

The adenomatous polyposis coli protein

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Abstract

Mutations in the adenomatous polyposis coli (APC) gene are associated with most colorectal cancers. The APC protein has been implicated in many aspects of tumour development. This article will discuss recent data suggesting that APC may have multiple functions in the cell. First, APC is a component of the Wnt signalling pathway; second, APC may have a role in cell migration; finally, APC may regulate proliferation and apoptosis.

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Mutations in the adenomatous polyposis coli (APC) gene are responsible for the familial form of colorectal cancer, familial polyposis (FAP).¹ Patients heterozygous for a mutant APC gene develop numerous polyps throughout their intestinal tract, which progress into adenoma and malignancies if left untreated.¹ In these polyps, the remaining wild-type copy of APC is lost.^{2,3} Most sporadic intestinal tumours also lack expression of the full length APC protein.⁴ Introducing APC mutations into cells specifically in the gut epithelium is sufficient to cause polyp formation, whereas the introduction of one or several classic oncogenes does not have this effect.⁵ Thus, loss of APC appears to be an extremely early event that initiates colon cancer.⁶

A number of important cellular processes depend on APC function, as indicated by the variety of different APC binding partners. APC has emerged as a component of the Wnt signalling pathway. In addition, it is linked directly to the cytoskeleton and plays a role in the migration of epithelial cells and neuronal growth cones. Involvement of APC in progression through the cell cycle has also been suggested. Evidence for each of these roles will be discussed in turn.

APC in the Wnt signalling pathway

The Wnt signalling pathway is crucial for embryonic development of the body axis in xenopus and the establishment of correct segment polarity in drosophila.^{7,8} Binding of Wnt to its cell surface receptor, frizzled, causes inactivation of the protein kinase, glycogen synthase kinase 3 β (GSK3 β).⁸ GSK3 β is one component of a large protein complex also containing APC, axin, and β -catenin (fig 1A).^{9–15} In the absence of Wnt signalling, GSK3 β phosphorylates APC and β -catenin.⁸ Axin facilitates GSK3 β phosphorylation of APC and β -catenin in vitro and thus may act as a scaffold for this complex.¹⁰ Most importantly, phosphorylation of β -catenin leads to its ubiquitination and targeting to the proteasome, resulting in β -catenin degradation.¹⁶ Degradation of axin, on the other hand, is decreased in response to its phosphorylation by GSK3 β (fig 1B).¹⁷ This ensures that, in the absence of Wnt signalling, axin is available for the axin–APC– β -catenin–GSK3 β complex to support the degradation of β -catenin. APC protein interacts directly with β -catenin,^{18,19} and this interaction is required for proteasome mediated degradation of β -catenin.²⁰ However, APC is not required for β -catenin phosphorylation in vitro. It is possible that APC provides a link between β -catenin and the ubiquitinating enzymes that are required for the targeting of β -catenin to the proteasome. Recently, the β -TrCP protein was identified as a negative regulator of the Wnt pathway in xenopus.²¹ The sequence of β -TrCP contains motifs that are known to be involved in binding to ubiquitinating enzymes,²¹ and it will be of great interest to test the association of APC with β -TrCP or its homologues.

Wnt signalling inactivates GSK3 β and leads to the accumulation of free intracellular β -catenin that can bind to the Tcf/Lef (T cell factor/lymphoid enhancer factor) family of HMG box transcription factors.^{22–28} The β -catenin–transcription factor complex regulates transcription of target genes including c-myc.^{28,29} This link between β -catenin and c-myc activation provides one model for how loss of APC in the gut epithelium may lead to transformation. Loss of APC function would prevent β -catenin degradation so that concentrations of free β -catenin would increase and be available for Tcf/Lef activation. This would result in the inappropriate transcription of genes like c-myc and lead to transformation. This model suggests that the expression of genes regulated by Tcf/Lef is tightly controlled. Indeed, Tcf negative mice lack proliferative compartments and do not develop intestinal crypts.³⁰

