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Review

Multiple oncogenic roles of nuclear β-catenin

RAJU KUMAR[1,2] and MURALI D BASHYAM[1]*

[1]*Laboratory of Molecular Oncology, Centre for DNA Fingerprinting and Diagnostics, Hyderabad, India*

[2]*Manipal University, Manipal, Karnataka, India*

**Corresponding author (Email, bashyam@cdfd.org.in, bashyam69@gmail.com)*

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β-Catenin is essential for embryonic development and required for cell renewal/regeneration in adult life. Cellular β-catenin exists in three different pools: membranous, cytoplasmic and nuclear. In this review, we focus on functions of the nuclear pool in relation to tumorigenesis. In the nucleus, β-catenin functions as both activator and repressor of transcription in a context-dependent manner. It promotes cell proliferation and supports tumour growth by enhancing angiogenesis. β-Catenin-mediated signalling regulates cancer cell metabolism and is associated with tumour-initiating cells in multiple malignancies. In addition, it functions as both pro- and anti-apoptotic factor besides acting to inhibit recruitment of inflammatory anti-tumour T-cells. Thus, β-catenin appears to possess a multifaceted nuclear function that may significantly impact tumour initiation and progression.

Keywords. Anti-tumour immunity; cancer cell metabolism; epithelial-mesenchymal transition; tumour-initiating cells; tumour micro-environment

1. Introduction

β-catenin, a 781-amino-acid protein, is well known as the effector molecule of canonical Wnt signalling. It was discovered (along with α- and γ-catenin) as an E-cadherin-associated protein in the late 1980s (Ozawa *et al.* 1989). Human β-catenin is a highly conserved protein having 67% identity to its Drosophila homolog Armadillo, whereas only 6 amino acids differ between the human and Xenopus proteins (as reviewed in Shapiro and Weis 2009). The central region (residues 141–664) consists of 12 Armadillo (ARM) repeats (R1–12), flanked by well-defined N- and C-terminal domains (NTD and CTD). β-Catenin binding partners interact with the ARM repeats R3–R9 and form salt bridges with amino acid residues Lys312 and Lys435, whereas rest of the ARM repeats strengthen the interactions (Huber *et al.* 1997). Terminal domains (NTD and CTD) may also contribute to the binding (Solanas *et al.* 2004). During embryonic development, β-catenin regulates cell fate determination and body axis patterning in all metazoans (as reviewed in Clevers 2006 and van Amerongen and Nusse 2009). It is also required for cell renewal/regeneration and tissue homeostasis in later stages of animal life. Cellular β-catenin exists in three different pools: membranous, cytoplasmic and nuclear (summarized in figure 1). Freshly synthesized β-catenin localizes to Adherens Junctions (AJs) via interaction with E-cadherin (membranous pool), whereas excess β-catenin is captured by a destruction complex (cytoplasmic pool). In the presence of a sub-optimally functioning destruction complex, excess β-catenin translocates into the nucleus (nuclear pool) (as reviewed in Grigoryan *et al.* 2008). Conformation change and interaction with different binding partners may contribute to its varied functions as discussed in detail below. Of note, β-catenin is associated with various pathological conditions like cancer, neurodegenerative disorders and osteoporosis (as reviewed in MacDonald *et al.* 2009). In this review, we will focus on function of β-catenin in the different pools in relation to cancer biology, with particular emphasis on the nuclear pool.

2. Three cellular pools of β-catenin and tumorigenesis

2.1 *The membranous pool*

As a structural protein localized to the cell membrane, β-catenin plays crucial role in maintaining cell adhesion. Using the entire ARM domain, it interacts with the cytoplasmic domain of E-cadherin and connects α-catenin to E-cadherin; the N-terminus of β-catenin (residues 120–147) forms the

