational processes in the cytosol and regulate transcriptional processes in the nucleus. In conclusion, p120 can localize to the nucleus through several diverse mechanisms, leading to the binding and relief of Kaiso transcriptional repression, which might indirectly modulate canonical WNT signaling (Fig. 3).

Functional redundancy of p120 family members

Removal of p120 results in loss of membranous E-cadherin. Upon overexpression of the p120 family members ARVCF, δ-catenin or p0071, membranous E-cadherin localization is restored *in vitro* (Anastasiadis and Reynolds, 2000; Davis et al., 2003; Hatzfeld, 2005). However, genetic ablation of p120 in mice leads to embryonic lethality at embryonic day 8.5 (Davis and Reynolds, 2006), indicating that under these circumstances there is no functional redundancy among the p120 family members. Corroborating this are tissue-specific p120 knockout mice in which p120 loss was targeted to the eye, brain, kidney, GI tract and salivary glands. In these mice, p120 ablation unanimously resulted in dysfunctional AJs and aberrant tissue morphogenesis (Israely et al., 2004; Davis and Reynolds, 2006; Elia et al., 2006; Smalley-Freed et al., 2010; Marciano et al., 2011; Stairs et al., 2011; Tian et al., 2012). Moreover, and in contrast to other conditional knockout mice, p120 ablation in the mammary gland resulted in cell death due to apoptosis (Kurley et al., 2012). Together, these findings suggest that functional redundancy depend on expression levels of the p120 family members, their affinity for binding to the classical cadherins, or genetic composition of the cell systems used (i.e. the presence of any mutations in tumor suppressor genes or oncogenes).

Overall, p120 has been established as an important regulator of AJ stability, actin dynamics, GFR signaling and transcriptional regulation and is crucial for normal development of many organ systems. Besides being involved in normal cellular processes, such as facilitating cell–cell interactions, migration and regulation of growth, these mechanisms are also strongly associated with cancer. As a result, p120 has become a prominent subject in cancer research.

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Roles for p120 in cancer

Loss of E-cadherin expression is an established hallmark of cancer progression (Hanahan and Weinberg, 2011). Because p120 controls stability and turnover of E-cadherin, regulates Rho GTPases and influences Kaiso-dependent transcriptional repression, it has received increasing attention in the context of cancer progression, as discussed below.

Oncogenic functions of p120

Mutational inactivation of E-cadherin has been strongly linked to tumor progression in multiple tumor types (Berx et al., 1998). Since then, multiple independent groups have established a causal role for E-cadherin dysfunction or loss in tumor development and progression (Perl et al., 1998; Derksen et al., 2006; Ceteci et al., 2007). It is well recognized that inactivation of E-cadherin leads to cytosolic translocation of p120 in colon, breast, bladder, lung, pancreas, prostate and stomach tumors, which has been associated with tumor malignancy (reviewed by Thoreson and Reynolds, 2002). Indeed, studies in breast and colon cancer indicated that cytosolic p120 controls the invasive phenotype of E-cadherin-deficient tumor cells (Shibata et al., 2004; Bellovin et al., 2005). Furthermore, a switch from E-cadherin expression to P-cadherin, which is associated with a more invasive behavior, in ovarian and pancreatic cancer cell lines results in the translocation of p120 to the cytosol, which in turn induces cell migration by activating RAC1 and CDC42 (Taniuchi et al., 2005; Cheung et al., 2010).

In E-cadherin-negative breast cancer cells, p120 induces anchorage-independence and increased tumor growth *in vivo* (Soto et al., 2008; Schackmann et al., 2011). It appears that in breast cancer, timing and mode of E-cadherin inactivation can be roughly divided into two groups. Inactivation can either occur during tumor development as a result of early mutational inactivation, or can be induced through epigenetic mechanisms during the later stages of disease progression. Intriguingly, this affects how the Rho GTPases are influenced by p120. In human breast cancer cells that are characterized by E-cadherin loss due to hypermethylation, p120 controls anchorage-independent growth through the activation of a RAC1-mitogen activated protein kinase pathway (Soto et al., 2008). Alternatively, we showed that in E-cadherin mutant invasive lobular carcinoma (ILC) cells, cytosolic p120 binds to the Rho antagonist MRIP, thereby preventing MRIP from inhibiting Rho-ROCK signaling, and resulting in anchorage-independent tumor growth and metastasis (Schackmann et al., 2011). Vice versa, our data also suggested that MRIP simultaneously prevents p120 from exerting its inhibitory role on Rho activity. These findings exemplify that biochemical signals downstream of cytosolic p120 can be differentially regulated and are highly dependent on cancer type, cellular context and timing of E-cadherin inactivation (Fig. 4B).

