

Chapter 6

The Two Faces of Notch in Solid Cancers

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Abstract Aberrant Notch signalling is associated with a variety of solid tumours. Therefore, understanding the role Notch signalling plays during the development and progression of cancer is an area of considerable interest, and a deeper knowledge of its influence on cellular processes will potentially lead to improvements in both the prevention and treatment of cancer.

Keywords Cancer stem cells • Differentiation • Inflammation • Tumour stroma • SCC • ECM

Interestingly, Notch can act as an oncogene or tumour suppressor depending on the tissue context (Koch and Radtke 2007) (Fig. 6.1). Thus, some cancers display increased Notch signalling activity and are dependent on Notch for growth and malignant progression. Conversely, in other cancers, inactivation of Notch signalling is essential for carcinogenesis, indicating that Notch can function as an important tumour suppressor. In the following sections, the supporting evidence for both oncogenic and tumour suppressive roles of Notch will be discussed, as will the mechanisms by which Notch signalling influences carcinogenesis.

6.1 Cancers Associated with Active Notch Signalling

Historically, the evidence supporting an oncogenic role for Notch signalling has been provided predominantly by the study of the haematological malignancy T-cell acute lymphoblastic leukaemia (T-ALL). In this disease, activating mutations in

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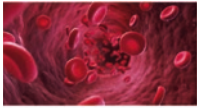
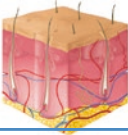








Oncogenic functions of Notch in	Ref.	Tumor suppressive function of Notch in	Ref.
	Koch and Radtke 2011		Nicolas et al. 2003 Pickering et al. 2014 Wang et al. 2011
	Gao et al. 2007 Kanamori et al. 2007 Purov et al. 2005 Zhao et al. 2010 Zhung et al. 2008 Gaetani et al. 2010 Fan et al. 2004		Alcolea et al. 2014 Gao et al. 2014 Song et al. 2014
	Zheng et al. 2013		George et al. 2015
	Sansone, P. et al. 2006 Shipitsin et al. 2007 Reedijk et al. 2005 Hu et al. 2006 Pece et al. 2006 Ayyanun et al. 2006		Viatour et al. 2011
	Miyamoto et al. 2003 Mazur et al. 2010 Plentz et al. 2009 Maniati et al. 2011 Cook et al. 2012 De La et al. 2008		Hanlon et al. 2010

Fig. 6.1 Schematic representation of tissues in which Notch signalling is oncogenic and/or tumour suppressive. *Left side* of the panel represents major human tissues in which an oncogenic role for Notch has been described, whereas the *right side* shows tissues where Notch exerts tumour-suppressive activities. References related to oncogenic and tumour-suppressive functions in a given tissue are indicated

Notch1 are present in 50–60% of cases, and there is considerable functional data indicating that Notch plays a crucial role in driving the development and growth of T-ALL (Koch and Radtke 2011a, b). However, numerous studies also suggest that Notch acts as an oncogene in a variety of solid tumours (Galluzzo and Bocchetta 2011; Reedijk 2012; Teodorczyk and Schmidt 2014).

For example, increased expression of Notch pathway components has been observed in human gliomas, which are a group of primary brain tumours derived from the glial tissue of the central nervous system. In these malignancies, increased expression of Notch receptors, Notch ligands and downstream targets such as Hey-1, is associated with increasing tumour grade (Somasundaram et al. 2005; Phillips et al. 2006; Xu et al. 2009, 2010; Hulleman et al. 2009). Furthermore, inhibition of Notch1 in glioma cell lines induces cell cycle arrest,

while constitutive activation of Notch signalling results in increase proliferation (Gao et al. 2007; Kanamori et al. 2007; Purow et al. 2005; Zhao et al. 2010, 2008). Inhibition of Notch1 or Dll1 in *in vivo* models also results in delayed tumour growth (Xu et al. 2010; Purow et al. 2005), and high expression of Hey-1 in human gliomas is associated with a poor prognosis (Hulleman et al. 2009; Gaetani et al. 2010).

Notch may also function as an oncogene in medulloblastoma, which is a brain tumour derived from neuronal precursor cells in the cerebellar cortex and is distinct from the gliomas discussed above. In this example, the expression of Notch2 and the target gene Hes-1 is upregulated in medulloblastoma and can promote proliferation when overexpressed (Xu et al. 2009; Fan et al. 2004).

