Minireview

Complex Interplay between the RUNX Transcription Factors and Wnt/β-Catenin Pathway in Cancer: A Tango in the Night

Kerri Sweeney[1], Ewan R. Cameron[2,*], and Karen Blyth[1,3,*]

[1]CRUK Beatson Institute, Garscube Estate, Glasgow G61 1BD, UK, [2]Glasgow Veterinary School, University of Glasgow, Glasgow G61 1QH, UK, [3]Institute of Cancer Sciences, University of Glasgow, Glasgow G61 1QH, UK
*Correspondence: Ewan.Cameron@glasgow.ac.uk (ERC); Karen.Blyth@glasgow.ac.uk (KB)
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Cells are designed to be sensitive to a myriad of external cues so they can fulfil their individual destiny as part of the greater whole. A number of well-characterised signalling pathways dictate the cell's response to the external environment and incoming messages. In healthy, well-ordered homeostatic systems these signals are tightly controlled and kept in balance. However, given their powerful control over cell fate, these pathways, and the transcriptional machinery they orchestrate, are frequently hijacked during the development of neoplastic disease. A prime example is the Wnt signalling pathway that can be modulated by a variety of ligands and inhibitors, ultimately exerting its effects through the β-catenin transcription factor and its downstream target genes. Here we focus on the interplay between the three-member family of RUNX transcription factors with the Wnt pathway and how together they can influence cell behaviour and contribute to cancer development. In a recurring theme with other signalling systems, the *RUNX* genes and the Wnt pathway appear to operate within a series of feedback loops. *RUNX* genes are capable of directly and indirectly regulating different elements of the Wnt pathway to either strengthen or inhibit the signal. Equally, β-catenin and its transcriptional co-factors can control *RUNX* gene expression and together they can collaborate to regulate a large number of third party co-target genes.