Furthermore, p120 is capable of associating with and stabilizing mesenchymal cadherins, such as cadherin-11 and N-cadherin, which do not establish stable AJs (Reynolds et al., 1994). These cadherins, in turn, facilitate p120-dependent activation of RAC1, thereby inducing anchorage-independent growth of the MDA-MB-231 breast cancer cell line, in which E-cadherin is hypermethylated, and an increase in motility and invasion. Taken together, these data indicate that p120 acts as a rheostat that promotes either epithelial integrity when it is bound to E-cadherin, or motility when it is associated with mesenchymal cadherins (Yanagisawa and Anastasiadis, 2006; Soto et al., 2008). Zeppo-1 (ZNF703), which is frequently amplified in breast cancer, might provide a link to the upstream activation of this pathway. Zeppo-1 promotes EMT by repressing the expression of E-cadherin and promoting localization of p120 to the cytosol. These processes in turn lead to increased migration of mammary epithelial cells, and enhanced tumor growth and metastasis in a transplantation-based mouse model of breast cancer (Slorach et al., 2011).

In pancreatic cancer, cytosolic localization of p120 is frequently observed and correlates with reduced patient survival, suggesting that p120 functions as an oncogene here (Karayiannakis et al., 1999; Chetty et al., 2008). Indeed, subsequent p120 knockdown experiments performed in pancreatic PaTu8889 and PANC-1 cells indicated that p120 induces proliferation, invasion and migratory behavior (Mayerle et al., 2003; Cheng et al., 2012). Overall, it is clear that loss of E-cadherin leads to cytosolic p120. Although the underlying mechanisms have only partially been solved, it is evident that aberrant regulation of the downstream Rho GTPases has a crucial function in the regulation of p120-induced tumor progression.

The role of Kaiso in cancer

As discussed above, p120 controls transcription through a direct interaction with Kaiso, which relieves the transcriptional repression of its target genes (Daniel and Reynolds, 1999; Daniel et al., 2002). Recent studies in cancer have examined localization of Kaiso in relation to p120. Overall, they indicated that nuclear Kaiso localization is decreased when p120 resides in the cytosol, although it appeared that the expression of Kaiso and its localization are highly variable, and depend on the cellular context and type of tumor examined (Soubry et al., 2005; Kantidze et al., 2009; Soubry et al., 2010; Zhang et al., 2011; Vermeulen et al., 2012). Notwithstanding this high variability, several *bona fide* Kaiso targets (e.g. WNT11, MMP7, CyclinD1) have been strongly linked to cancer (Christiansen et al., 1996; Ii et al., 2006; Musgrove et al., 2011; Uysal-Onganer and Kypta, 2012). Intriguingly, Kaiso knockout mice are viable, fertile, phenotypically normal and do not develop tumors (Prokhortchouk et al., 2006). Here, knockout of Kaiso did not influence the expression of any of the established Kaiso target genes (*MTA2* in brain, liver and spleen; Rapsyn (*RAPSN*) in muscle and *S100A4* in spleen) (Prokhortchouk et al., 2006), suggesting that within a noncancerous physiological context, there is some redundancy between Kaiso and other yet unidentified transcriptional repressors. Furthermore, when Kaiso was knocked out in the tumor-prone adenomatous polyposis coli $Apc^{Min/+}$ mice (min, multiple intestinal neoplasia), intestinal tumor onset was delayed (Prokhortchouk et al., 2006). This is an important paradox because most studies point to a possible tumor suppressor role for Kaiso. Perhaps the unexpected effect of Kaiso knockout in the Apc^{Min} mouse is a reflection of the differences between work performed in cell lines and *Xenopus* compared with the mouse models. Another possibility is that repression of currently unknown Kaiso targets might promote tumor formation. In favor of this hypothesis is the fact that the presence of nuclear Kaiso correlates with metastatic prostate cancer and high-grade invasive ductal carcinoma (IDC), suggesting that Kaiso-mediated transcriptional repression indeed exerts oncogenic properties (Jones et al., 2012; Vermeulen et al., 2012). By contrast, non-small-cell lung cancer (NSCLC) and ILC cells show reduced levels and/or cytosolic localization of Kaiso, a

