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Frizzled7 dictates embryonic morphogenesis: implications for colorectal cancer progression

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1. ABSTRACT

Recent insights from diverse fields of basic and clinical research reveal that the biological processes that govern embryonic development and organogenesis are also commonly involved in the pathologies that arise in that organ or tissue in the adult. This striking parallel between embryonic development and pathology is exemplified by Wnt signalling in the intestinal tract. Wnt signalling is critical throughout embryonic development of the mammalian gut. Moreover, competent Wnt signalling is essential for the homeostatic control of the adult intestinal epithelium. On the other hand, aberrant Wnt signalling in the adult intestine leads to cancer and other pathologies. This critical role of the Wnt pathway in gut development and homeostasis is conserved through evolution, emphasizing the importance of this pathway in this tissue. Interestingly, expression of the Wnt receptor FZD7 in gut tissue is also conserved through evolution, suggesting that this receptor may be integral to the important role assigned to Wnt signalling in gut tissues.

2. INTRODUCTION

Wnt glycoproteins are a family of highly conserved secreted, palmitoylated ligands that are essential for normal development. Wnts are also involved in tissue regenerative processes, and are necessary for the homeostatic control and repair of various tissues in the adult. Moreover, it is now clear that deregulated Wnt signalling is the basis of many diverse human diseases, including cancer. Indeed cancers, particularly solid tumours, are often viewed as corrupt forms of normal developmental processes since genes that are important in the embryonic development of an organ or tissue are frequently aberrantly expressed in the cancers that can arise in that tissue in the adult.

Wnts exert their biological effects via Frizzled (Fz) receptors. There are nineteen Wnt and ten Fz family members in the mammalian genome (http://www.stanford.edu/~rnusse/wntwindow.html). Based upon hydropathy analysis, Fz are heptahelical with a

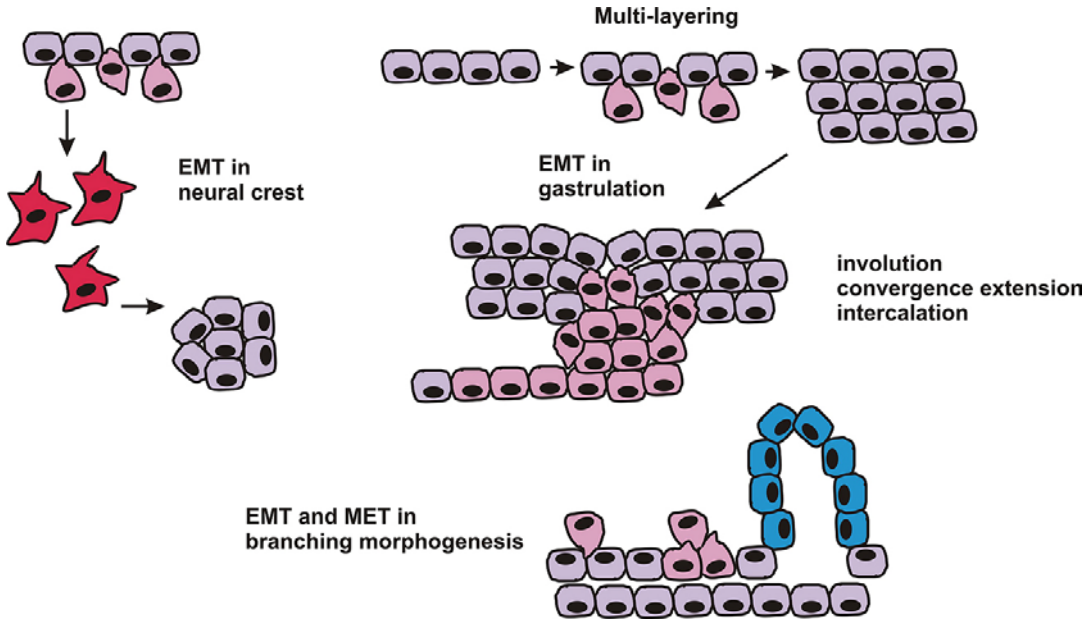

Figure 1. EMT is fundamental to the establishment of embryonic tissue architecture. During development, epithelial cells (purple cells) undergo partial (pink cells) or complete (red cells) epithelial-mesenchymal transitions (EMT) to allow integrated and individual cell movements that shape the embryo. The reverse transition, where mesenchymal cells give rise to epithelial cells, is also important during the development of some organs. Figure adapted from reference 18.