## THE WNT SIGNALLING PATHWAY IN CANCER

The identification and analysis of the top molecular drivers of cancer has been essential for the development of targeted therapies against the disease. One such driver, the Wnt signalling pathway, is an evolutionarily conserved pathway involved in numerous cellular and developmental processes including cell proliferation, differentiation, and stem cell self-renewal (Grigoryan et al., 2008; Steinhart and Angers, 2018; Wang et al., 2012). This key pathway and its components have been well characterised for their roles in the development and progression of several cancer types (Clements et al., 2002; Clevers, 2000; 2006; Luis et al., 2012; Satoh et al., 2000; Segditsas and Tomlinson, 2006). The functions of Wnt ligands can be facilitated through both the canonical and non-canonical branches of the pathway, with the former operating through β-catenin accumulation and translocation to the nucleus where it is able to activate its downstream targets (Anastas and Moon, 2013). Although Wnt signalling has been most intensively studied in colorectal cancer, where almost all tumours present with altered Wnt signalling (Cancer Genome Atlas Network, 2012), aberrant Wnt signalling is also observed in several other cancer types (Fig. 1A). One no-
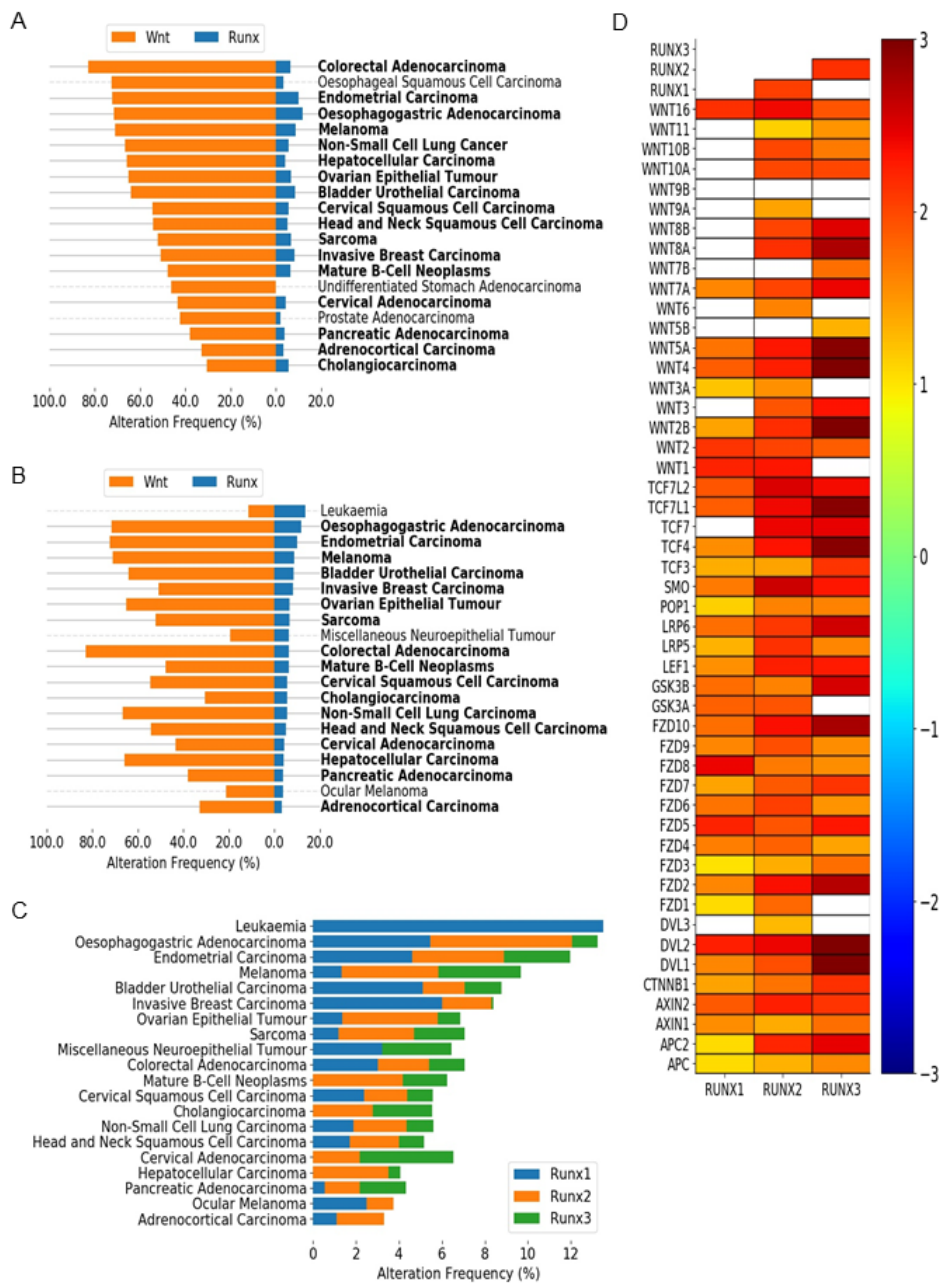
Fig. 1. Wnt pathway and *RUNX* gene alterations in a pan-cancer analysis of the TCGA database. Top 20 cancer types where alterations in Wnt pathway components (A) or all three *RUNX* genes (B) are most frequently observed, including matched information on the percentage of samples with reciprocal *RUNX*/Wnt alterations. Shown in bold are the cancer types that appear in both top 20 lists. (C) The top 20 cancer types with *RUNX* alterations were each analysed for their percentage alteration of individual *RUNX* genes (*RUNX1*, blue; *RUNX2,* orange; *RUNX3,* green). Note that alterations of the *RUNX* genes are not always mutually exclusive and there can be co-occurrence in *RUNX* alterations (as demonstrated in Fig. 1D). Therefore, the maximum alteration frequency (%) displayed in Figure 1C is not necessarily representative of the total *RUNX* alteration frequency in Figures 1A and 1B, particularly in cancer types where more than one *RUNX* family member is altered. (D) A co-occurrence matrix was generated to observe co-occurrence between alterations in *RUNX* genes and listed Wnt pathway components in a pan-cancer analysis. The heat map, showing the $\log_2$ odds ratio, quantifies how strongly the presence or absence of alterations in gene X are associated with the presence or absence of alterations in gene Y. The heat maps are displayed only in the boxes of gene matches where the co-occurrence or mutual exclusivity was shown to be significant using the q-values (Derived from Benjamini-Hochberg false discovery rate [FDR] correction procedure). Wnt pathway components were selected for these analyses from the Wnt homepage, created by the Nusse Lab (http://web.stanford.edu/group/nusselab/cgi-bin/wnt/). All data for this figure was obtained through cBioPortal for Cancer Genomics (https://www.cbioportal.org/) using the TCGA PanCancer Atlas Studies (Cerami et al., 2012; Gao et al., 2013).

