Wnt-5a is one of the most highly investigated non-canonical Wnts and has been implicated in almost all aspects of non-canonical Wnt signalling. In terms of cancer development, Wnt-5a has, until recently, lived in the shadow of its better-characterised relatives. This was largely because of its apparent inability to transform cells or signal through the canonical $\beta$-catenin pathway that is so important in cancer, particularly colorectal cancer. Recent work in a wide range of human tumours has pointed to a critical role for Wnt-5a in malignant progression, but there is conflicting evidence whether Wnt-5a has a tumour-promoting or -suppressing role. Emerging evidence suggests that the functions of Wnt-5a can be drastically altered depending on the availability of key receptors. Hence, the presence or absence of these receptors may go some way to explain the conflicting role of Wnt-5a in different cancers. This review summarises our current understanding of Wnt-5a and cancer.

Keywords: Wnt signalling; Wnt-5a

WNT SIGNALLING PATHWAYS

The Wnt signalling pathways are usually activated through binding of the secreted Wnt molecules to the conserved C-terminal cytosolic domain of a family of nine large multipass transmembrane receptors called the Frizzled receptor proteins (Fz). However, Wnts do not signal exclusively through these receptors as others, such as the ROR2 receptor, have been identified (Oishi et al, 2003). The interaction between individual Wnts and their specific receptors is thought to dictate the type of downstream signalling pathways that are activated. Accordingly, the Wnts have historically been divided into two classes: those that signal through the 'canonical' or the 'non-canonical' signalling pathway.

The canonical signalling pathway performs a variety of different functions throughout development. Canonical Wnts are thought to activate a signal-transduction pathway that induces the nuclear accumulation and transcriptional activation of $\beta$-catenin (Giles et al, 2003). A process that can cause duplication of the embryonic axis in Xenopus (x) (xWnt-1, xWnt-3a, xWnt-8a and xWnt-8b) (Du et al, 1995) and transform mouse (m) mammary epithelial cells (mWnt-1, mWnt-2, mWnt-3, mWnt-3a) (Shimizu et al, 1997), this pathway is essential for the development of dorsal polarity during gastrulation (Brannon et al, 1997). In addition to a role in normal development, deregulation has been shown to be integral to cancer development and progression by, among other functions, promoting cancer cell proliferation and migration (Giles et al, 2003).

The non-canonical signalling pathway is essentially an umbrella term for all Wnt-activated cellular signalling pathways that do not promote $\beta$-catenin-mediated transcription, and numerous pathways have been identified. In contrast to the canonical Wnts, the non-canonical Wnts do not signal through $\beta$-catenin, do not cause duplication of the embryonic axis in Xenopus (xWnt-4, xWnt-5a and xWnt-11) (Du et al, 1995) and are unable to transform mouse mammary epithelial cells (mWnt-4, mWnt-5a, mWnt-5b, mWnt-6 and mWnt-7b) (Shimizu et al, 1997). Furthermore, it is well established that non-canonical Wnts can antagonise the functions of canonical Wnts (Torres et al, 1996). A recent study provided further evidence of the opposing roles of different Wnts as $\beta$-catenin gene targets upregulated in B16 murine melanoma cells treated with Wnt-3a were universally downregulated in B16 cells.
treated with Wnt-5a (Chien et al., 2009). Although involved in many processes (Veeman et al., 2003; Semenov et al., 2007), non-canonical Wnts are generally considered to control morphogenic movements. The most well-recognised categories of non-canonical signalling are the planar cell polarity pathway (PCP) and the Wnt calcium signalling pathway. Wnt-5a is one of the most highly investigated non-canonical Wnts, and has been shown to be involved in almost all aspects of non-canonical Wnt signalling.

Interestingly, the convention of two independent Wnt pathways has remained for some time, but emerging evidence suggests that the pathways are not as autonomous as originally thought. For instance, although Wnt-5a is thought to primarily function through the non-canonical pathway, it can, under certain circumstances, signal through the canonical pathway. The possibility of interaction between these two pathways may explain in part the uncertainties of the role of Wnt-5a in cancer.

