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Desmosomes: new perpetrators in tumour suppression

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Abstract

Adherens junctions, which are intercellular adhesive complexes that are crucial for maintaining epithelial homeostasis, are downregulated in many cancers to promote tumour progression. However, the role of desmosomes — adhesion complexes that are related to adherens junctions — in carcinogenesis has remained elusive. Recent studies using mouse genetic approaches have uncovered a role for desmosomes in tumour suppression, demonstrating that desmosome downregulation occurs before that of adherens junctions to drive tumour development and early invasion, suggesting a two-step model of adhesion dysfunction in cancer progression.

More than 90% of human cancers are of epithelial origin[1]. Elaborating the factors that promote the normal architecture and function of epithelia, and the mechanisms through which these are perturbed, is therefore fundamental for understanding the genesis of most human cancers. The formation, maturation and homeostasis of epithelia require carefully choreographed programmes of cell proliferation, adhesion, polarity, migration and differentiation[2]. Vital for the unity of cells in epithelial sheets are adhesion junctions, such as adherens junctions and desmosomes. These structures not only facilitate intercellular adhesion to ensure tissue integrity but also serve as crucial regulators of processes such as epithelial morphogenesis, differentiation and wound healing[3,4]. Moreover, dysfunction of either junctional complex is associated with specific epithelial diseases. However, until recently, only adherens junctions had been linked to the suppression of cancer development. In this Progress article, we discuss the newly appreciated role of desmosomal adhesion complexes in tumour suppression, highlighting recent mouse genetic studies and addressing how the p53 and p63 pathways might intersect with desmosome-mediated adhesion in this context.

Adherens junctions and cancer

Adherens junctions are key intercellular adhesion complexes[5]. Three main protein families constitute traditional adherens junction complexes: transmembrane cadherins, armadillo proteins and cytoskel-etal adaptors (FIG. 1). Classical cadherins, including the family prototype E-cadherin (encoded by *CDH1*), mediate cell–cell interactions in a calcium-dependent, homophilic manner through their extra-cellular domains[6–9]. The cytoplasmic tails of cadherins bind members of the armadillo protein family, such as β-catenin (encoded by *CTNNB1*) and p120 catenin (encoded by *CTNND1*)[9–11]. Cadherins communicate with the actin cytoskeleton through contacts with β-catenin, which can interact with actin-binding proteins such as α-catenin (encoded by CTNNA genes)[12–16]. When not bound to cadherins, β-catenin can translocate to the nucleus to promote WNT signalling, by binding to LEF/TCF

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transcription factors and regulating the transcription of LEF/TCF-dependent target genes[17–19].

Although constitutive and tissue-specific ablation of adherens junction protein-encoding genes in mice has underscored the importance of adherens junctions in epithelial tissue function and homeostasis, it is the dynamic regulation of such structures that promotes tissue plasticity and reorganization during processes such as developmental epithelial to mesenchymal transition (EMT), wound healing, and cancer progression and metastasis[20]. Indeed, it is well established that E-cadherin-based cell–cell adhesion is lost during the progression of many types of human cancers as they acquire invasive and metastatic potential. Importantly, down-regulation of both E-cadherin and p120 catenin in human tumours is commonly associated with a poor clinical outcome[21–25]. The importance of adherens junction dysfunction in promoting cancer progression has been definitively demonstrated using mouse genetic models. For example, in the *Rip1Tag2*-transgenic mouse model, in which SV40 large T antigen expression in pancreatic β-cells causes neuroendocrine pancreatic tumours, the maintenance of E-cadherin expression causes tumours to stall at the adenoma stage. By contrast, the forced disruption of adherens junction-mediated adhesion through the expression of dominant-negative E-cadherin drives the transition of adenomas to carcinomas, which is accompanied by tumour invasion and metastasis[26]. Similarly, *Cdh1* deletion in the mammary epithelium of mice that are prone to breast cancer — because of the loss of the tumour suppressor *Trp53* — is associated with accelerated tumour development and increased invasion and metastasis[27]. In addition, conditional inactivation of *Ctnnd1* in mouse salivary gland or skin drives tumorigenesis[28,29], and ablation of *Ctnna1* in mouse skin induces squamous cell carcinoma development[30]. Collectively, the data compiled from *in vitro* cell culture experiments, human tumour analysis and mouse model studies support an unambiguous function for adherens junction-mediated adhesion in tumour suppression.