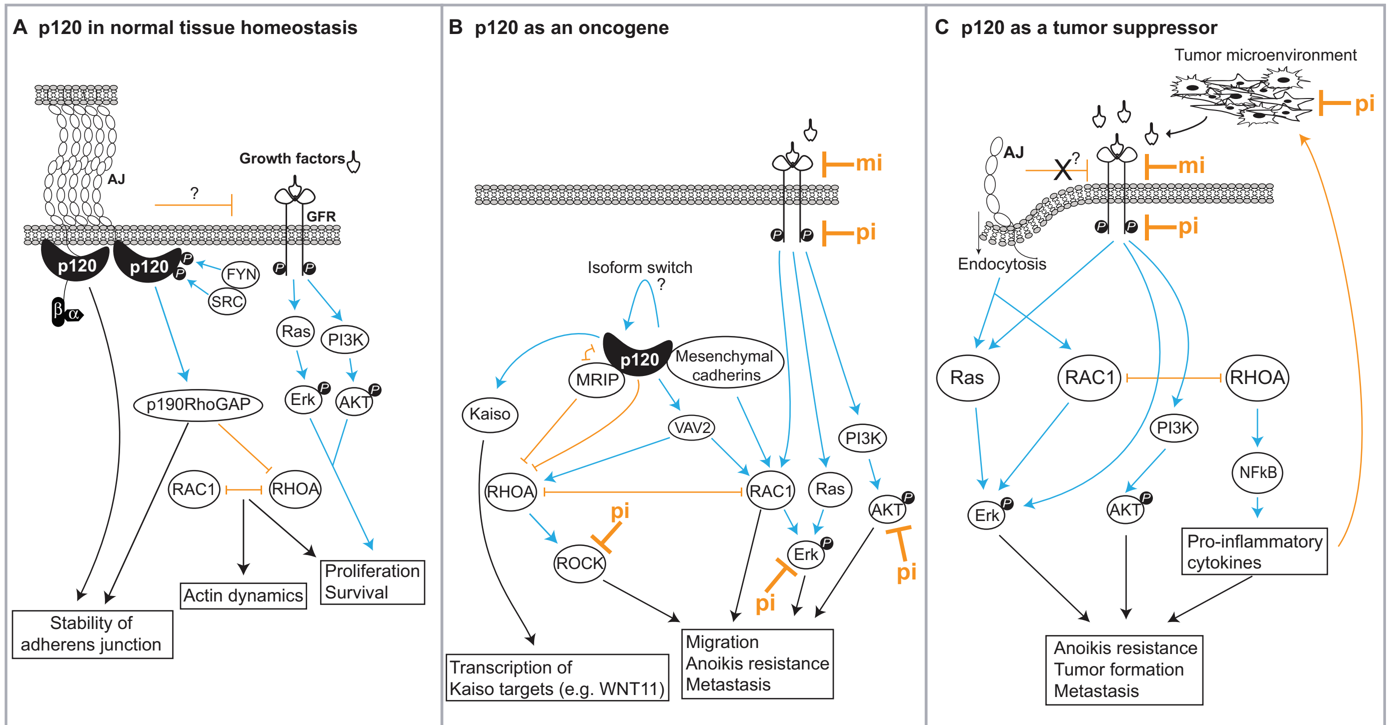

Fig. 4. p120 at the center of cancer development and progression. (**A**) p120 controls epithelial homeostasis. p120 is crucial for the regulation of AJ formation, migration and proliferation through a balanced control of Rho GTPase activity and GFR signaling. (**B**) Loss of E-cadherin results in the non-membranous localization of p120. Depending on the context and cell type, p120 can interact with MRIP, which will result in active Rho-Rock signaling. Alternatively, cytosolic p120 might lead to the activation of Ras, Rac and PI3K-AKT signaling through the relief of GFR inhibition. Furthermore, cytosolic and/or nuclear translocation of p120 might influence Kaiso-dependent transcriptional regulation. Together, these processes underlie the oncogenic activity of cytosolic p120 and can induce tumor progression. (**C**) Loss of p120 destabilizes the AJ, which induces sensitization to GFRs, which in turn leads to anoikis resistance, tumor formation and metastasis through the activation of Ras- and Rac-induced signaling. Furthermore, loss of p120 can result in increased RHOA activity, leading to the activation of NFκB, and the production of pro-inflammatory cytokines, which results in the development of a prometastatic tumor microenvironment. Indicated in blue and orange are activating and inhibitory signaling events, respectively. Potential therapeutic treatment options are also highlighted. mi, monoclonal antibody inhibitor; pi, pharmacological inhibitor; α, α-catenin; AJ, adherens junction; β, β-catenin; GFR, growth factor receptor.

finding that is in line with the assumption that Kaiso represses the expression of oncogenic proteins (Dai et al., 2011; Vermeulen et al., 2012). Much remains unclear concerning the putative targets of Kaiso *in vivo* in mammalian systems, and although correlation studies suggest both oncogenic and tumor suppressor functions for nuclear Kaiso, additional biochemical data are required to fully understand the role of Kaiso in different tumor types.

In summary, a large amount of data implicates p120 in the regulation of cancer development and progression (as summarized in Fig. 4). p120 can function as an oncogene that drives migration and anchorage independence, both of which are established hallmarks of metastatic cancer. Although the molecular events downstream of p120 might differ depending on the cellular context and tissue type, the acquired invasive phenotypes are largely consistent with a functional inactivation of the AJ. However, as discussed below, p120 has also been suggested to act as a tumor suppressor.

Loss of p120 reveals tumor suppressor functions

Breast cancer