THE ROLE OF WNT-5A IN WNT SIGNALLING AND IMPLICATIONS FOR CANCER

The non-canonical pathway, PCP, was identified in Drosophila, and is essential for organising the orientation of cells in tissues. In Drosophila, PCP is a complex process involving the spatial organisation of multiple signalling molecules (Jones and Chen, 2007). Signalling results in the activation of a number of cytoskeleton regulators including DAAM1, Rac, Rho and Rho kinase (Jones and Chen, 2007). Although this pathway was identified in Drosophila, it is by no means confined to this organism and has also been identified in vertebrates (Green and Davidson, 2007), but the extent of the similarities are unknown (Mlodzik, 2002). Furthermore, vertebrates use PCP to allow cells to undergo convergence and extension movements during organogenesis (Wallingford et al., 2002). As a result, PCP is now thought to be essential for the organisation, orientation and morphogenic movements of multiple invertebrate and vertebrate epithelial and mesenchymal cells throughout normal development and is thought to be activated in cancer (Jones and Chen, 2007). Wnt-5a was recently shown to be essential for controlling PCP in vertebrates (Qian et al., 2007) (Figure 1A). In addition, Wnt-5a, in the presence of a CXCL12 chemokine gradient, was able to polarise the cellular cytoskeleton of WM239a melanoma cells through a process dependent on dishevelled (DSH), RhoB and Rab4 to promote cellular migration towards the source of the chemokine (Witze et al., 2008). Although these reports shed some light on the role of Wnt-5a in PCP, the downstream signalling pathways activated to bring about its effects are still enigmatic, but it is clear that it

![Figure 1](https://example.com/figure1.png)

**Figure 1** An overview of Wnt-5a signalling. (A) Wnt-5a can activate PCP through a process dependent on Roh A and possibly Roh B leading to the control of cellular movement. (B) Wnt-5a uses numerous signalling molecules leading to the release of Ca\(^{2+}\) resulting in various cellular effects including cell movement and inhibition of the canonical Wnt signalling pathway. (C) Wnt-5a can bind the ROR-2 receptor activating JNK and the cytoskeleton as well as inhibiting \(\beta\)-catenin/TCF dependent transcription. (D) Wnt-5a can inhibit \(\beta\)-catenin/TCF-dependent transcription through Shia-1. (E) In the presence of FZ4 and LRP-5, Wnt-5a can activate \(\beta\)-catenin/TCF-dependent transcription. (F) Wnt-5a can activate PKA, which in turn can inhibit GSK-\(\beta\) to promote \(\beta\)-catenin/TCF-dependent transcription. Figure adapted from Semenov et al. (2007).
operates through the cytoskeleton to control cell orientation and movement. This ability of Wnt-5a to promote cell movement has crucial implications for cancer progression.

The second main Wnt-5a-dependent pathway is the calcium-dependent signalling pathway. Here, the non-canonical Wnts can trigger intracellular calcium flux, which can lead to the activation of calcium-dependent signalling molecules such as calmodulin-dependent protein Kinase II (CAMKII) and protein kinase C (PKC) (Kuhl et al, 2000b). The pathways activated downstream perform many different tasks, and there is a degree of crossover between the calcium-dependent pathway and the PCP pathway. In contrast with the canonical pathway, this pathway can control the fate of ventral cells in Xenopus (Kuhl et al, 2000a). Some of the earliest experiments carried out in Xenopus embryos showed that Xenopus Wnt-5A (Xwnt-5A) was able to activate Rat (r) FZ-2, resulting in intracellular Ca\(^{2+}\) release (Slusarski et al, 1997b). The components of the signalling pathway upstream of the release of Ca\(^{2+}\) are still debated, but it is clear that a number of signalling molecules such as DSH (Sheldahl et al, 2003) and p38 (Ma and Wang, 2007) are activated as is G-protein-linked phosphatidylinositol signalling (Slusarski et al, 1997a). The Ca\(^{2+}\) release is thought to lead to activation of CamKII ensuring correct axis formation and the promotion of ventral cell fate (Kuhl et al, 2000a). Studies have also shown that XWnt-5A can bind to FZ-2 to activate PKC (Sheldahl et al, 2003) (Figure 1B). CamKII and PKC activation by Wnt-5a is maintained in higher organisms and is essential for invasion of cancer cells (Weeraratna et al, 2002; Dissmannayake et al, 2007). Therefore, it can be concluded that overexpression of Wnt-5a could have an oncogenic effect by stimulating cancer cell invasion.