Desmosomes fortify cell adhesion

Although adherens junctions are fundamental both for intercellular adhesion in epithelia and for enabling the dynamic rearrangements of epithelia, desmosomes have traditionally been viewed as static protein complexes that reinforce adhesion between epithelial cells[31]. The strong intercellular adhesion that is provided by desmosomes is particularly important for conferring strength to tissues that must resist large amounts of mechanical stress. Especially prominent in the skin and heart, desmosomes connect cell–cell contact sites at the plasma membrane to the intermediate filament cytoskeleton to promote tissue integrity and homeostasis[4,32]. Compromised desmosome function can result in various human diseases, symptoms of which typically include epidermal fragility and blistering, thickened skin of the palm or soles (palmoplantar keratoderma) and/or cardiomyopathy[33].

Like adherens junctions, desmosomes comprise three main protein families: cadherins, armadillo proteins and plakins, which are arranged in a similar manner to that of adherens junction complexes (FIG. 1). However, the precise molecular composition of desmosomes can be variable and can depend on the tissue-specific or differentiation-specific expression of particular isoforms of the constituent proteins[4]. The two types of desmosomal cadherins — the desmogleins (DSG1–4) and the desmocollins (DSC1–3) — mediate adhesion between apposing cells through interactions of their ectodomains[34–40]. Intracellularly, desmosomal cadherins bind to the armadillo proteins junction plakoglobin (JUP)[41–44] and plakophilins (PKP1–3)[45–47], which help to bridge the cadherins to the intermediate filament cytoskeleton. Additionally, JUP is highly homologous to β-catenin and can substitute for β-catenin in adherens junctions, as well as localize to the nucleus where it can regulate the transcription of LEF/TCF-target genes[48–52]. PKPs also exhibit dual localization at the

desmosome and in the nucleus, where their ability to affect gene expression is implicated but incompletely understood[46,47,53]. The most important plakin family member is desmoplakin (DSP; also known as DP), which interacts with JUP and intermediate filaments, providing the final link in the chain from the plasma membrane to the cytoskeleton[54–57]. Another key desmosomal protein, which was identified by its dramatic loss-of-function blistering phenotype in the epidermis and in other stratified epithelia of knockout mice, is p53 apoptosis effector related to PMP-22 (PERP)[58]. PERP is a tetraspan membrane protein that is transcriptionally activated by the p53 tumour suppressor during DNA damage-induced apoptosis, and by the related transcription factor p63 during the development of stratified epithelia[58,59]. Although PERP has been unequivocally localized to desmosomes in stratified epithelia and found to be crucial for proper desmosome assembly, its interacting partners within the desmosome remain elusive. Importantly, PERP provides a key link between the p53 family of transcriptional regulators and cell–cell adhesion. Further support for this connection is the documented activation of various cell–cell adhesion components by p63 in mammary epithelial cells[60]. Thus, as a target of both p53, which is inactivated in at least 50% of all human cancers, and p63, which is an important tumour suppressor in specific contexts[61], PERP is a potentially crucial mediator of tumour suppression downstream of these transcription factors (FIG. 2).