table example is breast cancer, where Wnt pathway components are amplified and overexpressed in ~50% of patients and where expression positively correlates with poor prognosis (Dey et al., 2013; Khramtsov et al., 2010; Li et al., 2014; Lin et al., 2000; Monteiro et al., 2014). The role of Wnt in tumorigenesis was initially discovered in mouse models where the mouse *Wnt* gene was found to be a preferential integration site for the mouse mammary tumour virus (MMTV), a retrovirus capable of inducing mammary carcinomas with long latency (Nusse and Varmus, 1982). Transcriptional activation of the *Wnt1* gene via proviral insertion mutations or using an MMTV promoter to drive transgenic overexpression of *Wnt1* caused mammary gland hyperplasia and tumorigenesis, establishing a connection between the Wnt pathway and cancer (Bocchinfuso et al., 1999; Nusse and Varmus, 1982; Tsukamoto et al., 1988). A key early demonstration that the Wnt pathway had a major role in human cancer arose from the observation that mutations of the adenomatous polyposis coli (*APC*) gene, which encodes a protein that negatively regulates Wnt/β-catenin signalling (Korinek et al., 1997; Rubinfeld et al., 1993; 1997; Su et al., 1993), were the cause of familial adenomatous polyposis, a hereditary colon cancer syndrome (Kinzler et al., 1991; Nishisho et al., 1991). Since these initial discoveries, many important regulatory genes have been identified in the Wnt signalling pathway, and their function characterised. Such information will be valuable in designing future therapies that block or attenuate the pathway in neoplastic disease. Because Wnt signalling has been identified to be a key player in several aspects of tumorigenesis — including metastasis, metabolism, immune evasion, and stemness (Zhan et al., 2017) — the Wnt pathway, particularly the highly characterised canonical (β-catenin-dependent) pathway, provides a promising potential as a future therapeutic target (Barker and Clevers, 2006; Goldsberry et al., 2019; Novellasdemunt et al., 2015; Wang et al., 2018; Zhang et al., 2018).

RUNX TRANSCRIPTION FACTORS IN DEVELOPMENT, REGULATION, AND CANCER

Consisting of three individual proteins with distinct functions, the RUNX family of transcription factors are essential for several cellular and developmental processes, as was elegantly reviewed recently by Mevel et al. (2019). RUNX1, RUNX2, and RUNX3 each form complexes with their obligate cofactor, core binding factor beta (CBFβ), which is essential for facilitating the binding of the transcription factors to DNA in order for them to either activate or repress their downstream targets. Interaction between the RUNX transcription factors and CBFβ, and between the CBF complex and DNA, is enabled through the highly conserved runt-homology domain (RHD) in the N-terminus of all RUNX proteins. Gene knockout studies in mice have helped to reveal the discrete functions of each *Runx* family member in specific systems in the body (Brenner et al., 2004; Komori et al., 1997; Levanon et al., 2002; Li et al., 2002; North et al., 1999; Okuda et al., 1996; Otto et al., 1997) with subsequent studies illuminating their functions in other tissues, comprehensively reviewed elsewhere (Mevel et al., 2019).