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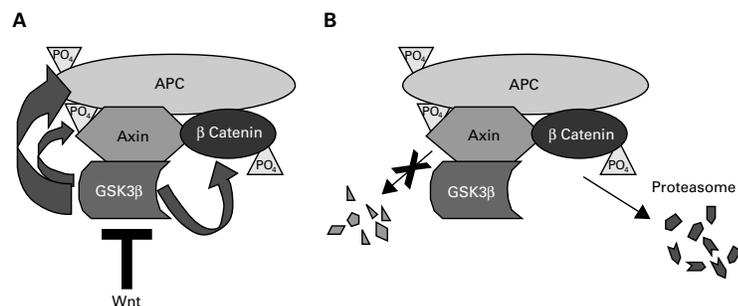


Figure 1 (A) Adenomatous polyposis coli (APC), axin, glycogen synthase kinase 3 β (GSK3 β), and β -catenin form a complex resulting in the phosphorylation of axin, APC, and β -catenin. GSK3 β activity is inhibited by Wnt signalling. (B) Phosphorylation of β -catenin leads to its degradation by the proteasome. The stability of axin is increased when it is phosphorylated by GSK3 β .

But is APC function really that simple? Overexpression of the APC gene specifically in gut epithelium *in vivo* does not lead to a decrease of β -catenin.³¹ Ectopic expression of the APC gene in developing *xenopus* causes axis duplication,³² the same phenotype achieved by ectopic expression of the β -catenin gene.³³ Moreover, levels of β -catenin gene expression are not affected in developing *drosophila* mutants that lack APC.³⁴ In fact, these flies develop normally and have minor defects, mostly in the central nervous system (CNS).³⁴

Normal intestinal epithelial cells do not appear to contain appreciable amounts of free β -catenin, which is the pool of β -catenin that is regulated by the APC-axin complex; untransformed cultured epithelial cells also do not contain free β -catenin.³⁵ On the other hand, transformed cells contain a large pool of free β -catenin that is sensitive to downregulation when wild-type APC concentrations are increased.^{20, 35} The inability of mutant APC to decrease β -catenin concentrations may allow this large pool of β -catenin to remain unchecked and hence contribute to the progression of colorectal cancer at later stages. How mutations in APC are involved in the initial steps of polyp formation may in turn be related to the role played by APC in the migration of cells.

APC in cell migration and adhesion

The APC protein can bind to and bundle microtubules *in vitro* and induce their assembly.^{36, 37} The C-terminal domain of APC contains a tau protein-like domain and colocalises with microtubules when overproduced in tumour cells.³⁶⁻³⁸ In epithelial cells, endogenous APC localises to the tips of microtubules invading areas of the membrane involved in migration.³⁹ Depolymerising microtubules using nocodazole inhibits this type of migration in epithelial cells and disrupts APC localisation.³⁹ These observations have led to the hypothesis that the APC protein is involved in stabilising microtubules in specific areas of the cell, resulting in the formation of stable cellular protrusions that are actively involved in migration.

This type of migration may be particularly important in neurons, where a requirement for microtubule dynamics in the extension and guidance of growth cones has been well documented.⁴⁰ In cultured neuronal cells, the APC protein is enriched in growth cones and this distribution requires an intact microtubule network.^{41, 42} The synthesis of APC in the nervous system coincides with the ability of neurons to undergo morphological changes, such as process extension and synapse formation, and its pattern of synthesis parallels that of microtubule associated protein 2 (MAP2) and other microtubule associated proteins.⁴³ Similarly, PC-12 cells treated with nerve growth factor (NGF) increased the production of APC as they extended nerve growth cone-like structures.⁴⁴ In *drosophila*, loss of APC results in CNS defects that may be related to the inability of specific neuronal structures

to elongate properly, consistent with a cytoskeletal defect.³⁴ In this context, it is noteworthy that the incidence of neuronal brain tumours is significantly raised in patients with familial polyposis,⁴⁵ suggesting that loss of APC function might be related to neuronal abnormalities in humans. All these data are consistent with the idea that APC plays an important role in cell migration involving microtubules, which is particularly important in neuronal and epithelial cell migration.