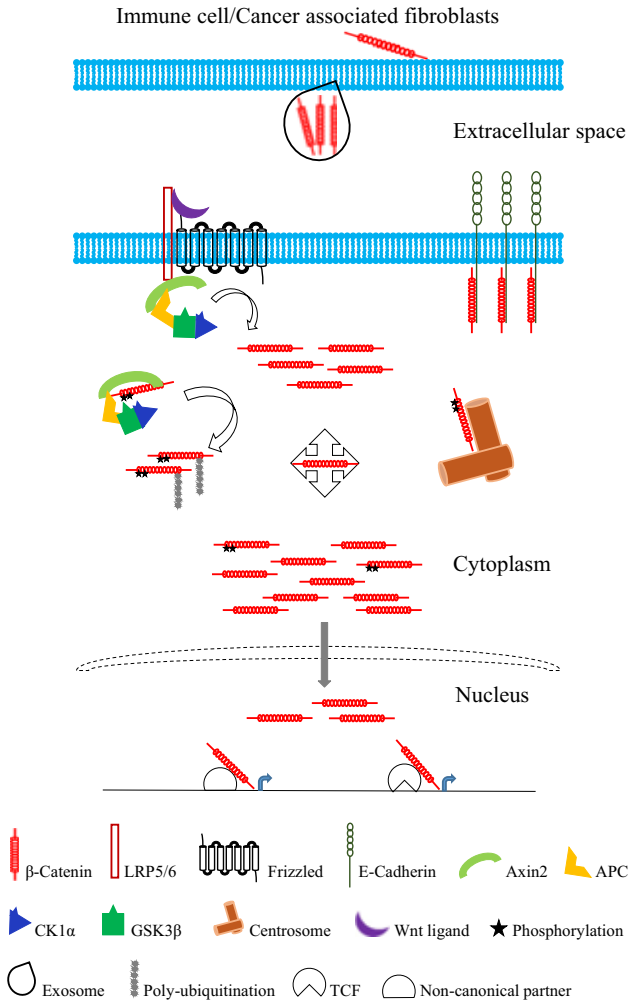

Figure 1. Diagrammatic representation of various cellular locations of β-catenin.

binding site for α-catenin. Binding of α-catenin to β-catenin distorts the continuity of the first ARM repeat and creates a hinge region which in turn permits β-catenin to bind both E-cadherin and α-catenin (Pokutta *et al.* 2000). The β-catenin–α-catenin complex links cadherin to the actin cytoskeleton (as reviewed in Takeichi 1995 and Morin 1999); this link is crucial for assured cadherin-mediated cell adhesion (as reviewed in Shapiro and Weis 2009). The catenin-cadherin interaction is dynamic in nature and its disintegration promotes release of β-catenin from the membrane (as reviewed in Heuberger and Birchmeier 2010). β-Catenin release from membrane is promoted by protease-mediated cadherin (Ito *et al.* 1999) or β-catenin (Abe and Takeichi 2007) cleavage. β-Catenin phosphorylation at Tyr142 by the Fer/Fen tyrosine kinase notably diminishes α-catenin binding and thus weakens its adhesive function (Piedra *et al.* 2003). Perturbed cadherin-catenin interaction results in loss of cell adhesion causing polarized epithelial cells to 'transform' into motile mesenchymal cells; a phenomena popularly termed epithelial–mesenchymal transition (EMT) (as reviewed in Martin *et al.* 2013 and Huber *et al.* 2005). EMT plays a crucial role during embryonic development (as reviewed in Thiery *et al.* 2009) as well as in tumour invasion and metastasis (as reviewed in Lamouille *et al.* 2014). In contrast, Tyr654 phosphorylation reduces β-catenin binding to cadherin and may direct β-catenin into cytoplasmic and nuclear pools (Piedra *et al.* 2001). Phosphorylation driven β-catenin release (from membrane) is counter-balanced by phosphatases (protein tyrosine phosphate 1B, PT1B) that dephosphorylate β-catenin at Tyr654 (Balsamo *et al.* 1996).

2.2 *The cytoplasmic pool*

Free β-catenin in the cytoplasm, when recognized by a multi-protein destruction complex, is first phosphorylated at S45 by casein kinase 1 alpha (CK1α) and then at S33, S37 and T41 by glycogen synthase kinase 3 beta (GSK3β) (as reviewed in Heuberger and Birchmeier 2010) (Fig. 1) and targeted for proteasome-mediated degradation by β-TrCP, an E3-ubiquitin ligase (as reviewed in Stamos and Weis 2013). Surprisingly, not all cytoplasmic β-catenin undergoes degradation. A fraction of phosphorylated β-catenin localizes to centrosomes and regulates proper mitotic spindle establishment (Chilov *et al.* 2011; Kaplan *et al.* 2004) (figure 1). In the beginning of mitotic spindle formation, β-catenin participates in centrosome cohesion and dissociation and its depletion obstructs *de novo* formation of microtubules (Huang *et al.* 2007). During cell division, a centromeric serine/threonine-protein kinase NEK2 (NIMA-Related Kinase 2), regulates β-catenin stability at centrosomes (Bahmanyar *et al.* 2008). NEK2 phosphorylates β-catenin at GSK3β phosphorylation sites and competes with β-TrCP to block β-TrCP and β-catenin interaction, leading to inhibition of β-catenin proteosomal degradation, which results in accumulation of phosphorylated β-catenin at centrosomes (Mbom *et al.* 2014). During interphase, phospho-β-catenin localizes mostly to the mother centriole; whereas localization is favoured towards daughter centriole during mitosis (Fuentealba *et al.* 2008; Huang *et al.* 2007). Taken together, above findings suggest a role of phosphorylated β-catenin in centrosome and microtubule functioning. It is not clear how β-catenin-mediated centromeric cohesion ensures proper spindle formation. Future studies on β-catenin interacting proteins located to centrosomes can give insight into its role in regulating mitotic spindles.