similar structure to G-protein coupled receptors. The Fz protein contains a putative N-terminal signal peptide, a cysteine-rich domain (CRD) containing 10 cysteine residues, seven hydrophobic transmembrane domains, and a C-terminal tail. The cysteine residues are highly conserved and the CRD (also referred to as the 'Fz' domain) is considered to be the Wnt binding domain of Fz receptors. Although Fz are usually depicted as a serpentine structure, the seven transmembrane segments are most likely organised in a bundle, as has been demonstrated for other G-protein coupled receptors (1). Moreover, Fz receptors form homo- or hetero-dimeric complexes to signal (2-4), which implicates other receptor domains, as well as the CRD, in transmitting the Wnt signal. Although the biological significance of specific Fz dimer complexes is not known, the inclusion of a particular Fz family member into a dimer complex will presumably affect the ultimate outcome of Wnt and Fz interactions. Activation of beta-catenin-dependent (canonical) Wnt signalling requires the involvement of co-receptors belonging to the LRP (LDL-related-protein) family (5-7). Fz-mediated non-canonical (beta-catenin-independent) signalling may also involve co-receptors; however an LRP equivalent for non-canonical Wnt signalling has not been definitively defined. In addition, beta-catenin independent signalling might not be transduced exclusively by Fz but may also be through ROR2, Derailed and RYK receptors (8-10). Therefore, the signalling pathway activated by a particular Fz is influenced by the inherent properties of the receptor (11, 12), its subcellular localization (13) and the cellular (co-expressed receptors, co-receptors, ligands and modulators) and environmental context (14). Important parallels have been drawn between the functional consequences of Wnt activation in developmental and pathological contexts, which has had and will continue to have a significant impact on our understanding of cancerous and degenerative disease process (15, 16).

3. DEVELOPMENTAL MORPHOGENESIS

Metazoan embryonic morphogenesis involves evolutionarily conserved processes that allow the co-ordinated movement of individual cells or groups of cells to establish the basic body plan of the embryo and subsequent formation of various tissues and organs. Embryonic morphogenetic events rely on altering cell behaviour to achieve migration or movement of cells in a spatiotemporal manner. This can involve dissolution of cell-cell contact allowing individual cell migration or re-organisation of cell-cell contact to achieve mass migration of tissues (17).

Cell migration through dissolution of cell-cell contact involves the transdifferentiation of cells from an epithelial to a mesenchymal state (Figure 1). Epithelial cells exhibit apical-basal polarity and maintain intimate interactions with adjacent cells. In contrast, mesenchymal cells have a front end-back end polarity and the ability to migrate through extracellular matrix. Several morphogenetic events involve transitions of cells from an epithelial to a mesenchymal state, a process that is referred to as epithelial-mesenchymal transition (EMT) (18). This allows single cells to dissociate from the primary tissue mass and to travel to secondary locations to establish derivative organs and tissues. EMT is indispensable for developmental events such as gastrulation, neural crest cell formation and heart-valve formation. In some instances, the reverse occurs, whereby mesenchymal cells transdifferentiate to an epithelial phenotype. This process is