The mutations described in patients with FAP usually consist of truncations leading to loss of the C-terminal region of APC, which contains the microtubule binding site.⁴ This is conceivably the reason for polyp formation, the earliest detectable change in patients with FAP. Such mutant APC proteins cannot bind to and stabilise microtubules; this might compromise the migration of gut epithelial cells and prolong their residence near the proliferative environment of the crypt, and increase the time they are exposed to the toxins present in the gut. Receiving inappropriate proliferative signals in the crypt might cause abnormal growth of the polyps and increased exposure to the toxins present in the gut may lead to the accumulation of additional mutations that ultimately result in transformation. At this later stage, it is likely that there is an increase in the pool of free β -catenin, which cannot be regulated by the mutant APC, so that increased Tcf/Lef transcriptional activation occurs, further advancing transformation.

Some direct evidence for a role of APC in the migration of gut epithelial cells is now available. In the intestinal epithelium, each proliferative crypt supplies differentiating enterocytes to surrounding villi.⁴⁶ Normally, enterocytes migrate upwards in orderly columns and do not mix with cells derived from neighbouring crypts.³¹ When the APC gene was overexpressed in gut epithelium, cells migrated in a disorderly manner, so that mixing between enterocytes from neighbouring crypts was observed.³¹ It is possible that the observed change in cell migration was caused by a decrease in intracellular adhesion that may have been induced by excess APC. However, the expression of E-cadherin and catenins, and the distribution of these proteins in cells overproducing APC were indistinguishable from neighbouring wild-type cells.³¹ In addition, barrier function in tissues overexpressing the APC gene appeared to be perfectly intact.³¹ These observations suggest that excess APC did not cause alterations in intracellular adhesion and are consistent with a direct role for APC in regulating the migration of enterocytes in the gut.

One question that has emerged is how the interaction between APC and microtubules is related to the interaction of APC with the axin- β -catenin complex. A non-degradable form of β -catenin accumulated in APC containing clusters in epithelial cells.⁴⁷ Cells producing this stabilised form of β -catenin did not migrate normally, and neither were they able to extend stable protrusions to migrate into a surrounding matrix when treated with

scatter factor.⁴⁸ These observations suggest that a stable complex of non-degradable β -catenin with APC caused a decrease in the ability of APC to interact with microtubules, so that the formation of stable cellular protrusions was inhibited. This could explain why overproduction of this non-degradable form of β -catenin in gut epithelium correlated with decreased migration in intestinal cells *in vivo*.⁴⁹ An alternative interpretation of these observations is that overexpression of the β -catenin gene caused an increase in intercellular adhesion, which led to the observed decrease in migration. Indeed, overexpressing the β -catenin gene in gut epithelium led to an apparent increase in E-cadherin. However, overexpression of the E-cadherin gene specifically in gut epithelium affected not only migration but also proliferation and apoptosis of enterocytes.⁵⁰ This indicates that the upregulation of E-cadherin induced by the overproduction and stabilisation of β -catenin in gut epithelium does not simply mimic the upregulation of E-cadherin, and that the interaction of the additional β -catenin with APC may contribute directly to the observed decrease in migration. However, the confirmation of β -catenin as a possible key regulator of APC-microtubule interactions will require *in vitro* analysis.

It is important to note that the upregulation of β -catenin production in the studies described above did not lead to the formation of polyps or adenoma, as would be expected if excessive amounts of β -catenin were available for binding to Tcf/Lef transcription factors. One likely explanation is that the additional β -catenin was not available for binding to the Tcf/Lef transcription factors because it was bound to E-cadherin. The observed decrease in enterocyte migration should also lead to the formation of polyps if the model suggested above is correct. However, the observed increase in cell adhesion is likely to have obscured any effect on cell migration, illustrating how difficult it is to separate cell adhesion and migration in the context of the gut epithelium, where these processes are tightly coupled.

Further support for a role for APC in cell migration comes from examinations of the earliest detectable polyps in Min (multiple intestinal neoplasia) negative mice, which are heterozygous for mutated APC and develop multiple polyps throughout their intestinal tract.⁵¹ The initial step in polyp formation appears to be the formation of outpocketing pouches from the proliferative zone, which then migrate backwards.⁵² This morphology of early polyps is consistent with a defect in their migration. Furthermore, the migration of enterocytes in these mice was reduced by 25% when compared with that of normal litter mates.⁵³ Importantly, restoring the migration rate of Min negative enterocytes to normal levels by administering the non-steroidal anti-inflammatory, sulindac, led to a significant reduction in the number of polyps.^{53, 54}