It is no surprise that, given the essential roles of the RUNX proteins in fundamental cellular and developmental processes, disrupted expression of these transcription factors has been frequently observed in various cancer types (Figs. 1B and 1C). However, it has also been revealed that context is key, as both pro-tumour and anti-tumour roles have been observed for each of the RUNX proteins (Blyth et al., 2005; Ito et al., 2015). For example, *RUNX1* mutations are found to be among the most common mutations observed in a wide variety of haematological malignancies (De Braekeleer et al., 2009; Niini et al., 2000; Osato, 2004). Paradoxically, *RUNX1* has been shown to act as a dominant oncogene in some subtypes of leukaemia, and acute leukaemia cells actually rely on the presence of wild type RUNX1 expression for their survival (Ben-Ami et al., 2013; Choi et al., 2017; Goyama et al., 2013). Similar contradictory roles for *RUNX1* have been identified in solid tumours (Riggio and Blyth, 2017; Taniuchi et al., 2012) as is reviewed elsewhere in this special issue by Lie-a-ling et al. (2020). RUNX2 has been associated with several cancer types in which it is often overexpressed compared to matched normal tissues, including osteosarcoma where it also correlates with poor response to chemotherapy (Kurek et al., 2010; Martin et al., 2011; Sadikovic et al., 2010), papillary and thyroid carcinomas (Dalle Carbonare et al., 2012; Endo et al., 2008), and in breast and prostate cancer where there are associations with metastasis (Akech et al., 2010; Barnes et al., 2003; 2004; McDonald et al., 2014; Owens et al., 2014; Pratap et al., 2006; Rooney et al., 2017). Previous research has indicated a role for RUNX3 in gastric cancers (Ito et al., 2005; Li et al., 2002), as well as cancers of the pancreas (Whittle and Hingorani, 2017; Whittle et al., 2015), lung (Araki et al., 2005; Lee et al., 2013; Sato et al., 2006), and hepatocellular carcinoma (Shiraha et al., 2011; Tanaka et al., 2012; Xiao and Liu, 2004). In most cases, RUNX3 has been reported to be downregulated with cancer progression (Chuang et al., 2017) although there is also compelling evidence that RUNX3 may modulate epithelial cancer indirectly through its effects on immune regulation and inflammation (Lotem et al., 2015; 2017).

RUNX/WNT INTERACTIONS IN DEVELOPMENT AND CANCER

There is a large overlap in the cancers most commonly associated with Wnt pathway activation and *RUNX* gene alteration (Fig. 1, Table 1), with significant co-occurrence between certain Wnt pathway components and the *RUNX* genes across all cancer types (Fig. 1D). Indeed there is evidence in the literature that some of the developmental and regulatory functions of the RUNX family are enabled through interactions with (or modulation of) the Wnt pathway, particularly the canonical Wnt/β-catenin pathway (Gaur et al., 2005; Haxaire et al., 2016; Jarvinen et al., 2018; Kahler and Westendorf, 2003; Luo et al., 2019; Osorio et al., 2011; Qin et al., 2019; Wu et al., 2012). In the sections below we briefly discuss the interaction with the Wnt signalling pathway and the individual *RUNX* genes. It should be appreciated, however, that due to their use of a common binding site and considerable homology between the family members, that a reported in-

Table 1. Overlapping incidence of *RUNX* gene and Wnt pathway alterations in cancer