In addition to Frizzled receptors, Wnt-5a can also bind and activate the ROR2 tyrosine kinase receptor resulting in the activation of the actin-binding protein, filamin A, and the JNK signalling pathway (Oishi et al, 2003; Nomachi et al, 2008) (Figure 1C). A potential role for these pathways in cancer was established when Wnt-5a was shown to signal through ROR2 to induce cellular migration and invasion in murine fibroblast NIH3T3 cells (Nomachi et al, 2008); if the same occurred in cancer cells, oncogenic potential could be conferred by Wnt-5a through the promotion of cancer cell invasion.

In addition to activating non-canonical signalling, Wnt-5a is also able to inhibit the activation of the canonical signalling pathway by a number of mechanisms, either by calcium signalling through CamKII (Torres et al, 1996) or through the ROR2 signalling pathways (Mikels and Nusse, 2006) (Figure 1 B and C). In turn, these pathways can stimulate the TAK1–NLK pathway to phosphorylate (Winkel et al, 2008) and inactivate the active \(\beta\)-catenin transcription complex (Ishitani et al, 2003). Another proposed mechanism for the inhibition of \(\beta\)-catenin-mediated transcription is through the upregulation of Sha2, which occurs in response to Wnt-5a-mediated calcium release in APC mutant cells (MacLeod et al, 2007) (Figure 1D). In accordance with this, Wnt-5a has been shown to reduce the activation of \(\beta\)-catenin-mediated transcription in HCT116 (Ying et al, 2008) and HT-29 colon cancer cells (MacLeod et al, 2007). The lack of inhibition of canonical Wnt signalling, the expression of Wnt-5a is likely to confer a tumour-suppressive role in tumours that rely on canonical signalling for survival.

Although the ability of Wnt-5a to inhibit the activation of \(\beta\)-catenin-mediated transcription is well established, there is evidence to suggest that in the presence of FZ-4 and LRP-5 and the absence of ROR2, Wnt-5a can stimulate \(\beta\)-catenin transcriptional activation (Mikels and Nusse, 2006) (Figure 1E). Research has also shown that Wnt-5a can activate phosphokinase A (PKA) in primary cultured human dermal fibroblasts, which in turn can inactivate GSK3-\(\beta\) resulting in stabilisation and nuclear accumulation of \(\beta\)-catenin, and concomitantly promote the activation of an important co-transcription factor of \(\beta\)-catenin, the CRE-binding protein (CREB) (Tori et al, 2008) (Figure 1F). Therefore, Wnt-5a, in the presence of specific FZ isoforms, could promote tumour growth by activation of the cancer-promoting canonical Wnt signalling pathway. Nevertheless, it is important to note that this influence on \(\beta\)-catenin-mediated transcription may only be effective in some cell types as Wnt-5a was shown to have no effect on the activation of transcription in MCF-7 breast cancer cells (Pukrop et al, 2006).

Wnt-5a is one of the most highly investigated non-canonical Wnts, and has been shown to be involved in almost all aspects of the non-canonical Wnt signalling pathway. Wnt-5a has ample opportunity, therefore, to influence cancer development.