Genetic loss-of-function studies in mice have reinforced the importance of desmosomes for normal tissue function. For example, constitutive deletion of *Dsc3*, *Dsg2* or *Dsp* causes early embryonic lethality probably owing to defective adhesion in processes essential before, at or after implantation, respectively[62–64]. By contrast, $Jup^{-/-}$ animals typically die later in embryogenesis primarily owing to severe heart abnormalities[65,66], and $Perp^{-/\&\ minus;}$ mice die perinatally with profound epithelial blistering[58]. Mice with constitutive knockout of *Dsc1* or *Dsg3* or with conditional deletion of *Dsp* or *Dsc3* in the skin survive, but exhibit epidermal integrity defects[67–70]. Supporting a pivotal role for desmosomes in tissue function are human diseases in which desmosome components are inactivated by mutation, targeted by autoantibodies or proteolysed by bacterial toxins. These diseases are characterized by phenotypes such as severe abnormalities of the skin, the ectodermal appendages and/or the heart and provide evidence for a crucial function for desmosome-mediated adhesion *in vivo*[71]. Interestingly, although inactivation of adherens junction components can cause tissue degeneration or can instigate cancer development and metastasis, compromised desmosome function is typically thought to only result in degenerative diseases, such as palmoplantar keratoderma and ectodermal dysplasia, and has not been clearly associated with cancer predisposition[31].

Desmosomes and cancer

Direct genetic loss-of-function studies querying the role of desmosomes in cancer have been impeded by the aforementioned lethality that is typically associated with the constitutive deletion of desmosome genes in mice. In addition, data correlating the expression of particular desmosome components in human tumours with tumour progression are contradictory and confusing, with upregulation, downregulation or maintenance of desmosome components observed. For example, the expression of some desmosome proteins, including DSG2, DSG3 and PKP3, is increased compared with normal tissue in certain cancers of the skin, head and neck, prostate and lung, and this increased expression is associated with enhanced tumour progression and/or reduced patient survival[72–76]. By contrast, the loss or reduction of one or more desmosome components, including DSG1–3, DSC2, DSC3, JUP, PKP1–3 and DSP, is observed on the development and/or the progression of various human epithelial cancers, including skin, head and neck, gastric, colorectal, bladder, breast, prostate, cervical and endometrial cancers, often correlating with advanced tumour grade, increased metastasis and/or poor prognosis[76–95]. Finally, in other

instances, no obvious changes in the levels of desmosomal proteins have been noted during cancer progression[75,77,80,96]. Attempts to clarify the role of desmosomal adhesion in cancer by modulating the expression of desmosome components in cultured cells have produced confounding results. In some cases, overexpression of desmosome components in cultured cells promotes proliferation, inhibits apoptosis and increases invasion, characteristics that are advantageous to tumour cells[74,97,98]. Moreover, ectopic expression of DSG2 in the upper layers of mouse skin induces tumour development[99]. By contrast, other experiments have shown that overexpression of desmosome components in cell lines suppresses tumour-promoting behaviour, such as invasion and anchorage-independent growth[93,100]. Consistent with a potential role for desmosomes in tumour suppression, overexpression of JUP in SV40-transformed fibroblasts or bladder cancer cells, and overexpression of desmosomal cadherins in squamous cell carcinoma (SCC cells, suppresses tumour formation and/or invasion in mouse xenograft assays[101–103]. Additionally, knockdown of PKP3 in colon cancer cells promotes anchorage-independen growth and tumour growth in immunocom-promised mice[104]. Adding to the uncertainty regarding the role of desmosomes in cancer is the observation that although potentially oncogenic mutations that occur in or near putative JUP phosphorylation sites have been noted in prostate and gastric cancers[91,105], mutations in desmosome components seem to be rather uncommon.

Overall, the fact that some experiments support a tumour-suppressive role for desmosomes in cancer and others provide evidence for an oncogenic function could reflect real context-dependent differences in the contribution of desmosomes to cancer. Alternatively, the disparate findings could result from limitations in these surrogate models for carcinogenesis — such as, the artificial conditions under which cultured cells are grown, the analysis of transformed cells with numerous genetic alterations and the failure to recapitulate normal tissue architecture or a functional immune system in mouse xenograft tumour models. Therefore, to definitively unveil the role of desmosomes in cancer, it is imperative to use physiologically relevant *in vivo* genetic cancer models to accurately mimic the complexities of human cancer.