Increased Notch signalling activity is also linked to the development and progression of breast cancer. High expression levels of Notch1, Notch3 and Jag1 are observed in many cases of breast cancer and are associated with a poor prognosis (Sansone et al. 2007; Shipitsin et al. 2007; Reedijk et al. 2005). Consistent with this, overexpression of Notch1 and Notch3 in mice promotes mammary tumour development (Sansone et al. 2007; Hu et al. 2006). Furthermore, loss of numb expression, which is a negative regulator of Notch activity, is frequently observed in primary human breast cancers (Pece et al. 2004). Notch signalling can also cooperate with other signalling cascades, such as Wnt, to promote the transformation of human primary mammary epithelial cells (Ayyanan et al. 2006) further supporting the hypothesis that overactive Notch signalling is oncogenic in this tissue.

Pancreatic cancer has also been linked to increased Notch signalling. Notch target genes are frequently expressed in PDAC cells, suggesting that Notch activity is associated with development and progression of the disease (Miyamoto et al. 2003). Perhaps more significantly, several studies demonstrate that inhibition of Notch signalling, either by genetic ablation of Notch2 or by administering gamma-secretase inhibitors, can prevent or reduce PDAC following activation of oncogenic k-ras (Mazur et al. 2010; Plentz et al. 2009). Notch signalling has also been shown to cooperate with Nf-KB during k-ras-driven murine PDAC development (Maniati et al. 2011), and pharmacological inhibition of Notch signalling can sensitize PDAC to chemotherapeutic drugs by disrupting the tumour vasculature (Cook et al. 2012). In addition, a synergistic role for Notch during k-ras-mediated carcinogenesis in the pancreas has been reported (De La et al. 2008). However, in direct contrast to these studies, genetic ablation of Notch1 in a mouse model of k-ras-induced PDAC resulted in an increase in high-grade PanIN lesions (Hanlon et al. 2010) suggesting that Notch1 exerts a tumour suppressive function. In addition, the genetic status of members of the Notch pathway in pancreatic ductal adenocarcinoma (PDAC) remains to be resolved. Thus, further work is needed to definitively establish the role of Notch signalling during pancreatic carcinogenesis, although at present, the balance of the evidence supports an oncogenic function.

Mouse models also suggest an oncogenic role for Notch signalling in non-small-cell lung cancer (Zheng et al. 2013). In this example, tumour-propagating cells express high levels of components of the Notch cascade, and Notch3 appears to be essential for their capacity to initiate tumour development. However, it should be noted that in small-cell lung cancer, which is a distinct disease, Notch is thought to be a tumour suppressor (see below).

6.2 Cancers Associated with Loss of Notch Signalling

The strongest evidence of a tumour-suppressive function for Notch signalling is provided by the analysis of squamous cell carcinomas (SCC) that occur in stratified epithelial tissues such as the skin. Initial studies found that genetic ablation of Notch1 in the murine epidermis substantially increased the susceptibility to chemical-induced carcinogenesis (Nicolas et al. 2003). Subsequently, analysis of other SCC types using mouse models also indicated a tumour-suppressive function for Notch signalling. For example, urothelium-specific deletion of the Notch transcriptional effector RBPJk or presenelins, which is essential for Notch receptor activation, results in accelerated development of bladder SCC following chemical carcinogenesis (Maraver et al. 2015). Furthermore, ablation of Notch signalling in this model is strongly associated with the predomination of highly invasive SCC.

In the mouse oesophagus, genetic inhibition of Notch signalling in epithelial progenitor cells promotes the expansion of preneoplastic clones carrying carcinogenic mutations, thus establishing a field from which oesophageal SCC can develop (Alcolea et al. 2014). This therefore indicates that loss of Notch signalling in the oesophagus is likely to be an early event during tumorigenesis, similar to the findings from analysis of cutaneous SCC.

Validation of the results obtained from mouse models has now been made possible with the advent of next-generation sequencing technology, which has enabled the mutational landscape in several types of human SCC to be determined robustly from clinical specimens. This has revealed that loss-of-function mutations in Notch family members are among the most recurrent mutations in a variety of SCC, including head and neck SCC (Agrawal et al. 2011; Stransky et al. 2011), cutaneous SCC (Pickering et al. 2014; South et al. 2014; Wang et al. 2011), bladder SCC (Rampias et al. 2014) and oesophageal SCC (Gao et al. 2014; Song et al. 2014). The mutations identified to date are predominantly found in the Notch receptors, particularly Notch1, and include missense mutations in critical functional regions, nonsense mutations that result in truncated proteins lacking the C-terminal transactivation domain, mutations in splice sites that result in truncation or deletion and frameshift insertion/deletions (indel) (Agrawal et al. 2011; Stransky et al. 2011; South et al. 2014; Gao et al. 2014). In addition, a clinical trial of semagacestat, a γ -secretase inhibitor evaluated for the treatment of Alzheimer's disease, reported an increased risk of skin cancer in patients who received the drug,

providing further evidence that Notch signalling performs an antitumour function in humans (Extance 2010).