**EXPRESSION OF WNT-5A IN CANCER**

Unsurprisingly, given its functional promiscuity, investigations to elucidate the role of Wnt-5a in cancer have shown paradoxical results and studies indicate that it may have a tumour suppressing or an oncogenic effect depending on the cancer type (Table 1). A large number of studies have indicated that Wnt-5a commands a tumour-suppressing effect, and it was shown to be downregulated in a number of different cancers such as colorectal cancer (Dejmek et al, 2005a; Ying et al, 2008), neuroblastoma (Blanc et al, 2005), ductal breast cancer (Jonsson et al, 2002; Dejmek et al, 2005b) and leukaemias (Liang et al, 2003; Roman-Gomez et al, 2007; Ying et al, 2007). Downregulation of Wnt-5a has been associated with higher tumour grade (Kremenevskaja et al, 2005; Dejmek et al, 2005a; Liu et al, 2008) and was shown to be an independent factor indicating poor prognosis in a number of different tumour subtypes (Jonsson et al, 2002; Roman-Gomez et al, 2007). These results suggest that for cancer to progress, Wnt-5a must be actively silenced, a characteristic feature of tumour suppressors. This tumour-suppressive role was further evidenced by studies that reintroduced Wnt-5a into SW480 colorectal cancer or thyroid cancer FTC-133 cell lines resulting in decreased invasion, migration, colonogenicity and proliferation (Kremenevskaja et al, 2005; Dejmek et al, 2005a). Further evidence of a potential tumour-suppressive role was shown by a synthetic peptide synthesised to mimic the biological properties of Wnt-5a. This peptide could reduce the invasion of breast cancer cell lines in vitro and inhibited the metastatic spread of 4T1 breast cancer cells from the mammary fat pad to the lungs and liver by 70–90% in athymic BALB/c mice (Satholm et al, 2008).

Most studies have involved limited sample sets in terms of numbers and a significant number have not detailed expression at both the RNA and protein levels. Studies with much larger sample sets will provide the necessary statistical power to validate the extent of the downregulation of Wnt-5a in cancer. However, the current data do indicate that reduced expression is likely to occur in over half of each of the tumour types investigated. As the majority of these studies investigated Wnt-5a protein expression, a mechanim for this loss of expression has not been established. It is possible, however, that epigenetic regulation is involved, as methyltransferase of the Wnt-5a promoter was identified in a large proportion of lymphoblastic leukaemia patients and in colorectal cancer patients (Roman-Gomez et al, 2007; Ying et al, 2007, 2008). The precise mechanisms governing cancer promotion caused by Wnt-5a downregulation are still unknown. As Wnt-5a can counteract the effects of canonical Wnt signalling, it seems clear that its downregulation would be advantageous to cancers driven by canonical Wnt signalling. However, the mechanisms that inhibit tumour growth in tumours without active canonical Wnt signalling remain unclear. It has recently been determined that Wnt-5a can promote the association of \(\beta\)-catenin and E-cadherin complexes on the cell membrane leading to increased cellular adhesion (Medrek et al, 2009). Therefore, reducing Wnt-5a expression may diminish cellular adhesion through reducing membrane-bound E-cadherin.
This explanation is especially persuasive as reduced WNT-5a expression has been identified in a large proportion of ductal breast cancers (Jonsson et al, 2002; Dejmek et al, 2003b), which rarely have inactivation mutations in E-cadherin (Cleton-Jansen, 2002).

Although there is firm evidence that Wnt-5a has a tumour-suppressive role, a few studies have pointed to Wnt-5a having an oncogenic role in tumours arising from a variety of different tissues (Table 2). Increased expression of Wnt-5a, a hallmark of oncogenesis, was identified in melanoma skin cancer (Da Forno et al, 2008), breast cancer cells (Fernandez-Cobo et al, 2007), gastric cancer (Karayoshi et al, 2006), pancreatic cancer (Ripka et al, 2007), non-small-cell lung cancer (Huang et al, 2005) and prostate cancer (Wang et al, 2007). Increased expression has been associated with increasing tumour grade (Karayoshi et al, 2006; Da Forno et al, 2008), and multivariate analysis showed that expression was an independent risk factor for reduced metastasis-free and overall survival in patients with melanoma (Da Forno et al, 2008) or non-small-cell lung cancer (Huang et al, 2005). A cancer-promoting function was also shown in UACC 1273 melanoma cancer cells (Weerrarana et al, 2002), MKN-74 and MKN-45 gastric cancer cells (Karayoshi et al, 2006) and in Panc1, HT1080, ImimPc1 and MiaPaca pancreatic cancer cell lines (Ripka et al, 2007), where overexpression of Wnt-5a promoted cell proliferation and invasion.