An unequivocal approach to establishing the contribution of desmosomes to cancer is the use of mouse models with intact immune systems in which cancers develop in the appropriate tissue microenvironment as a result of defined genetic lesions. Two recent studies have used this approach, consequently providing direct causal evidence linking desmosome deficiency to cancer development. The first study sought to pinpoint proteins that are crucial for restricting tumour invasion in the *Rip1Tag2* model of pancreatic islet cell tumorigenesis, which proceeds from non-invasive to focally invasive and to broadly invasive carcinomas[106]. Gene expression analysis of non-invasive and broadly invasive pancreatic lesions derived from these mice showed that the expression of genes encoding various desmosomal components, including *Dsp*, *Dsg2*, *Dsc2* and *Pkp2*, was significantly reduced in highly invasive tumours compared with non-invasive ones, suggesting that desmosome downregulation may contribute to malignant progression[106]. To test the importance of the downmodulation of desmosome genes, conditional *Dsp*-knockout mice were analysed. Although conditional deletion of *Dsp* in the pancreatic β-cells did not detrimentally affect the survival of the mice or tumour growth, loss of *Dsp* did enhance local invasion of tumours, without affecting broad invasion or metastasis. Interestingly, expression of E-cadherin was maintained in the locally invasive *Dsp*-deficient tumours, highlighting the independent nature of the desmosomes and the adherens junctions in this context, despite the fact that these two junctions are thought to regulate each other's stability[68,107]. These results demonstrate that loss of desmosome function is an important step towards malignant conversion by facilitating local invasion and, therefore, that desmosome-mediated adhesion is a key impediment to tumour progression. Moreover, in conjunction with previous experiments in the *Rip1Tag2* mouse model, these findings

suggest a two-step model for cancer progression, in which desmosomal downregulation causes local invasion in an EMT-independent manner, and subsequent loss of adherens junctions promotes full cancer progression[26] (FIG. 3).

To address the role of desmosomes in a model of human skin cancer, mice with conditional deletion of *Perp* in the epidermis were exposed to chronic ultraviolet B (UVB) radiation to induce SCCs[108]. *Perp* loss in the skin reduced the latency of tumour development and increased the multiplicity of tumours compared with UVB-treated wild-type controls, indicating that *Perp* deficiency promotes tumour initiation. Moreover, tumours that developed in the *Perp*-deficient mice were typically less differentiated than those in control mice, suggesting that *Perp* loss also facilitates tumour progression. Three mechanisms were proposed to explain the propensity of *Perp*-deficient mice to develop skin cancer. First, as *Perp*-deficient keratinocytes had an impaired apoptotic response to UVB radiation, the inappropriate survival of damaged cells in *Perp*-deficient skin following exposure to mutagenic stimuli probably contributed to tumorigenesis. Indeed, the enhanced cell survival that is observed in UVB-treated keratinocytes, which can lack functional p53, is associated with increased carcinogenesis[109]. Second, *Perp* deficiency also compromised desmosome-mediated intercellular adhesion. Although *Perp* loss partially impaired desmosome function in the skin, desmosome component expression was completely lost on the development of *Perp*-deficient SCCs. Intriguingly, although *Perp*-deficient tumours showed a clear downregulation of desmosomal components, adherens junction components were maintained, suggesting that PERP and desmosome loss promote cancer by a specific mechanism rather than by a general change in differentiation status, such as EMT. The downregulation of desmosomes with the retention of adherens junctions was also observed in SCCs that formed with a longer latency in wild-type mice, indicating that although *Perp* depletion facilitates desmosome disassembly, it also occurs in a wild-type context. Moreover, on examining samples from different stages of human SCC development, PERP-deficient, E-cadherin-positive tumours were found to constitute a major group, suggesting that this is an important stage in human skin cancer development. Thus, as in the *Rip1Tag2* model, reduced expression of desmosome proteins could be an early driver of tumour progression, and subsequent loss of adherens junctions could promote later stages, including wide-spread invasion and metastasis. Finally, gene expression profiling of the epidermis on *Perp* ablation revealed the induction of genes that are involved in inflammatory responses. Moreover, *Perp* deficiency, in conjunction with chronic UVB treatment, led to the recruitment of inflammatory cells, especially mast cells. Given the known role for inflammation in promoting cancer, this inflammatory signature and consequent infiltration of immune cells provides a clear basis for how *Perp* loss can enhance tumorigenesis at the cellular level. Together, these data demonstrate that *Perp* deficiency promotes cancer development and progression by multiple mechanisms, clearly supporting the idea that desmosomes can function as tumour suppressors (FIG. 3). Furthermore, the phenotypes induced by *Perp* loss may also contribute to carcinogenesis in cases of p53 or p63 inactivation (FIG. 2).