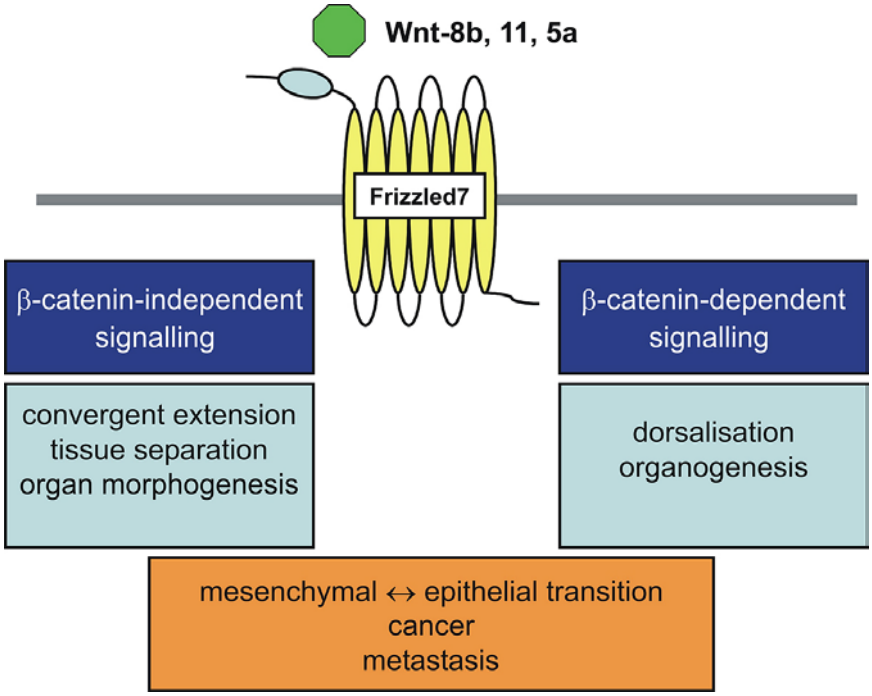

Figure 2. Frizzled-7 can act in different branches of the Wnt-signalling cascade. The Frizzled -7 receptor can bind to several Wnt ligands such as Wnt-8b, 11 and 5a. In embryos Frizzled-7-mediated, β-catenin-independent signalling regulates morphogenetic cell behaviours and movements. The activation of β-catenin-dependent Wnt signalling promotes dorsalization and regulates organogenesis. Both β-catenin-dependent and independent signalling is involved in reversible EMT in metastasizing tumour cells.

referred to as mesenchymal-epithelial transition (MET) and is necessary for the formation of epithelial organs such as the kidney and the urogenital tract. Permanent transitions, where epithelium gives rise to mesenchyme (EMT), and the converse, where mesenchyme gives rise to epithelium (MET), are at the opposite extreme poles of transitions between epithelial and mesenchymal states (Figure 1).

Developmental morphogenesis also relies on partial transition between these two extremes, without complete dissolution of cell-cell contact and transdifferentiation. Partial EMT and MET, and epithelial morphogenesis (re-shaping of epithelial cells), involves the re-organisation of the cytoskeleton, and cell-cell and cell-matrix contacts so that cell locations relative to each other are re-organised in three-dimensions to re-shape tissues (18). This type of tissue remodelling is the basis of convergence and extension of mesoderm and neuroectoderm where the tissue is narrowed and lengthened without altering the number of cells (19). Another important morphogenetic cell behaviour is tissue separation, which prevents mixing of cells of the ectoderm and mesendoderm (20). Later in development when organs form, cells such as neural crest cells or insulin producing cells in the pancreas have to become motile and assume defined positions in the body (21). Whether permanent or transient, it is becoming clear that transitions between mesenchymal and epithelial states are orchestrated by complex signalling networks that include the Wnt signalling pathway.

4. FRIZZLED7 DICTATES EMBRYONIC MORPHOGENESIS

4.1. Wnt signalling is a highly conserved developmental signalling pathway

The Wnt/Fz signalling pathway has several branches that are referred to as canonical (beta-catenin-dependent) and non-canonical (beta-catenin-independent) (14, 22) (Figure 2). Canonical signalling regulates differentiation and proliferation events that are central to tissue patterning in both vertebrates and invertebrates, while non-canonical Wnt pathways regulate cell adhesion, cell polarity and migration events, which are essential for morphogenetic movement. Wnt/Fz signalling pathways are exquisitely regulated with naturally occurring positive and negative regulators at virtually every step along the pathway. The central components and regulators of the pathway will not be reviewed here. The reader is referred to excellent recent reviews on this topic (14, 16, 22, 23) and elsewhere within this feature issue.