APC in proliferation and apoptosis

Transformation is often associated with increased cell proliferation and/or decreased apoptosis, and a role for APC in both of these processes has been postulated. So far, no consensus regarding the effect of APC on apoptosis has been reached because both induction and inhibition of apoptosis by APC have been described.⁵⁵⁻⁵⁷ Most importantly, however, overexpressing the APC gene in normal intestinal epithelia does not alter the rates of proliferation or apoptosis,³¹ and cells in the earliest detectable polyps show no changes in proliferation or apoptosis when compared with normal tissue.⁵²

APC has multiple consensus sites for cyclin dependent kinases (CDKs) and is a substrate for these kinases.⁵⁸ APC overexpression led to cell cycle arrest in tissue culture cells.⁵⁹ Mutant APC induced the arrest less efficiently and the arrest could be overcome by the overexpression of CDK genes.⁵⁹ This is consistent with the finding that overexpression of APC appeared to downregulate cyclin-CDK complex activity.⁵⁹ One trivial explanation for these observations is that excessive amounts of the CDK consensus sites contained in the APC protein diminished the amount of CDK available for other substrates, thus leading to cell cycle arrest. Because no difference in APC phosphorylation was observed in cells at different stages of the cell cycle, the involvement of APC in CDK mediated cell cycle regulation remains unclear.⁵⁸

Additional evidence for a possible role for APC in the cell cycle is the discovery of another APC-binding protein, EB1.⁶⁰ The EB1 protein localises to interphase and mitotic microtubules,⁶¹ and is required for a cell cycle check point in yeast.⁶² It is not known whether the binding of EB1 to APC is related to the role of EB1 in the cell cycle because the association of EB1 with microtubules does not depend on APC and a homologue of APC has not been identified in yeast.⁶¹ However, it is possible that EB1 is sufficient for the simpler cell cycle machinery of yeast, whereas both APC and EB1 are required in more complex mammalian systems. In summary, APC may play a role in both apoptosis and cell cycle regulation. However, *in vivo* data suggest that in the context of a normal epithelium, APC does not affect either of these processes.

Summary and conclusions

APC is important for tissue homeostasis and loss of its functions is associated with familial and sporadic cases of colon cancer. It is a large protein with many binding partners, and many more are likely to be identified over the next few years. The data so far support at least two major roles for APC: a role in cell migration via its direct link with the cytoskeleton and a role in gene expression via its ability to regulate the amount of β -catenin available for regulating transcription (fig 2). A role in regulating cell migration could explain the early stages of disease. A migration defect could lead to the accumulation of cells to form polyps, the earliest detectable change in the progression to

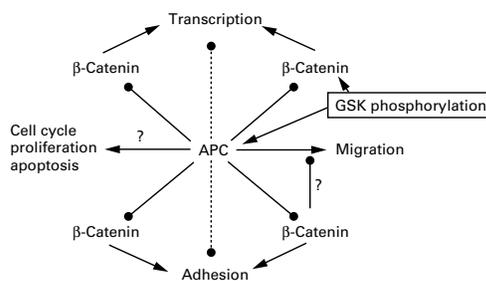


Figure 2 The adenomatous polyposis coli (APC) protein can regulate the turnover of β -catenin and thus can indirectly affect gene transcription and cell adhesion (indicated by the dotted lines). The interaction between APC and β -catenin is regulated by glycogen synthase kinase 3 β (GSK3 β) phosphorylation. APC may also have roles in cell proliferation and apoptosis. Arrows denote enhancing or positive effects, whereas inhibitory or negative effects are denoted by lines ending in closed circles.

colon cancer. A role in regulating β -catenin concentrations may be important in the later stages in colorectal cancer. It is also possible that in normal tissue, APC participates in additional signalling pathways and functions in the regulation of the cell cycle and apoptosis.

APC has been referred to as a “gatekeeper” in the progression of colon cancer.⁶³ In fact, it may hold the key to several gates through which cells pass on their way to malignancy. It is in a key position to regulate the balance between cell adhesion and migration and may also be involved in proliferation and apoptosis. The balance between these processes is particularly crucial in developing tissues and in the maintenance of renewing tissues, such as the gut, which explains why APC loss manifests itself in this organ most strongly.

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