How desmosome loss promotes cancer

Various models have been proposed to provide a molecular explanation for how desmosome downregulation could promote cancer. The most extensively studied model suggests that desmosome dysfunction can provoke the release of specific desmosomal constituents that can display oncogenic activity, such as JUP. Most notably, JUP manifests β-catenin-like signalling activity, as originally shown by its ability to induce axis duplication in *Xenopus laevis* embryos[110]. Interestingly, the similar capacity of plasma membrane-anchored JUP to induce axis duplication, among other studies, suggested that the effects of JUP on WNT–β-catenin signalling were indirect and probably attributable to the ability of JUP to promote β-

catenin nuclear localization and transcriptional activity[111–114]. Indeed, JUP can replace β-catenin in adherens junctions, freeing β-catenin to stimulate the transcription of WNT target genes (FIG. 1a), including oncogenic targets such as *CCND1* (encoding cyclin D1) and neuronal cell adhesion molecule (NRCAM)[52,115–119]. In addition to these indirect effects on gene regulation via β-catenin, JUP can itself transit to the nucleus on release from junctions, directly activating oncogenic β-catenin–LEF/TCF target genes or potentially stimulating the expression of uncharacterized JUP-specific targets to promote proliferation or transformation[51] (FIG. 1b,c). This concept was originally derived from the observation that JUP can activate β-catenin-responsive target genes in *Ctnnb1*-null cells or tissues[52,120–122]. Adding to the complexity, however, is evidence from model organisms demonstrating that JUP can antagonize WNT–β-catenin signalling. For example, cardiac-specific deletion of *Dsp* in mice results in the nuclear accumulation of JUP and the suppression of WNT–β-catenin signalling[123], and the ablation of *Jup* in murine hearts or zebrafish embryos induces β-catenin transcriptional activity[124,125]. Although JUP-mediated inhibition of WNT–β-catenin signalling may be important in certain physiological settings, its relevance to cancer is unclear and requires further investigation.

The redistribution of PKPs from desmosomes, where they promote adhesion and differentiation, to the nucleus may also contribute to carcinogenesis. The nuclear localization of PKPs in certain settings suggests that they could modulate gene expression, and, indeed, PKP2 can interact with β-catenin and can potentiate endogenous β-catenin–TCF transcriptional activity[46,126,127] (FIG. 1b). Whether PKPs regulate transcription in a β-catenin–LEF/TCF-independent manner, however, remains to be determined (FIG. 1c). In addition, PKP1 and PKP3 can localize to cytoplasmic particles where they can interact with translation-initiation factors to stimulate translation[128,129] (FIG. 1d). This observation implies an oncogenic function for cytoplasmic PKPs, a concept that is supported by the observed redistribution of PKPs from the plasma membrane to the cytoplasm during tumour development[75,130].

In addition to releasing components with oncogenic potential, desmosome dysfunction could also promote carcinogenesis through other means. One such mechanism is by activating signalling pathways that impinge on cancer development. For example, activation of p38MAPK is triggered by autoantibody targeting of DSG3 in the blistering disease Pemphigus vulgaris[131] (FIG. 1e), and activation of ERK1, ERK2 and AKT signalling is induced by DSP knock-down in human keratinocytes[132]. Whatever the exact molecular alterations that occur with desmosome impairment, such changes could induce pro-tumorigenic cellular phenotypes that are associated with desmosome loss, including increased proliferation, augmented survival and enhanced inflammation. Moreover, the simple loss of the exceptional adhesive strength that is imparted by desmosomes to tissues may also contribute to cancer progression in some contexts by relieving a barrier to invasion and metastasis, perhaps in conjunction with adherens junction loss[133,134].