The first indications that p120 has tumor suppressor activity came from studies in which p120 was conditionally deleted in the salivary and mammary glands (Davis and Reynolds, 2006). Conditional inactivation using MMTV-Cre resulted in a block in acinar development and induced intra-epithelial ductal hyperplasia of the salivary gland (Davis and Reynolds, 2006). Owing to the fact that mice died shortly after birth, it remained unclear what the function of p120 was in the postnatal mammary gland. Follow-up studies using mosaic mammary-specific conditional p120 mice revealed that loss of p120 is not tolerated in the mammary gland owing to the lack of adherence of cells and their subsequent exclusion from mammary gland formation (Kurley et al., 2012). These data are in agreement with a crucial role for p120 in the maintenance of AJs, because previous knockout experiments in mice had demonstrated that mammary-specific loss of E-cadherin also resulted in cellular apoptosis (Boussadia et al., 2002; Derksen et al., 2011). Moreover, the fact that loss of E-cadherin or p120 is not tolerated in breast cancer implies that inactivation of the AJ in breast cancer has to be preceded by loss of a tumor suppressor gene or activation of an oncogenic protein.

p120 expression and localization can be used to establish the differential diagnosis of breast cancer. For instance, whereas loss of E-cadherin and subsequent cytoplasmic localization of p120 are typical for ILC, IDC mostly retain membrane-localized E-cadherin and p120 (Gamallo et al., 1993; Dabbs et al., 2007). However, several studies indicated that ∼10% of all IDC cases

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show a complete or partial loss of p120, which correlates with disease progression (Dillon et al., 1998; Thoreson and Reynolds, 2002; Talvinen et al., 2010; Schackmann et al., 2013). Despite these findings, to date only one missense p120 mutation (1081C→A) and one nonsense mutation (1963C→T) were found in breast cancer (Stephens et al., 2012). Although a confounding factor for the lack of identification of somatic inactivating mutations is that loss of p120 is often only observed in part of the tumor (Dillon et al., 1998), it suggests that mutational inactivation of p120 in cancer is a rare event. A more likely scenario is that loss of p120 expression in cancer is caused by epigenetic modifications such as hypermethylation, or transcriptional and miRNA-mediated gene repression. In support of this notion, the transcriptional repressor FOXC2 has been shown to inhibit p120 expression and subsequently cause E-cadherin degradation in non-small-cell lung cancer (Mortazavi et al., 2010). FOXC2 is also expressed in metastatic murine cell lines and metastatic basal-like breast cancer, but p120 expression has unfortunately not been studied in these systems (Mani et al., 2007), so it remains unclear whether this possible mechanism is relevant in breast cancer.