Cancer type	Alteration frequency (%)				
	RUNX	Wnt	*RUNX* + Wnt	*RUNX*/Wnt analysis	*RUNX*/Wnt overlap
Colorectal adenocarcinoma	6.4	83	89.4	83.33	6.07
Endometrial carcinoma	9.9	72.35	82.25	72.87	9.38
Oesophagogastric adenocarcinoma	11.87	71.6	83.47	73.54	9.93
Melanoma	8.78	70.95	79.73	72.75	6.98
Non-small cell lung cancer	5.51	66.76	72.27	67.9	4.37
Hepatocellular carcinoma	4.07	65.85	69.92	66.67	3.25
Ovarian epithelial tumour	6.68	65.24	71.92	66.78	5.14
Bladder urothelial carcinoma	8.52	63.99	72.51	65.69	6.82
Cervical squamous cell carcinoma	5.58	54.58	60.16	56.97	3.19
Head and neck squamous cell carcinoma	5.16	54.3	59.46	56.21	3.25
Sarcoma	6.67	52.16	58.83	52.94	5.89
Invasive breast carcinoma	8.12	50.92	59.04	54.15	4.89
Mature B-cell neoplasms	6.25	47.92	54.17	47.92	6.25
Cervical adenocarcinoma	4.35	43.48	47.83	45.65	2.18
Pancreatic adenocarcinoma	3.8	38.04	41.84	38.59	3.25
Adrenocortical carcinoma	3.3	32.97	36.27	34.07	2.2
Cholangiocarcinoma	5.56	30.56	36.12	33.33	2.79

The cancer types that appeared in both top 20 lists for *RUNX* and select Wnt pathway alterations in Figures 1A and 1B were further analysed for overlapping occurrence of Wnt pathway and *RUNX* alterations. *RUNX* refers to alteration in any of the three genes (*RUNX1*, *RUNX2*, *RUNX3*). When the incidence of *RUNX* and Wnt pathway alterations were analysed individually, the total percentage of these was higher than the alteration frequency obtained by analysing the frequency of *RUNX* and Wnt pathway alterations simultaneously, indicating that these alterations co-occur (and supporting the data shown in Fig. 1D). The percentage overlap in Wnt pathway and *RUNX* alterations was obtained for each of the analysed cancer types by calculating the difference between the *RUNX*/Wnt simultaneous analysis alteration frequency and the individual *RUNX* and Wnt pathway alteration frequencies added together. The same Wnt pathway components analysed in Figure 1, selected from the Wnt homepage (http://web.stanford.edu/group/nusselab/cgi-bin/wnt/), were also used for this analysis. Data was mined from cBioPortal for Cancer Genomics using the TCGA PanCancer Atlas Studies (https://www.cbioportal.org/) (Cerami et al., 2012; Gao et al., 2013).

teraction with one member could potentially extend to other members of the family in different contexts or lineages.

RUNX1 and Wnt signalling in leukaemia and epithelial tumours

Interaction between Wnt and RUNX1 activity was reported over 20 years ago when it was shown that the β-catenin co-factor lymphoid enhancer factor 1 (LEF1) enhanced RUNX1 binding to chromatin and potentiated transcriptional activity of the T-cell receptor alpha (TCRα) enhancer (Mayall et al., 1997). Subsequently the mutual interdependence of these pathways has been described in systems as diverse as haematopoietic stem cells and ovaries, with RUNX1 capable of affecting the Wnt pathway at several discreet components of the pathway (Cheng et al., 2011; Friedman, 2009; Naillat et al., 2015; Wu et al., 2012).

The role of RUNX1 in leukaemia has been studied in the context of Wnt signalling whereby β-catenin is associated with the ability of leukaemia stem cells to self-renew. Treatment of haematopoietic progenitor cells with purified Wnt3a ligand increased the transcription of *ETO* and *RUNX1* in addition to enhancing their spatial proximity. These events could precipitate translocation events between *RUNX1* and *ETO* genes, resulting in the formation of the RUNX1-ETO fusion protein, which is a common mutation found in AML patients (Ugarte et al., 2015). Following from this work, it was found

that, through Wnt3a treatment of leukaemia-derived cell lines and CD34+ progenitor cells, the distal P1 promoter of *RUNX1* harboured a T-cell factor/lymphoid enhancer factor (TCF/LEF) binding site identifying this isoform as a *bona fide* target of β-catenin (Medina et al., 2016). It can be hypothesised that dysregulation of the Wnt pathway in haematopoietic progenitor cells leads to increased P1-*Runx1* and ETO transcription and fusion, facilitating the development of leukaemia.