Wnt signalling pathways are conserved in metazoans, from the evolutionary ancient metazoan phylum Cnidaria through to man. Although Cnidaria is the second oldest phylum diverging prior to the appearance of the bilaterians, members of this ancient phylum have an intact Wnt signalling pathway. One of the best studied Cnidarians is the fresh water polyp *Hydra vulgaris* (24). The hydra expresses Wnt, Dsh, GSK3, beta-catenin, TCF/LEF (25) and an Fz homologous gene (26). Recent evidence

Table 1. FZD7 orthologs[1]

Organism	Gene name	Homology[2]
Chimpanzee (*Pan troglodytes*)	FZD7	100 (a)
Cow (*Bos taurus*)	Fzd7	97.2 (a)
Dog (*Canis familaris*)	LOC488478	93.55 (n) 98.08 (a)
Rat (*Rattus musculus*)	Fzd7_predicted	90.15 (n) 96.85 (a)
Mouse (*Mus musculus*)	Fzd7	90.09 (n) 96.68 (a)
Chicken (*Gallus gallus*)	FZD7	84.59 (n) 90.29 (a)
African clawed frog (*Xenopus laevis*)	Fzd7	86.68 (n)
Zebrafish (*Danio rerio*)	fzd7a	84.44 (n)
Fruit fly (*Drosophila melanogasta*)	fz	47 (a)
Worm (*Caenorhabditis elegans*)	mom-5	38 (a)

[1]Information in table is from Stanford University, website:http://genome-www.stanford.edu/cgi-bin/genecards/carddisp.pl?gene=FZD7 and references 29 and 30, [2]The percentage similarity to the human gene, with comparisons based on (n) nucleic acid or (a) amino acid sequences.

indicates that beta-catenin-dependent signalling is involved in patterning events (head induction), while beta-catenin-independent signalling orchestrates morphogenetic events (morphogenesis of tentacle and bud) (27). Thus both canonical and non-canonical Wnt signalling is conserved in this evolutionary ancient organism. Intriguingly, recent evidence indicates that Wnt signalling is conserved at the onset of animal evolution. All the central components of the canonical Wnt pathway have been identified in the desmosponge Amphimedon (formerly referred to as Reniera) (28). Although the sponge body plan differs from that of other metazoans, their development bears many of the hallmarks of metazoan embryogenesis (29). The expression patterns of the Wnt pathway components during desmosponge development suggest that the earliest role of Wnts in specification of embryonic polarity is conserved in sponges. Hence Wnt signalling and function are present in one of the most basal evolutionary lineages in the animal kingdom.

4.2. Frizzled7 is an evolutionarily conserved gene in the gut

FZD7 is highly conserved through evolution, with orthologs identified in nematodes, insects and vertebrates such as frog, fish, chicken, mouse, rat, dog, cow and chimpanzee (Table 1) (30, 31). Additionally, the expression patterns of Fz7 orthologs during organogenesis also implicate evolutionary conserved roles for Fz7. This is particularly well exemplified by gut development. As described above, both canonical and non-canonical Wnt signalling is intact in the ancient organism hydra. The hydra is essentially a gastric tube with a mouth and tentacles at its apical pole and a foot process at its basal pole. The body wall consists of an epithelial bilayer, an outer ectoderm and an inner endoderm separated by an extracellular matrix. The cells are in constant turnover. Epithelial and interstitial cells are continuously dividing along the body column and are displaced towards the poles, where they transdifferentiate and are eventually shed from the ends of the poles. A fixed adult length, despite continuous cell proliferation, is thus balanced by cell shedding and also by shunting cells into buds, the asexual form of reproduction. Compared to the ten known human Fz family members, the hydra Fz has the highest homology with FZD7. The hydra Fz is expressed only in the endoderm. This restricted pattern of expression in the adult hydra implicates a role in signalling pathways between the epithelial bilayer that control the balance between cell differentiation and cell proliferation, and the establishment and maintenance of three-dimensional gut tissue architecture.