2.3 *The nuclear pool*

Due to compromised function of the destruction complex, β-catenin escapes degradation and translocates to the nucleus

to participate in transcriptional reprograming (Munemitsu *et al.* 1995; Iwao *et al.* 1998; Sparks *et al.* 1998) (figure 1). Nuclear translocation mechanism of β-catenin is not completely understood (as reviewed in Städeli *et al.* 2006). β-catenin cannot bind to the promoter(s) of its transcriptional targets, as it does not possess any DNA binding domain. It functions by binding to other DNA binding transcription factors (Xing *et al.* 2008) and dictates transcriptional activation of a plethora of genes (Behrens *et al.* 1996; Herbst *et al.* 2014). Many β-catenin transcriptional co-factors have been identified, which indicates complexity of β-catenin-mediated transcription regulation. These mainly include proteins belonging to the T cell factor/lymphoid enhancer factor (TCF/LEF) family (as reviewed in Cadigan and Nusse 1997). Genes activated by the β-catenin–TCF complex regulate several biological processes ranging from cell proliferation to anti-tumour immunity (Schuijers *et al.* 2014; Spranger *et al.* 2015). The consensus DNA binding motif of TCF has been derived based on several single base substitution studies (Tuupanen *et al.* 2009; Wright *et al.* 2010). Other non-canonical β-catenin partners include AP-1 (Nateri *et al.* 2005), oestrogen receptor alpha (Kouzmenko *et al.* 2004), Forkhead box protein O1/4/3a (Essers *et al.* 2005), HIF1-alpha (Kaidi *et al.* 2007), hB1F (Botrugno *et al.* 2004), Oct-4 (Zhang *et al.* 2013), p50 (Kim *et al.* 2005) and SOX-17 (Sinner *et al.* 2004). β-catenin also interacts with the androgen receptor and regulates expression of several genes (Truica *et al.* 2000; Yang *et al.* 2002). In colorectal cancer cells, β-catenin-dependent transcription is inhibited by activation of vitamin D receptor to promote cell differentiation (Pálmer *et al.* 2001; Shah *et al.* 2006). Similarly, retinoic acid receptor-mediated inhibition of β-catenin signalling pathway is also validated (Easwaran *et al.* 1999). β-Catenin functions as both activator and repressor of transcription. Using its C terminus, it brings transcription activating complexes to promoters of target genes to ensure efficient transcription (Hecht *et al.* 2000; Barker *et al.* 2001); whereas β-catenin-mediated transcription repression mechanism is diverse and not well understood (as reviewed in Valenta *et al.* 2012). Recruitment of β-catenin to the promoter of *E-cadherin* in keratinocytes (Jamora *et al.* 2003) and *p16INK4a* in melanocytes (Delmas *et al.* 2007) represses their transcription.

The intestinal lumen epithelium undergoes rapid regeneration to maintain homeostasis. The lumen comprises sac like structures called crypts of Lieberkühn. Crypts harbour enterocytes, intestinal stem cells (ISCs) and paneth cells. Paneth cells play critical role in maintaining enterocyte and stem cell cohabitation (as reviewed in Clevers and Bevins 2013) whereas enterocyte functions mainly in nutrient absorption. ISCs divide in a highly controlled manner to replenish the lumen epithelium. Several studies have proposed a pivotal role for β-catenin signalling in functioning of ISCs. Nuclear β-catenin has been shown to localize near base of the intestinal crypts (and not in the apical region) (van de Wetering *et al.* 2002) and is essential for intestinal epithelium homeostasis (Fevr *et al.* 2007). Direct role of β-catenin in maintaining crypt homeostasis was shown in a study where Ephrin type-B receptor 3 (a β-catenin target) was found to be essential for proper allocation of paneth cells to the crypt bottom (Batlle *et al.* 2002).