Because conditional inactivation of p120 leads to cell death in the mammary gland (Kurley et al., 2012), we introduced conditional p120 alleles into a noninvasive breast tumor model, which is based on mammary-specific somatic inactivation of p53 (Derksen et al., 2011). In this model, somatic loss of p120 resulted in the formation of metaplastic carcinomas that metastasized to lungs and lymph nodes (Schackmann et al., 2013). Underlying this phenotype is the fact that loss of p120 strongly promotes anoikis resistance through hypersensitization of growth factor receptor signaling and the secretion of inflammatory cytokines that promote formation of the prometastatic microenvironment (Schackmann et al., 2013). Alternatively, previous observations in the human E-cadherin-positive breast cancer cells MCF7 indicated that knockdown of p120 resulted in activation of RAC1, Ras and subsequent MAPK (Soto et al., 2008). Whereas the exact underlying mechanism remains unsolved, a common denominator in these findings is the downregulation of E-cadherin, which subsequently leads to activation of Ras, Rac and PI3K-AKT-dependent signaling pathways.

On the basis of the aforementioned data, it has become clear that p120 functions as a tumor and invasion suppressor in breast cancer through the acquisition of anoikis resistance and the formation of a prometastatic microenvironment.

Other cancers

Human squamous cell carcinoma (SCC) has been associated with downregulation of p120, which correlates with a poor patient prognosis (Thoreson and Reynolds, 2002). Reduced expression of p120 is observed in skin and epidermal tumors, whereas the membrane localization of E-cadherin expression is retained here (Ishizaki et al., 2004). Furthermore, loss of p120 correlated with the presence of phosphorylated NFκB in the nucleus, which is a well-known driver of inflammation and has been strongly associated with cancer progression (Perez-Moreno et al., 2008; Karin, 2009). Conditional knockout of p120 in keratinocytes resulted in hyperproliferation and mitotic abnormalities, thereby substantiating its function as a tumor suppressor (Perez-Moreno et al., 2006). In line with the clinical observations, these studies reported that loss of p120 induced RHOA-dependent activation of NFκB and MAP kinases, which promoted the proinflammatory responses underlying the observed hyperproliferation.

p120 has also been implicated in a number of tumors of the gastro-intestinal tract such as human esophageal squamous cell carcinoma (ESCC), in which p120 often displays aberrant localization and reduced expression levels (Karatzas et al., 2000; Chung et al., 2007; Stairs et al., 2011), which correlates to lymph node metastasis (Karatzas et al., 2000; Chung et al., 2007). To establish genetic evidence that p120 acts as a tumor suppressor in this tissue type, Rustgi and co-workers recently used the L2 promoter to drive Cre-mediated conditional knockout of p120 in the upper GI tract. Tumors that developed upon loss of p120 phenocopied human ESCC, showing progression from preneoplasia to neoplasia (Stairs et al., 2011). Although the exact mechanism remains elusive, the authors uncovered that p120 ablation resulted in the development of invasive tumors through the excretion of proinflammatory cytokines such as GM-CSF (CSF2), MCP-1 (CCL2) and M-CSF (CSF1) (Stairs et al., 2011). Alike the skin, a possible mechanism that induces the inflammatory response may be the increased RHOA-dependent activation of NFκB, leading to the formation of a microenvironment favoring tumor formation.

p120 also appears to function as a suppressor of tumor progression in pancreatic cancer. By means of a mutagenic screen using the inducible transposon system 'Sleeping Beauty' in an oncogenic Kras-driven pancreatic mouse model (Mann et al., 2012), p120 was suggested as a candidate tumor suppressor. This assumption was strengthened by means of human tissue microarrays, in which decreased staining of p120 was associated with reduced survival (Mann et al., 2012).