The potential role for increased Wnt-5a expression in malignant melanoma has recently been outlined as a study established that nuclear β-catenin levels are higher in primary tumours than in metastases and that low expression of nuclear β-catenin expression in primary tumours predicts poor survival (Chien et al, 2009). This suggests that inhibition of canonical Wnt signalling may be important for progression of malignant melanomas and that the increased expression of Wnt-5a in high-grade tumours may serve to inhibit activation of the canonical signalling pathway and augment cancer growth. Therefore, there is a considerable body of data that supports the hypothesis that Wnt-5a can advance particular cancer types, but is unlikely to be a primary or initiating event.

**CONCLUSION**

Wnt-5a partakes in many of the Wnt-dependent signalling processes used during development, tissue homeostasis and cancer progression, but its role in the latter is still unclear. Further large-scale studies may help to clarify the role of Wnt-5a, but as it has been shown to elicit different downstream effects depending on receptor availability, these studies are unlikely to achieve clarification if the expression of Wnt-5a is monitored in isolation. We feel that the key will be to identify the most important signalling partners to record. Unfortunately, we do not currently have a comprehensive understanding of how Wnt-5a brings about its effects. Indeed, our understanding of the complexities of Wnt signalling is incomplete (Veeman et al, 2003). Recently, a number of studies have used siRNA to identify the genes responsible for controlling canonical Wnt signalling (Major et al, 2008), and

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**Table I** Studies where Wnt-5a has tumour-suppressing effect

| Tissue type (n)                  | Detection method | Expression in tumour                  | Disease outcome                                                                 | References                        |
|----------------------------------|------------------|---------------------------------------|---------------------------------------------------------------------------------|----------------------------------|
| Neuroblastoma (37)               | mRNA levels      | Reduced expression in some tumours    | Reduced expression associated with poor outcome tumours                          | Blanc et al (2005)               |
| Colon cancer primary dukes B (55)| IH               | Expression lost or reduced in 50% of tumours | Reduced expression strong predictor of adverse outcome and low expression correlated with shorter survival | Dejmek et al (2005a)             |
| Breast cancer (94)               | IH               | Reduced expression in 56% of breast tumours | Univariate regression analysis showed loss of Wnt-5a expression indicates an increased risk of death | Dejmek et al (2005b)             |
| Invasive ductal breast carcinomas (59) | IH | Loss of Wnt-5a expression in 44% tumours | Loss associated with a higher histological grade and loss was an independent predictor of recurrence | Jonsson et al (2002)              |
| Thyroid cancer                   | IH               | Low expression in normal tissue        |                                                                                  | Kremenevskaja et al (2005)       |
| Normal tissue (11)               |                 | High expression in differentiated tumours but low expression in non differentiated tumours | ND                                                                              | Liang et al (2003)               |
| Anaplastic (5)                   |                  |                                       |                                                                                  | Liu et al (2008)                 |
| Acute myeloid leukaemias (AML)   | mRNA levels      | Wnt-5a absent in 80% of ALL and at low levels or absent in all AML | ND                                                                              | Roman-Gomez et al (2007)         |
| or ALL (10)                      | IH               | Reduction or loss of Wnt-5a protein expression was found in 81% of tumours | Loss was significantly associated with higher tumour stage                        |                                   |
| Hepatocellular carcinoma (92)    | Gene methylation | Wnt-5a hypermethylation in all cell lines | Wnt-5a methylation was an independent prognostic factor predicting disease-free survival |                                   |
| Acute lymphoblastic leukaemia (ALL) cell lines (6) patients (307) | Gene methylation | Wnt-5a hypermethylation in all cell lines |                                                                                   |                                   |
| Leukaemia Cell lines NLI(4),     | mRNA levels      | Wnt-5a highly methylated and mRNA silenced in all cell lines | ND                                                                              | Ying et al (2007)                |
| Leukaemia (4) Burkert lymphoma (6) peripheral blood mononuclear cells (3) | IH | Wnt-5a methylated in 43% of ALL patients |                                                                                  |                                   |
| Lymphoblastoid cell lines (3)    |                  | Hypermethylation lead to reduced Wnt-5a mRNA expression |                                                                                  |                                   |
| Burkert lymphoma tumours (10) NL tumours (30) | IH | Low expression in normal tissue | Hypermethylation was detected in 48% of CRC tumours, but only in 13% of normal tissue paired normal P = 0.025) | Ying et al (2008)                |
| Non–Hodgkin’s lymphomas(36)      | Gene methylation | mRNA silenced in all cell lines |                                                                                   |                                   |
| Colorectal cancer (29)           |                  | Wnt-5a methylated was detected in 48% of CRC tumours, but only in 13% of normal tissue paired normal P = 0.025) | ND                                                                              |                                   |
| Normal colon tissues (15)        |                  |                                       |                                                                                  |                                   |