In addition to SCC, there is also evidence that Notch suppresses tumour development in other solid malignancies, including small-cell lung cancer (George et al. 2015), some types of brain cancer (Giachino et al. 2015) and liver cancer (Viatour et al. 2011)

6.3 Mechanisms Underlying Notch-Mediated Oncogenesis or Tumour Suppression

6.3.1 Regulation of Stem Cells

The capacity for Notch to operate as an oncogene or tumour suppressor in particular tissues is in part a consequence of its role in regulating stem and progenitor cells (Koch et al. 2013; Wilson and Radtke 2006). Advances in our understanding of cancer biology in recent years have revealed that aberrations in stem and/or progenitor cells are often essential steps during carcinogenesis, and considerable evidence supports the so-called ‘cancer stem cell’ hypothesis, which posits that the growth of tumours is driven by distinct populations of malignant cells that share many traits with normal stem cells, such as self-renewal, drug resistance and the capacity to repopulate all cell types within the tumour (Clevers 2011; Visvader and Lindeman 2012; Visvader 2011). Importantly, Notch signalling plays critical and diverse roles in regulating stem cell function in many tissues, including processes such as self-renewal, proliferation and differentiation (Wilson and Radtke 2006). Thus, abnormal Notch signalling activity can have a profound effect on stem cell compartments and as a consequence lead to carcinogenesis.

Notch-mediated oncogenesis frequently occurs in tissues where Notch functions to maintain or expand the stem and/or progenitor cell compartment (Fig. 6.2a). In the central nervous system, Notch plays an important role in the maintenance of neural stem cells (Yoon and Gaiano 2005). Consistent with this, cancer stem cells isolated from brain tumours frequently exhibit high expression of Notch family members (Lee et al. 2006; Fan et al. 2006; Gunther et al. 2008). Furthermore, *in vitro* studies indicate that high levels of Notch are associated with the maintenance of an undifferentiated phenotype in neurosphere cultures derived from brain tumour cancer stem cells, which also correlates with tumorigenicity and malignant traits such as invasiveness (Gunther et al. 2008).

Similar observations have been made with respect to the mammary gland. In this example, the propagation of mammosphere cultures, which is derived exclusively from mammary stem cells, was found to require Notch signalling activity (Dontu et al. 2004) indicating that maintenance of the mammary stem cell compartment is indeed Notch dependent. In addition, constitutive activation of Notch in subpopulations of progenitor cells in murine mammary glands resulted in tumour development