A number of studies have noted that *RUNX1* mutation and putative loss of function is restricted to the ER+ subset of breast cancers (Banerji et al., 2012; Ellis et al., 2012). In an elegant study Chimge et al. (2016) provided one possible rationale for this observation when they showed that RUNX1 could act to block oestrogen-mediated inhibition of AXIN1 and that loss of *RUNX1* could therefore release the oncogenic effects of oestrogen through stabilization of β-catenin. Conversely, in other cell lineages (for example, bone marrow), RUNX1 has been shown to potentiate β-catenin activity through other mechanisms, including the upregulation of activating Wnt ligands (Luo et al., 2019). However, studies in mouse skin demonstrated that the effects of RUNX1 on the Wnt signalling pathway are lineage dependent (Scheitz and Tumbar, 2013). As noted, reciprocal regulation between RUNX1 and β-catenin has been identified in a number of systems and may be expected given the complexity of gene reg-

ulation and cross talk between key regulators of survival, differentiation and proliferation. A more unique connection was reported by Jain et al. (2018) who suggested that RUNX1-induced changes in the structure of the cell membrane may render cells more sensitive to extracellular Wnt signals.

RUNX1 was found to be upregulated in colorectal cancer and this overexpression was linked to poorer survival in patients, as well as metastasis and induction of epithelial-to-mesenchymal transition (EMT) in colorectal cancer cells (Li et al., 2019). This aggressive phenotype was caused by RUNX1 activating the Wnt pathway via direct interaction with β-catenin, and interactions with the enhancer and promoter regions of KIT to promote its transcription and enhance Wnt/β-catenin signalling. Conversely, *Runx1* deficiency in the mouse intestine was sufficient for tumour formation and significantly enhanced tumorigenesis in an *Apc^{Min}* model of intestinal tumorigenesis (Fijneman et al., 2012). Gene expression analysis of colons from *Runx1* KO mice revealed upregulations in genes previously described as transcriptional targets of β-catenin; *Angiogenin4* (*Ang4*) and serine peptidase inhibitor, *Kazal type 4* (*Spink4*); both of which were also previously found to be upregulated in *Apc^{-/-}* colon cells (Andreu et al., 2008; Fijneman et al., 2012; Gregorieff et al., 2009). This potentially provides a mechanism by which *Runx1* loss in the colon results in the expansion of stem cell populations and subsequent susceptibility to tumour initiation. The role of RUNX1/Wnt interactions in solid cancers may also extend to other major tumour types, for example high *RUNX1* expression was predictive of a poor prognosis in clear cell renal cell carcinoma while Wnt signalling pathway was significantly enriched in tissues with high *RUNX1* expression (Fu et al., 2019).
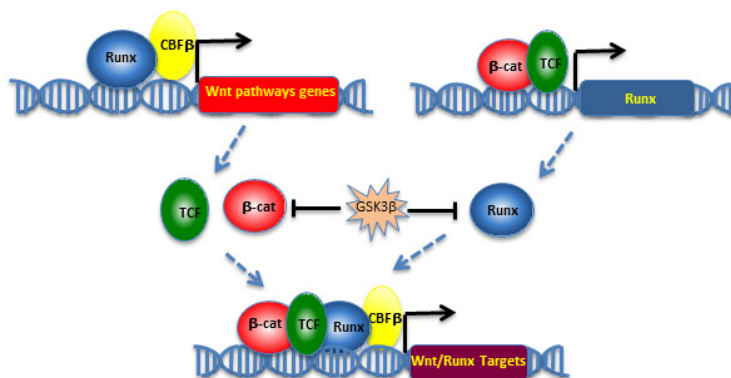
Interactions between RUNX2 and the Wnt pathway
Bone is a highly dynamic tissue and both the Wnt signalling pathway and RUNX2 are integral to its formation and homeostatic control. As such, the bone field has been a rich source for studying the intricate relationship between these players. *Runx2* is itself a downstream target of the canonical Wnt pathway (Fig. 2) and β-catenin/TCF activate *Runx2* expression through a TCF binding site in the proximal promoter (Gaur et al., 2005), or through protein-protein interactions on *Runx2* enhancer elements (Kawane et al., 2014). These studies reveal direct linkage between the osteogenic activity of the Wnt/β-catenin pathways and the key transcription factor mediating osteoblastic differentiation and bone development. Wnt induction of *Runx2* is not restricted to osteoblasts and direct regulation by β-catenin/LEF1 has also been shown in chondrocytes (Dong et al., 2006). The importance of this applies to other systems, including pathophysiological processes inducing the calcification of vascular smooth muscle cells, where two other TCF binding sites were identified in the *Runx2* proximal promoter (Cai et al., 2016).