Multiple independent studies observed decreased and/or complete loss of p120 expression in colorectal tumors. In a similar manner to the aforementioned tumor types, loss of p120 is associated with poor survival, increased tumor size and induction of metastatic disease (Skoudy et al., 1996; Gold et al., 1998; Karayiannakis et al., 1999). However, conditional p120 knockout by means of Villin-Cre resulted in massive intestinal barrier defects and chronic inflammation in mice (Smalley-Freed et al., 2010). Intriguingly, when reverting to mosaic p120 deletion in the mouse small intestine, the authors observed the development of tumors that expressed p120 (Smalley-Freed et al., 2011). These findings suggest that p120 ablation in the intestine promotes tumor formation by an indirect and non-cell-autonomous inflammatory mechanism (Smalley-Freed et al., 2011).

Future directions and clinical implications

Although p120 is recognized as a key factor in cancer progression, many mechanistic aspects of its prometastatic signaling remain unclear. For instance, how do specific isoforms, splice variants and the balance between them contribute to malignancy? In order to address these questions, the effects of simultaneous expression of the different p120 isoforms and splice variants need to be studied with regard to cellular properties, such as cell migration, proliferation and their *in vivo* capacity to form metastases. Moreover, very little is currently known regarding the contribution of post-translational modifications of p120 to cancer progression. Furthermore, the limited functional redundancy of the p120 family members and their role in cancer remains elusive and requires additional research. Finally, it is currently unknown which of the Kaiso

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target genes contribute to malignant progression and how they exert their roles. To address these unanswered questions, the role of p120 in cancer development is currently meticulously examined through the use of sophisticated tissue-specific conditional mouse models that not only provide insight into the *in vivo* effects of p120 in tumor development, but also serve as a basis for developing targeted treatment in a tumor-type-specific manner.

In the skin, colon upper GI tract and breast, loss of p120 was found in conjunction with an increased inflammatory response. Although for most organ systems it is yet to be determined whether this is the driving force behind tumor development and progression, the use of anti-inflammatory drugs such as inhibitors of cyclooxygenase (COX) or NFκB might reduce the influx of inflammatory cells, thereby inhibiting the formation of a prometastatic microenvironment (Dannhardt and Kiefer, 2001; Tak and Firestein, 2001; Mohammed et al., 2006; Perez-Moreno et al., 2008; Lyons et al., 2011).

In breast cancer, the cytosolic localization of p120 can be used as a predictive marker for possible treatment with ROCK inhibitors (Schackmann et al., 2011; Patel et al., 2012). Although the clinical use of ROCK inhibitors is currently limited to the suppression of vascular constriction (Fujita et al., 2010), our recent data suggest that ILC with mutant E-cadherin (in contrast to E-cadherin-negative IDC) depend on ROCK signaling for the formation and dissemination of tumors (Schackmann et al., 2011). These findings might pave the way for clinical inhibition of ROCK signaling in specific tumor subtypes such as ILC using already clinically approved inhibitors, for instance fasudil (Nakashima et al., 1998). In such a setting, breast cancer patients with mutant E-cadherin and cytosolic p120 could be treated with ROCK inhibitors. By contrast, breast cancers in which E-cadherin is silenced by hypermethylation during the later stages of tumor progression might benefit from drugs that target Rac and MAPK signaling (Soto et al., 2008).

The clinical intervention options for tumors that are characterized by loss of p120 are currently less clear. Given that, depending on tissue type, inactivation of p120 can lead to redundancy and differential activation of downstream signaling pathways, any intervention regimen will most probably need to be tailored towards specific tumor subtypes. However, a common denominator of p120 loss is the functional inactivation of AJs and the subsequent activation of Ras, Rac and PI3K-AKT signaling. Options for clinical intervention might therefore be based on targeting growth factor receptor pathways that are either directed towards the proximal cues that originate from the plasma membrane, or specifically directed against the kinases (downstream of) Ras, Rac and PI3K-AKT. Therefore, the recent findings from p120 knockout models might allow the identification of patients that are eligible for clinical intervention of GFR pathways and do not have activating mutations or genomic amplifications of these pathways. Given the recent advances made in the field of p120 cancer biology, the future holds great promise for the development of clinical interventions to successfully treat cancers that are characterized by the loss of p120 function.

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