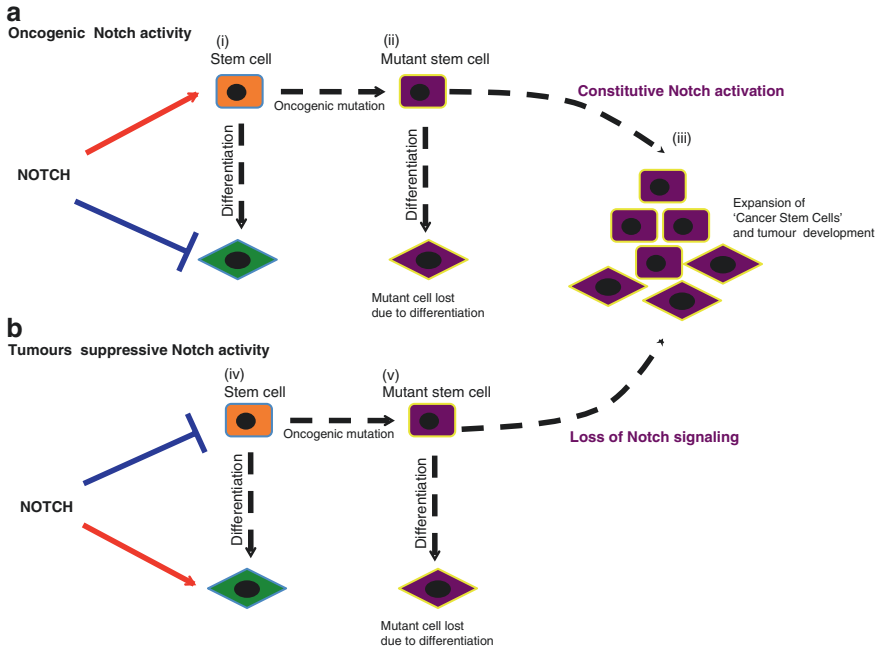


Fig. 6.2 Notch-mediated stem cell regulation and carcinogenesis. **(a)** Oncogenic Notch signalling can occur in tissues in which Notch functions to maintain stem cells and/or prevent their differentiation. In such cases, high Notch activity is normally restricted to the stem cell compartment and is down-regulated as cells differentiate (i). Stem cells that acquire potentially oncogenic mutations are therefore lost as they down-regulate Notch and initiate terminal differentiation (ii). However, if Notch signalling in stem cells remains active, for example, by activating mutations, mutant stem cells expand and can function as ‘cancer stem cells’ and drive tumour growth (iii). **(b)** Conversely, in tissues where Notch promotes differentiation, it functions as a powerful tumour suppressor by imposing terminal differentiation of mutant stem cells (iv), thus extinguishing clones that may initiate cancer development (v)

(Bouras et al. 2008). These examples highlight the link between the oncogenic function of Notch in specific tissues and its role in stem cell maintenance.

In contrast, in tissues where Notch functions as a tumour suppressor, active Notch signalling is strongly associated with cell cycle exit and the promotion of differentiation, thus extinguishing stem and/or progenitor cells that acquire oncogenic mutations (Fig. 6.2b).

The most prominent example of this is the epidermis. In this tissue, Notch activity is confined to the differentiating cells in the suprabasal layers and is absent in the proliferative stem/progenitor cells of the basal layer (Blanpain and Fuchs 2009; Nowell and Radtke 2013). Ablation of Notch signalling in the murine epidermis results in perturbed differentiation (Yamamoto et al. 2003), while activation induces commitment to differentiation (Blanpain et al. 2006). Furthermore, in vitro experiments show that Notch plays a functional role in promoting cell cycle exit and differentiation of epidermal stem/progenitor cells (Okuyama et al. 2004; Rangarajan

et al. 2001). At a molecular level, several studies indicate that Notch regulates factors that control the proliferation of epidermal stem/progenitor cells, such as p63 (Nguyen et al. 2006; Senoo et al. 2007), p21/CDKN1A (Rangarajan et al. 2001) and AP-1 (Eferl and Wagner 2003; Guinea-Viniegra et al. 2012; Murthy et al. 2012; Nowell et al. 2016) while also promoting differentiation via the induction of cascades such as retinoic acid signalling (Collins and Watt 2008). Consistent with the tumour suppressor activity of Notch being linked to its pro-differentiation function, cutaneous SCC that carry loss-of-function mutations in Notch family members express high levels of stem cell-associated factors, such as p63, and exhibit reduced expression of gene signatures associated with differentiation (Parsa et al. 1999; Rocco et al. 2006). Notch may perform a similar function in other stratified epithelia. For example, inhibition of Notch signalling in the murine oesophageal epithelium results in the expansion of undifferentiated progenitors, thus increasing the pool of cells that have the capacity to form tumours following the acquisition of oncogenic mutations (Alcolea et al. 2014).

6.3.2 Regulation of Inflammation

Recent developments in cancer biology have revealed that inflammatory cells perform important functions during tumour initiation, development and progression, and they thus constitute an important component of the tumour stroma (Grivennikov et al. 2010). Intriguingly, several studies have now shown that an important role of Notch signalling in stratified epithelial tissues is to attenuate inflammatory responses (Nowell et al. 2016; Demehri et al. 2008, 2010). Given that Notch is generally a tumour suppressor in stratified epithelia, a key element of the antitumour function of Notch may be related to its ability to negatively regulate the inflammatory response (Fig. 6.3).

Ablation of Notch signalling in the murine epidermis induces chronic inflammation, the severity of which is dependent on the degree of Notch signalling impairment. Ablation of Notch1 alone results in significant up-regulation of pro-inflammatory cytokine expression, and additional deletion of Notch2 causes a much more pronounced inflammatory response resembling atopic dermatitis (Demehri et al. 2008, 2010). Intriguingly, the inflammatory response induced following complete inactivation of Notch signalling actually prevents carcinogenesis due to the anti-tumorigenic function of T cells present in the inflammatory milieu (Demehri et al. 2012; Di Piazza et al. 2012). However, abrogation of T-cell-mediated immunity in this setting leads to rapid tumour development that is dependent on myeloid inflammatory cells present in the inflamed dermis. These studies demonstrate that loss of Notch signalling in the epidermis can induce pro- and anti-tumorigenic inflammation depending on the degree to which Notch signalling is impaired. Further investigations are needed to establish the precise cellular and molecular factors that underpin these observations. However, the outgrowth of tumours in the Notch-deficient epidermis is dependent on high levels of β -catenin