Reciprocal regulation of major signalling pathways is a common theme with the *Runx* genes and in turn RUNX2 has been shown to regulate a variety of Wnt ligands (Qin et al., 2019), Wnt inhibitors (James et al., 2006; Mendoza-Villanueva et al., 2011; Perez-Campo et al., 2016) and TCF/LEF co-activators (Hoeppner et al., 2009; Mikasa et al., 2011), and in this way modulate the strength and specificity of the canonical Wnt pathway (Fig. 2). Although Wnt signalling and RUNX2 can clearly collaborate in bone development, it has been shown that enforced expression of RUNX2 in osteoblast cells can reduce levels of β-catenin and inhibit its transcriptional activity, perhaps to ensure fine tuning in the control of terminal differentiation (Haxaire et al., 2016). Intriguingly, GSK3β, the central player of the β-catenin destruction complex, also phosphorylates and negatively regulates RUNX2, suggesting a coordinated approach to the regulation of these transcription factors (Kugimiya et al., 2007).

In addition to their ability to regulate each other, β-catenin and RUNX2 also collaborate in the regulation of common target genes (Fig. 2). RUNX2 and canonical Wnt interact to regulate *FGF18* (Reinhold and Naski, 2007) and *Osteocalcin* (Tang et al., 2009), whilst in other systems RUNX2 has been shown to be a fully paid-up member of the Wnt enhanceosome, the transcription complex that brings together TCFs and β-catenin (Fiedler et al., 2015). In some scenarios, how-

Fig. 2. Overview of RUNX/Wnt pathway interactions and co-regulation. A summary of the interaction between RUNX and Wnt signalling showing that RUNX can transcriptionally regulate a number of Wnt pathway genes whilst the *RUNX* genes themselves are subject to regulation by β-catenin, the transcriptional mediator of the canonical Wnt pathway. Also highlighted is the cooperation between both β-catenin and RUNX in the regulation of Wnt target genes. The kinase GSK3β is an important component of the β-catenin destruction complex but can also phosphorylate RUNX and inhibit function.

ever, β-catenin/LEF can block RUNX2 transcriptional activation by interacting directly with the DNA binding domain of RUNX2 (Kahler and Westendorf, 2003).

Wnt signalling has been implicated in different aspects of cancer development and progression. The role of this pathway in stem cell biology and tumour initiating cells is one area of intense interest. Our own work has shown that *Runx2* expression is upregulated by Wnt3a; enriched in cells with the capacity to form mammospheres; and is required for mammary gland reconstitution *in vivo* (Ferrari et al., 2015). Importantly, RUNX2 was upregulated in Wnt-driven mammary tumours, suggesting that *Runx2* was a Wnt target that could participate in both stem cell activity and tumour growth (Ferrari et al., 2015). The relationship between Wnt signalling and *Runx* genes in stem cells may extend to other lineages and may be ancestral as studies in *C. elegans* have revealed that the RUNX homologue RNT-1 acts on Wnt signalling through the suppression of POP-1 (TCF/LEF) to ensure stem cell renewal via symmetrical proliferation (van der Horst et al., 2019). At later stages of tumour development, RUNX2 has been associated with a more invasive phenotype of mammary cancer, an effect that may require co-activation of the Wnt pathway (Chimge et al., 2011). Conversely, RUNX2-induced inhibition of Wnt signalling in bone tissue may be involved in preparing the tumour site for colonisation (Mendoza-Villanueva et al., 2011).