IH = immunohistochemistry; ND = no data.
similar investigations are likely to be completed soon for non-canonical Wnt signalling, specifically the role of Wnt-5a. Once an in-depth understanding of the processes by which Wnt-5a brings about its cellular effects is achieved, it is likely that its role in cancer will be clarified.

In addition to its use as a prognostic indicator, the possibility of Wnt-5a being a target for therapeutics has been raised (Safholm et al., 2008). One proposed strategy is the use of peptides to mimic the properties of Wnt-5a (Safholm et al., 2008), although in our opinion this approach will require considerable caution because of the wide-ranging roles played by Wnt-5a in the cell. In the cancer cell, for instance, where Wnt-5a has been silenced, introduction of a Wnt-5a mimic may concomitantly activate non-canonical signaling, which also has cancer-promoting properties. Blocking downstream effectors of Wnt-5a may prove more effective, and hence the intense level of research into the therapeutic targeting of Wnt signalling (Ewan and Dale, 2008). With targeting will come a need to screen patients and their tumours for involvement of Wnt-5a and its associated signalling partners before chemotherapy to identify those most likely to benefit. The role of Wnt-5a in cancer and normal tissue is intriguing and the current intense level of research will further our understanding and identify novel targets for therapeutic intervention along with predictive biomarkers for targeted therapy regimes.

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British Journal of Cancer (2009) 101(2), 209 – 214

Table 2: Studies where Wnt-5a has a tumour-promoting effect

| Tissue type (n) | Detected by | Expression in tumour compared with normal | Disease outcome | References |
|----------------|-------------|------------------------------------------|----------------|-----------|
| Melanoma Primary tumours and matched metastases (59) | IH | Increased expression as disease progressed (P = 0.013) | Multivariate analysis showed Wnt-5a expression was an independent risk factor for reduced metastasis-free and overall survival | Da Forno et al (2008) |
| Breast cancer cell lines normal tissue (10) Metastatic tissue (9) | mRNA levels | Over expression of Wnt-5A in metastasis-derived breast cancer cells in comparison with normal tissues and to breast cancer cell lines | ND | Fernandez-Cobo et al (2007) |
| Normal breast cancer cell lines (11) | IH | Expression of Wnt-5A in 58% of patients | Wnt-5A expression was associated with reduced overall survival and was a bad prognostic indicator | Huang et al (2005) |
| Non-small-cell lung cancer (123) | IH | Increased expression detected in 30% of tumours and was frequently seen in tumours of a higher grade | Positivity correlated with advanced stage and poor prognosis | Kurayoshi et al (2006) |
| Gastric cancer (237) | IH | Expression in tumour compared with normal tissue | ND | Ripka et al (2007) |
| Pancreatic cancer (16) | IH | Upregulation in 81% of tumours compared with normal tissue | ND | Wang et al (2007) |
| Prostate cancer (17) | Gene methylation | Reduced methylation in 65% of tumours | ND | — |
| Melanoma Nevi (8) Primary melanoma (10) Metastases (9) | IH | Low expression 25% of Nevi, expression in 80% of primary melanoma, 89% of metastases showed large regions of expression | Wnt5A overexpression correlates strongly both to survival and time to the development of metastases | Weeraratna et al (2002) |

IH = immunohistochemistry; ND = no data.
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