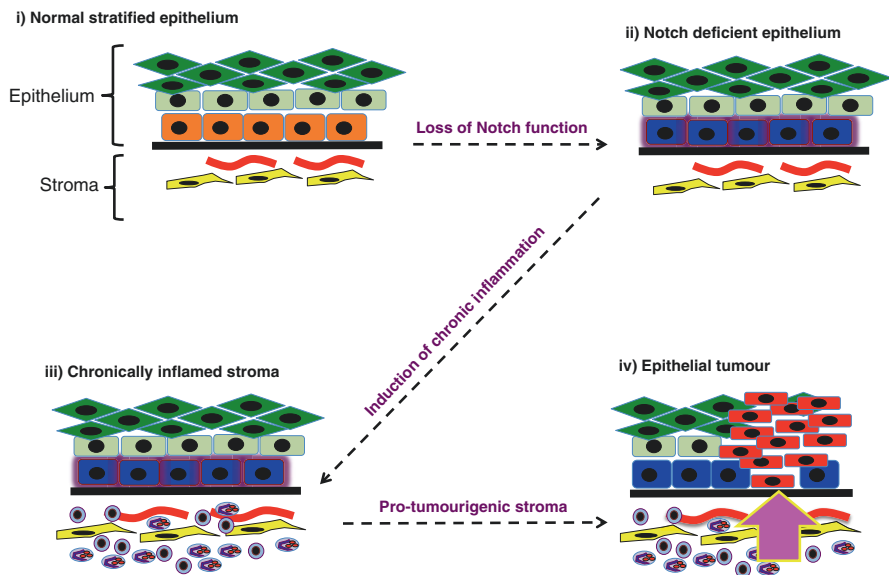


Fig. 6.3 Notch-mediated regulation of inflammation and carcinogenesis. A key function of Notch in many stratified epithelial tissues is to attenuate the inflammatory response and maintain normal tissue architecture (i). Thus, upon loss of Notch signalling in epithelia such as the epidermis, a chronic inflammatory response can be initiated in the underlying stroma (ii) and (iii). This can subsequently promote tumour development by eliciting a variety of responses in the epithelium (iv)

signalling, and pro-tumorigenic myeloid cells that accumulate following ablation of Notch signalling express high levels of Wnt ligands (Di Piazza et al. 2012) suggesting that induction of the Wnt/ β -catenin cascade by inflammatory cells is an important mechanism by which loss of Notch signalling promotes carcinogenesis. Other experimental models also support a link between Notch, inflammation and Wnt/ β -catenin signalling. For example, ablation of Notch1 in the corneal epithelium results in severe chronic inflammation on the ocular surface that induces squamous cell metaplasia in a β -catenin-dependent manner (Nowell et al. 2016). In this example, the induction of β -catenin signalling is due to inflammation-induced ECM deposition in the corneal stroma, which subsequently induces β -catenin signalling in epithelial cells through mechanotransduction. Although not directly related to carcinogenesis, this study highlights how loss of Notch signalling can induce Wnt/ β -catenin signalling, which is frequently pro-tumorigenic, via the induction of inflammation and stromal remodelling. Thus, in stratified epithelial tissues such as the epidermis, negative regulation of inflammation is likely to be a key mechanism by which Notch signalling mediates tumour suppression.

In light of the evidence obtained from the study of the epidermis, it will be important to address if Notch signalling has a similar influence on inflammation in other tissues and whether or not this is relevant with respect to carcinogenesis. Furthermore, delineating how Notch signalling controls the inflammatory response will potentially identify therapeutic targets that can ameliorate the effects of Notch

loss of function and so can potentially be used as anticancer therapeutic agents. In this respect, Notch signalling has been shown to interact with several factors that play an important role in regulating the inflammatory response, including Nf-KB (Espinosa et al. 2010) and AP-1 (Guinea-Viniegra et al. 2012; Murthy et al. 2012; Nowell et al. 2016) although detailed mechanisms remain to be resolved.

6.4 Concluding Remarks

It is clear that Notch signalling has an important impact on the development of many solid cancers, whether as an oncogene or tumour suppressor. In addition, continued advances in our understanding of the role of Notch signalling during development, homeostasis and disease have revealed that the mechanisms by which Notch influences carcinogenesis are diverse and include cell autonomous and non-cell autonomous effects. Therefore, the development of therapeutic strategies that aim to manipulate the Notch cascade directly or the downstream consequences it elicits will potentially lead to improvements in the prevention and treatment of cancer.

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