Attenuation of Wnt signalling by RUNX3 in cancer

A body of work has implicated RUNX3 as a tumour suppressor in the gastrointestinal tract as well as other cancer lineages, and a number of potential mechanisms have been proposed to explain this property. In this context RUNX3 was reported to form a complex with β-catenin and TCF4, the most predominant TCF/LEF factor in the intestine responsible for the recruitment of β-catenin to its target genes, resulting in reduced DNA binding and transcriptional activity at the *c-Myc* and *Cyclin D1* promoters (Ito et al., 2008). These results suggest, at least in part, that the tumour suppressor function of RUNX3 in the intestinal epithelium maybe facilitated through the attenuation of β-catenin/TCF4 factor activity. A follow up study added weight to the view that RUNX3 could physically interact with, and block, the activity of β-catenin/TCF (Ito et al., 2011), although it has also been reported that the same interaction could enhance β-catenin/TCF activity in gastric cell lines (Ju et al., 2014). The tumour-suppressing potential of RUNX3, through its attenuation of Wnt signalling, is not unique to the gastrointestinal tract as RUNX3 reduced β-catenin expression levels and the transactivation potential of β-catenin/TCF4, resulting in reduced proliferation and invasion of glioma cells (Sun et al., 2018). Further support for the concept that RUNX3 might negatively regulate β-catenin and act as a tumour suppressor came from examining oncogenic pathways in laryngeal cancer cells. This work showed that the polycomb protein, enhancer of zeste homolog 2 (EZH2), indirectly stimulates β-catenin activity by epigenetically silencing *RUNX3* (Lian et al., 2018).

DISCUSSION

It is clear, from the evidence laid out in the studies above, that interactions between RUNX factors and Wnt signalling are relevant to both normal tissue and in cancer settings, and that the consequences of such interactions often depend on the specific context in which these connections occur. The apparently paradoxical functions of *RUNX1* in breast cancer may be at least partially explained by their alternative interactions with the Wnt signalling pathway in different subtypes (Chimge et al., 2017). In studies relating to the role of RUNX2 in cancer, it has been shown that the oncogenic functions of the protein in both osteosarcomas and breast cancer are related to the regulation of RUNX2 by the Wnt pathway and reciprocal modulation of the Wnt pathway by RUNX2. There is evidence from several studies to suggest that RUNX3 attenuates the function of the Wnt pathway in some gastric and intestinal cancers.

Knowledge of the Wnt pathway and its modulators is essential in aiding the discovery of new ways to target cancer, especially since the canonical Wnt/β-catenin pathway is seen as such a promising target in cancer therapy. As outlined above, the RUNX proteins are key modulators and influencers of the downstream pathways and the phenotypic impact of Wnt signalling, and specific targeting of these RUNX/Wnt interactions may be a more elegant approach to therapy. β-Catenin itself is classified as a difficult-to-drug and yet-to-be-drugged target in cancer and inhibition of this protein could potentially lead to unpleasant side effects in patients (Cheng et al., 2019; Cui et al., 2018). It could, however, be possible to modulate canonical Wnt pathway activation by targeting the RUNX proteins. It is exciting that small molecule inhibitors against RUNX1 and RUNX2 have shown promise for treating some cancer types in which RUNX function drives pro-oncogenic effects, although their effects on the Wnt/β-catenin pathway were not specifically investigated (Bushweller, 2019; Illendula et al., 2016; Kim et al., 2017). However, it should be noted that, depending on context and tumour type, upregulation of RUNX rather than inhibition may augment approaches to therapy (Speidel et al., 2017). Nonetheless, this information offers an additional insight into one of the ways that oncogenic β-catenin signalling can be modulated in cancer, and may be vital for the development of targeted therapies.

Disclosure
The authors have no potential conflicts of interest to disclose.

ORCID

Kerri Sweeney   https://orcid.org/0000-0002-7697-881X
Ewan R. Cameron   https://orcid.org/0000-0001-8311-1491
Karen Blyth   https://orcid.org/0000-0002-9304-439X

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