Recent studies in the mouse indicate that the importance of Fz7 in the gut may be conserved from hydra to man – that is, Fz7 may play an important role in mammalian gut development and in the homeostatic control of adult gut tissue. As in the hydra, the epithelial lining of the mammalian intestine is continuously replaced. Proliferating stem/progenitor cells establish the epithelial lining during embryonic development and also maintain the epithelial lining in the adult. Competent canonical Wnt signalling is essential for the maintenance of the stem/progenitor cell compartment of the intestine (32); however the Fz receptor (s) that transmits the stem cell Wnt signal has not been identified. In the mouse gut, Fzd7 expression is restricted to these proliferative stem/progenitor compartments of both developing and adult intestine (33, 34). The restricted expression of Fzd7 to the stem/progenitor compartment strongly implicates a role for Fzd7 in transmitting the 'stem cell' Wnt signal/s. Moreover, competent canonical signalling is necessary for homeostatic control of stem cell compartments in other adult tissues as well the intestine (34) and recently it was demonstrated that Fz7 is one of a panel of genes that are linked with the stem cell phenotype (35, 36). Collectively, these findings strongly support a role for Fz7 in maintaining the gut stem cell phenotype, both in the embryo and in the adult; however a direct link remains to be demonstrated experimentally. Importantly, loss of homeostatic control of stem cell-maintained compartments is associated with human diseases such as cancer. Thus an understanding of Fz7 function in the stem/progenitor compartment of the gut may provide insight into disease processes. Moreover, the status of non-canonical signalling in mammalian gut development or adult tissue homeostasis is not known. Given that Fz7 can activate several Wnt pathways and that both canonical and non-canonical Wnt signalling have been demonstrated in the hydra, an investigation of Fz7 signalling properties may reveal a role for non-canonical Wnt pathways in the mammalian gut.

4.2. Frizzled7 activates different Wnt signalling pathways

In addition to being highly conserved through evolution, Fz7 has several properties that make it unique in the Fz family. Fz7 is the one Fz family member that has been demonstrated to robustly activate several Wnt signalling branches (37) (Figure 2). Moreover, Fz7 appears to be the Fz orchestrating the vertebrate planar cell polarity pathway (PCP) in frogs (22, 38), fish (39) and mice (40) and is critical for several developmental processes that involve PCP e.g. gastrulation in the frog (41). Indeed, much of what is known about Fz7 function and its signalling properties have been derived from studies in the frog, *Xenopus laevis*. Xfz7, first cloned by Wheeler and Hoppler

(42), is dynamically expressed during *Xenopus* development and, depending on the cellular context, Xfz7 is able to activate beta-catenin, PCP and Fz/PKC pathways (43-45). The molecular mechanism by which the Xfz7 receptor selectively triggers the different branches of Wnt signalling is not yet fully understood. A key point however is that Xfz7 can interact with a number of Wnt ligands such as Wnt-8b, 11, and 5a (37, 43, 46) and can form hetero-dimer complexes with several other Fz family members (3).

Xfz7 expression pattern during early development implicated a role in early patterning and morphogenesis (42). Indeed, it was soon shown that maternally derived Xfz7 synergises with Wnt-11 protein and functions upstream of beta-catenin in dorsoventral axis induction (45). It is interesting to note that zygotic Xfz7 and Wnt-11 activate β-catenin-independent PCP signalling, which regulates convergent extension movements in the gastrulating embryo (43). This indicates that the cellular context, in which a specific ligand receptor combination works, is essential for the initiation of a specific Wnt read out. Winklbauer and colleagues demonstrated that depletion of Xfz7 with an antisense morpholino caused severe gastrulation defects and that Xfz7-dependent Wnt/PKC signalling controls tissue separation (41). Further analysis of tissue separation revealed that Xfz7 interacts with the extracellular domain of paraxial protocadherin (PAPC) (47). In gain-of-function experiments it was demonstrated that this interaction is required for the induction of separation behaviour in animal cap tissue. These data suggest that binding of non-Wnt proteins to Fz receptors can activate receptor-mediated signalling. Thus Xfz7 is involved in both canonical and non-canonical Wnt-signalling pathways (37). The strong maternal and zygotic expression of zebrafish Fz7a (48) indicates that other vertebrate Fz7 orthologs are also likely to display similar signalling diversity. FZD7-mediated canonical Wnt signalling has been demonstrated in mammalian contexts, mostly in human cancer cells (49-52), and several studies implicate Fz7 in mammalian non-canonical Wnt pathways (40, 52), thus the multi-part signalling properties of Fz7 orthologs appears to be conserved in diverse organisms, from hydra to man.