Conclusions and future study

Although our understanding of the role of desmosomes in cancer is still evolving, genetic loss-of-function studies *in vivo* in physiological mouse models of cancer have revealed a causal relationship between the loss of specific desmosome proteins and the development of certain cancers. Additional studies are certainly necessary to understand the complete complexities of this relationship, but the conclusions so far support the majority of the human cancer expression data and functional studies in cultured cells, suggesting that desmosomes normally function as tumour-suppressive complexes and that loss of desmosome proteins and desmosome-mediated adhesion is associated with cancer development and/or progression.

Considerable evidence supports a tumour-suppressive function for desmosomes but this may not be the case in all circumstances, as desmosome proteins have been linked to oncogenic effects in human cancer and experimental systems. These data suggest that altered expression of desmosome proteins might promote cancer development in certain contexts. Differences in how desmosomes influence carcinogenesis could relate to differences in their composition, as well as to the expression level, subcellular localization and tissue-specific or differentiation-specific functions of their constituent proteins. Future investigation will further clarify the contribution of various desmosomal components to the development of diverse cancer types.

Interestingly, although impaired desmosome function is associated with various autoimmune, genetic and infectious human cutaneous diseases, as well as cardiomyopathy syndromes[71], to our knowledge no clear cancer predisposition has been observed in individuals with these syndromes. The lack of such reports might reflect the rarity of these diseases in the general population or the often-reduced lifespan of these patients, which is perhaps not sufficient for revealing a propensity to cancer development. Alternatively, it is possible that the influence of desmosome dysfunction on cancer may be relevant only in particular contexts, such as when a specific desmosome component is targeted or in the background of particular oncogenic mutations. Future studies that assess the cancer predispositon in this population, as well as studies using patient-derived cells or tissues could help to clarify the role of impaired desmosome function in cancer and could have implications for cancer treatment.

The fact that recent genetic loss-of-function studies describe tumours that exhibit loss of desmosomes while retaining adherens junctions[106,108] has considerable clinical implications. As loss of E-cadherin is a common but late event in epithelial cancer progression, identifying markers such as PERP or DSP that may be downregulated earlier could improve the diagnosis, staging and prognostication of cancers, and could also inform therapeutic decisions (FIG. 3). For example, as PERP loss seems to promote tumour progression, tumours with a PERP-deficient status might warrant more aggressive treatment approaches. Indeed, gene expression profiling identified *PERP* as one component of a gene signature the down-regulation of which predicts poor response to treatment in oesophageal cancers[135]. Additionally, reduced expression of DSP in oropharyngeal cancer was associated with poorly differentiated tumours that metastasized within a follow-up period of 3 years[90]. Ultimately, broadening our understanding of desmosomes and tumorigenesis, as well as context-specific distinctions in their relationship, will enhance our ability to diagnose, stage, prognosticate and treat human cancer.

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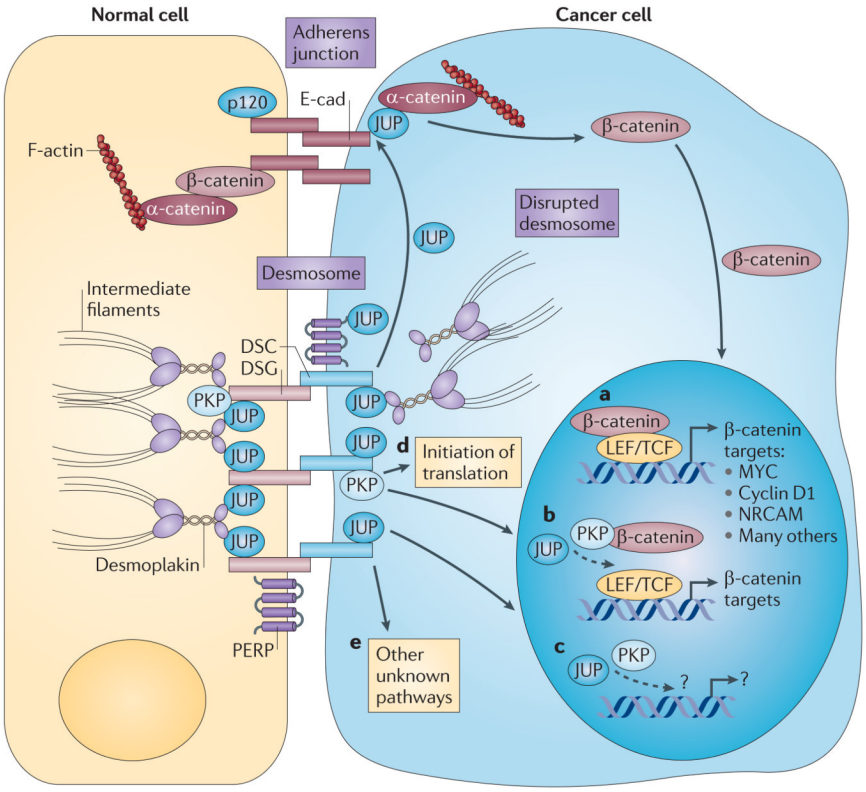