4.3. Frizzled7-mediated canonical signalling during development

During development, canonical Wnt signalling (Figure 2) is generally involved in tissue patterning and epithelialisation (epithelial differentiation) events and Fz7 has been implicated in orchestrating some of these events. Xfz7 is expressed in the developing nervous system (42, 53) and Xfz7-mediated canonical signalling induces expression of engrailed-2 and the neural crest markers, slug and twist. This expression pattern implicated Xfz7-mediated canonical signalling in neural crest cell induction, a hypothesis that was confirmed experimentally recently (54). Moreover, a role for Fz7 in neural crest cell induction may be conserved through evolution. Although there are differences between neural crest cell induction in frogs and birds, neural crest cell induction in the chick also appears to be via Fz7. In the chick, neural crest cell induction, which is mediated by Wnt-6 (55, 56), was inhibited by a truncated dominant-negative form of Fz7 (56). Interestingly, canonical Wnt signalling is involved in the development of neural crest cells in the zebrafish (57); however a specific role for Fz7 in this context has not yet been demonstrated.

Canonical Wnt signalling is involved in many epithelialisation events, an example is the epithelial organisation of somites (58, 59). This is another developmental process where a role for Fz7 was first implicated by expression studies (60) and recently confirmed experimentally (61). Indeed, it appears that canonical Wnt-induced epithelial organisation or epithelialisation is a recurring theme during development. Canonical Wnt signalling reporter gene activity is transiently induced during eye lens epithelial development (62), and Wnt9b-mediated canonical signalling governs MET during organogenesis of the mammalian urogenital tract (63). However it remains to be determined which Fz family member/s orchestrates these canonical Wnt-induced events.

4.4. Frizzled7-mediated non-canonical signalling during development

As discussed above, Fz7-mediated non-canonical signalling (Figure 2) is essential for morphogenetic movement during *Xenopus* gastrulation. Indeed, the capacity of Fz7 to activate different Wnt signalling pathways was first demonstrated in the *Xenopus*. Xfz7 engages both Wnt/Ca^{++} and vertebrate PCP pathways at different stages during *Xenopus* gastrulation (41, 43). Intriguingly, development of the neural crest also appears to involve different Fz7-mediated Wnt signalling pathways at different stages. As discussed above, Fz7-mediated canonical signalling controls neural crest cell induction. An additional role in neural crest cell development has recently been assigned to Fz7. De Calisto and colleagues demonstrated that Wnt11/Fz7-mediated non-canonical signalling is essential for neural crest cell migration (64). Hence, Fz7 is involved in the induction and migration of neural crest cells, and appears to mediate this functional duality by activating different branches of Wnt signalling.

5. FRIZZLED7 IN TUMOUR MORPHOGENESIS

Many of the cellular processes that are central to developmental morphogenesis appear to also be important in tumour spread to secondary organs (metastasis). Hence, in broad terms, similar programmes seem to instruct cells to detach from the confines of the primary tissue, to invade and migrate through extracellular matrices, and to travel to and lodge in permissive niche/s to establish secondary tissue/s. The analogies between developmental and tumour morphogenesis, and the involvement of the Wnt signalling pathway in orchestrating these events, is especially well documented for gut development and cancers that arise from the adult gut epithelium such as colorectal cancer (CRC) (65-69).