Figure 1. Desmosome deficiency can promote cancer in multiple ways

Stable adherens junctions and desmosomes facilitate adhesion between epithelial cells. The best-characterized components are shown; the position of p53 apoptosis effector related to PMP-22 (PERP) in the desmosome is speculative. Several mechanisms through which disrupted desmosomes could promote cancer are indicated. Junction plakoglobin (JUP) is the desmosome component with the best-characterized effect on the phenotypic changes that occur in cancer cells. At high levels, JUP can compete with β-catenin for inclusion in adherens junctions and/or for interaction with the adenomatous polyposis coli (APC)-mediated degradation machinery, which regulates cellular β-catenin levels (not shown). Both scenarios result in increased nuclear β-catenin, which can stimulate the transcription of LEF/TCF -dependent target genes, promoting oncogenic effects (part **a**). JUP itself can also shuttle between adhesion junctions at the plasma membrane and the nucleus, where it can increase expression of LEF/TCF target genes independently of β-catenin (part **b**). Additionally, plakophilins (PKPs) can also shuttle between the desmosome and the nucleus, and PKP2 has been demonstrated to interact with β-catenin and to enhance LEF/TCF-mediated transactivation (part **b**). JUP and PKPs may also have dedicated LEF/TCF-independent target genes (part **c**). PKPs may also function in the cytoplasm to stimulate translational initiation (part **d**). Other uncharacterized molecular mechanisms of cancer promotion might also exist (part **e**). DSC, desmocollin; DSG, desmoglein; E-cad, E-cadherin; NRCAM, neuronal cell adhesion molecule; p120, p120 cadherin.