5.1. Colorectal cancer morphogenesis

The majority of colorectal carcinomas are well differentiated, forming organized three-dimensional tubular or villous structures, yet they still metastasize. That is,

tumour cells are able to dissociate from the confines of this organised structure, disseminate to distant organs and establish secondary tumours (metastases). Both primary and secondary tumours have clearly defined, localised invasive areas, where the tissue architecture is reorganised, yielding tumour cell sheets and isolated tumour cells interspersed with the underlying stroma (70, 71). Tumour cells engaged in tubular or villous structures are differentiated, polarized epithelial cells that are actively proliferating. In contrast, cell proliferation is decreased or undetected in the de-differentiated tumour cells at the invasive front (70). Moreover, the de-differentiated tumour cells have a more mesenchymal appearance, a phenotype that is associated with migratory and invasive behaviour. Based on these phenotype changes, de-differentiation at the invasive front is referred to as an EMT. Notably, there is no difference between the pathology of primary and secondary tumours for most colorectal carcinomas. It follows then that in the secondary organs, the reverse transition (MET) must occur, which re-instates the epithelial, proliferative phenotype (68). A reversion to the phenotype of the primary tumour through MET appears to also be a common feature in other cancers (72). Transitions of tumour cells between epithelial and mesenchymal states are thus dynamic and reversible. Presumably, this reversion of de-differentiated disseminated cells to an epithelial phenotype is necessary to re-instate cell division so that the tumour structure can be re-built at the secondary site.

The ordered arrangement of CRC tumour cells into the tubular or villous structures appears to involve beta-catenin/TCF-mediated transcription programmes that are analogous to patterning during embryonic gastrulation (67). The intra-tumorous distribution and intensity of nuclear beta-catenin expression correlates with the expression distribution observed during analogous gastrulation processes. Nuclear beta-catenin is dramatically increased in the CRC tumour cells at the invasive front and many of the molecules associated with tumour invasion and metastasis are co-expressed by these cells. Moreover, many of these genes are transcriptional targets of beta-catenin/TCF (73). The spatial predominance of nuclear beta-catenin in invasive tumour cells implicates the microenvironment as a driving force for this transcriptional programme. Indeed, a decisive role for the microenvironment during *Xenopus* gastrulation was established recently. Goto and colleagues demonstrated that morphogenetic movement during gastrulation is, at least in part, due to deposition of a fibronectin gradient in the extracellular matrix (74). As discussed above, loss-of-function studies show that Fz7 is necessary for *Xenopus* gastrulation. Larrain and colleague have recently linked this pivotal role of Fz7 to transducing the fibronectin cues from the microenvironment. They demonstrate that the molecular interaction between Fz7, syndecan 4 (a heparin sulphate proteoglycan) at the cell surface, and fibronectin in the extracellular matrix governs convergent extension movements during *Xenopus* gastrulation (75). Interestingly, elevated fibronectin deposition (gradient) in the extracellular matrix provides a permissive niche for incoming tumour cells (76). This corroborates previous studies showing increased fibronectin in the extracellular matrix from normal to carcinoma, and then from carcinoma centre to invasive front of colorectal carcinoma tissue (70). Fibronectin is one of the first canonical target genes identified (77), yet the consequences for tumour morphogenesis have not been extensively studied.

5.2. Frizzled7 in colorectal cancer morphogenesis

The paucity in current understanding of the molecular mechanisms controlling CRC tumour morphogenesis is primarily due to the complexity and difficulty of studying the *in vivo* situation. On the other hand, *in vitro* model systems using traditional 2-dimensional (2D) monolayer culture can mimic some aspects of tumour epithelial cell behaviour, but fail to accurately recapitulate many of the characteristics displayed by tumour cells *in vivo*. It is now clear that 3D culture systems are better models of *in vivo* tumour cell behaviour (78). Bridging this gap between the simplicity of *in vitro* 2D cell culture systems and the complexity of *in vivo* models with *in vitro* 3D culture systems has dramatically advanced current understanding of breast cancer metastasis. Employing 3D *in vitro* culture systems promises to have the same impact on understanding CRC progression. Bates and colleagues have shown that a unique human CRC cell line LIM1863, which spontaneously forms 3D highly organised multicellular spheres (79), can be induced with cytokines to undergo EMT (80, 81) and that integrins induced during this transition are also increased during CRC progression (82). Hence the utilisation of this 3D cell line to model CRC EMT has already yielded important novel indicators of CRC progression.

Another important feature of CRC progression is the reversible nature of the phenotype transitions, thus a model system that could recapitulate this in an *in vitro* setting would also present a great advantage. A model system that accurately recapitulates the cyclical features of CRC morphogenesis was recently established using the LIM1863 cell line (52, 83). This culture system is an adaptation of the parental cell line and is referred to as LIM1863-*Mph* (for morphogenetic). In this model system de-differentiated LIM1863-*Mph* cells growing as a 2D monolayer undergo MET to assemble the 3D multicellular spheres. In many ways, the 3D spheres resemble enclosed carcinoma tubules and are referred to as organoids (or carcinoids). The organoid epithelial cells are well differentiated but subsequently undergo EMT, dispersing the spherical organisation of the organoids to form monolayer patches on the tissue culture plastic. The cyclic transitions between 2D and 3D take several days to complete. Although these transitions occur spontaneously without added cytokines, presumably they are initiated by localised release of endogenous cytokines and the changing dynamics of cell-cell, cell-substrate contact. Importantly, the dynamic phenotype transitions between 2D and 3D mimic the pathology of invasive (deconstruction of tubular structure) and central (construction of tubular structures) areas of carcinoma tissues (52).

Employing a loss-of-function approach that depends on RNAi (interference)-mediated silencing of FZD7 expression in LIM1863-*Mph* cells, it was

demonstrated that FZD7 is necessary for MET and 3D organization of epithelial cells into mature organoids. In addition, FZD7 is also necessary for migration of the monolayer cells along the tissue culture plastic. The intensity and distribution of nuclear beta-catenin implicates canonical Wnt signalling preferentially governs the organisation of the epithelial cells into organoids rather than migration of the monolayer cells (52). Intriguingly, these observations again draw parallels with developmental processes. During development, Fz7-mediated canonical signalling governs epithelialisation events, while Fz7-mediated non-canonical signalling governs morphogenetic movement. While employment of different Wnt signalling pathways by FZD7 in the context of CRC remains to be demonstrated directly, these loss-of-function studies suggest that FZD7 displays similar functional duality in cancer as in embryonic development. Moreover, akin to developmental studies, the potential involvement of FZD7 in interpreting fibronectin cues from the tumour microenvironment is another intriguing question that warrants investigation.

6. PERSPECTIVES

Wnts, FZDs and modulators of Wnt-FZD interaction are aberrantly expressed in CRC implicating their involvement (84). Several naturally occurring inhibitors of Wnt-FZD interaction are now recognised tumour suppressors in CRC (85-87), which further strengthens the notion that Wnt and FZD *per se* play important roles in the genesis of this cancer. Hence, in addition to the recognised involvement of Wnt signalling through mutations in downstream components of the pathway (66), recent evidence strongly suggests that additional modulation of Wnt signalling, at the level of receptor-ligand interaction, is also critical for both the initiation and progression of CRC. The apparent requirement for deregulation of the Wnt signalling pathway at several levels is perhaps not that surprising as this developmentally important signalling pathway is tightly regulated at multiple levels. Importantly, the recognition that naturally occurring inhibitors of Wnt-FZD interaction are *bona fide* tumour suppressors provides novel avenues for therapeutic intervention. That is, this suggests that removal or blocking of the Wnt signal is a rational therapeutic strategy since active elimination of negative regulators promotes cancer. Therapeutic targeting of the Wnt-FZD receptor interaction is clearly indicated by the profound anti-tumour effects that are achieved by inhibiting Wnt-FZD interaction (88, 89). Indeed, Fz7-signalling targeted approaches are proving to be highly effective anti-tumour agents in experimental systems (90, 91). Moreover, it is also becoming clear that the tumour cell responses are influenced by the tumour microenvironment, which opens up additional avenues for targeted therapy. Drawing on our knowledge from developmental systems will undoubtedly expedite our understanding of the function of these molecular interactions in cancer.

7. ACKNOWLEDGEMENTS

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Abbreviations: CRD: cysteine rich domain; EMT: epithelial-mesenchymal transition; Fz: generic Frizzled; FZD: human Frizzled; Fzd: mouse Frizzled; XFz: Xenopus Frizzled; LRP: LDL-related protein; MET: mesenchymal-epithelial transition; PCP: planar cell polarity

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