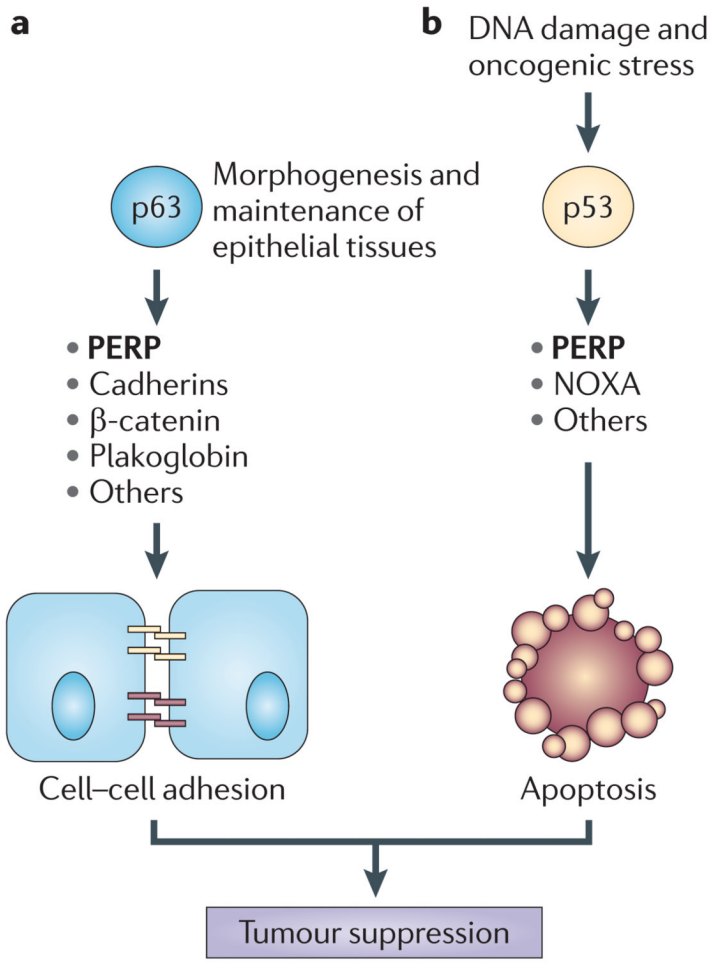

Figure 2. The p53–p63 pathway regulates homeostasis in epithelial tissues

This figure represents some of the ways in which p53 and p63 family members can regulate epithelial homeostasis. **a** | During the development and maintenance of epithelial tissues, p63 can directly or indirectly regulate the expression of various classes of genes, including genes that encode cell–cell adhesion proteins, such as p53 apoptosis effector related to PMP-22 (PERP). These proteins can then assemble into the intercellular adhesive complexes adherens junctions and desmosomes, which promote adhesion between adjacent epithelial cells. Adhesion between cells within a tissue contributes to its integrity, organization and function. **b** | Cellular stressors such as DNA damage or oncogene expression activate p53. As a sensor of stress, p53 induces the expression of genes that are involved in apoptosis, including *PERP* and *NOXA*. PERP and NOXA, and other proteins, contribute to the apoptotic programme, triggering the death of cells the survival of which would be detrimental to a tissue. Both cell–cell adhesion and apoptosis are important cellular mechanisms that contribute to tumour suppression.

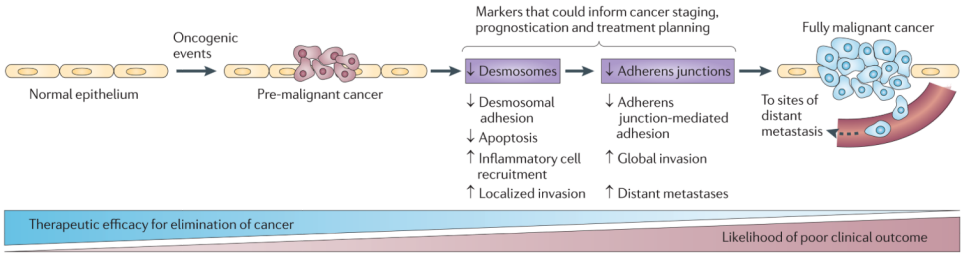

Figure 3. Desmosome downregulation is one in a series of steps occurring during cancer development

Two recent studies using mouse cancer models in which desmosome components were ablated have demonstrated key contributions of desmosome deficiency to epithelial cancer development and progression. Mutations in proto-oncogenes or tumour suppressors drive the development of nascent tumours in epithelia. In this context, desmosome deficiency, occurring before adherens junction loss, promotes several cellular phenotypes that can contribute to cancer progression: decreased desmosome-mediated intercellular adhesion, increased cell survival and inflammatory cell recruitment in ultraviolet B (UVB)-induced squamous cell carcinomas in p53 apoptosis effector related to PMP-22 (*Perp*)-deficient mice and increased local invasion in desmoplakin (*Dsp*)-deficient *Rip1Tag2*-driven pancreatic neuroen-docrine tumours. Subsequent dissolution of adherens junctions in tumours is associated with impaired adherens junction-mediated adhesion, enhanced global invasion and increased distant metastasis, which are features of full-blown malignancy. As desmosome downmodulation precedes that of adherens junctions, and as early diagnosis and treatment is key to achieving the optimal clinical outcome, establishing the status of desmosome and adherens junction constituents in tumours could potentially augment the current tools that are used in the staging, prognostication or treatment of cancers.