Elevated nuclear levels of β-catenin are found in several cancers including colorectal (Cheah *et al.* 2002), adrenocortical (Gaujoux *et al.* 2011), endometrial (Scholten *et al.* 2003), glioblastoma (Liu *et al.* 2011), hair follicle (Doglioni *et al.* 2003) and hepatocellular carcinoma (Liu *et al.* 2010). β-catenin exhibits heterogeneous distribution pattern in colorectal cancer; well differentiated cancer cells present at the centre of tumour possess membrane expression akin to normal colon epithelium whereas undifferentiated invasive fronts and stroma manifest nuclear expression (as reviewed in Brabletz *et al.* 1998 and Fodde and Brabletz 2007). More importantly, β-catenin is associated with patient survival, however different studies report different direction of association. Nuclear stabilised β-catenin predicts poor (Li *et al.* 2013; Inagawa *et al.* 2002) as well as better prognosis (Hommura *et al.* 2002) in non-small cell lung carcinomas. Nuclear phospho β-catenin predicted better prognosis in colon cancer (Chung *et al.* 2001) whereas nuclear overexpressed β-catenin was associated with poor prognosis (Nazemalhosseini Mojarad *et al.* 2015; Kazem *et al.* 2014). The contradictory effect(s) of β-catenin on cancer prognosis is not surprising. Reduced expression is expected to destabilize Adherens junctions leading possibly to increase migration and invasion resulting in poor prognosis. In contrast, increased expression particularly in the nucleus is expected to promote tumorigenesis due to transcriptional activation of oncogenic targets, thus also potentially resulting in poor prognosis. In addition, different forms (phosphorylated vs non-phosphorylated) may have different effect on cancer prognosis. Moreover, its differential prognostication in different cancers may also stem from the presence/absence of cross-talk with other pathways/proteins.

2.3.1 Nuclear β-catenin and tumour proliferation and growth: Sustained cell proliferation is a hallmark of cancer cells (as reviewed in Hanahan and Weinberg 2011). Activation of β-catenin in mouse intestinal villi causes increased proliferation which in turn leads to adenomatous lesions and polyposis (Harada *et al.* 1999). β-Catenin activation promotes cell proliferation through cell cycle progression (G1 to S) (as reviewed in Davidson and Niehrs 2010). Possibly, G1 progression takes place through upregulation of the β-catenin transcriptional target, c-Myc and cyclin D1 (He *et al.* 1998; Shtutman *et al.* 1999). c-Myc serves a dual function in G1 progression. It upregulates *cyclin D1* (Daksis *et al.* 1994) while repressing *p21* and *p27* expression (Gartel *et al.* 2001; Yang *et al.* 2001). Other β-catenin transcriptional targets that induce tumour cell proliferation and growth are listed in

Table 1. List of β-catenin transcriptional targets with possible role(s) in cancer

Targets	Biological process	Cancer/cells	References
c-Myc	Proliferation	Colorectal	He *et al.* (1998)
Cyclin D1	Proliferation	Colorectal	Shtutman *et al.* (1999)
JAG1	Proliferation	Colorectal	Rodilla *et al.* (2009)
EGFR	Proliferation	Prostate	Guturi *et al.* (2012)
Aurora kinase A	Proliferation	Myeloma	Dutta-Simmons *et al.* (2009)
MITF	Proliferation	Melanoma	Widlund *et al.* (2002)
FGF 9	Proliferation	Ovarian	Hendrix *et al.* (2006)
VEGF	Angiogenesis	Colorectal	Easwaran *et al.* (2003)
Twist	EMT	Breast	Howe *et al.* (2003)
Slug	EMT	Colorectal	Conacci-Sorrell *et al.* (2003)
Zeb1	EMT	Colorectal	Sanchez-Tillo *et al.* (2011)
BOP1, CKS2 and NFIL3	EMT	Colorectal	Qi *et al.* (2015)
HEF1	Migration	Colorectal	Li *et al.* (2011)
MMP2	EMT	T-cells	Wu *et al.* (2007)
MMP9	Migration	Neural stem cells	Ingraham *et al.* (2011)
MMP7	Migration	Colorectal	Brabletz *et al.* (1999)
MMP26	EMT	Epithelial cancers	Marchenko *et al.* (2002)
S100A4	Metastasis	Colorectal	Stein *et al.* (2006)
Tenascin C	EMT	Colorectal	Beiter *et al.* (2005)
CST1 and EDN3	Metastasis	Ovarian	Schwartz *et al.* (2003)
ALDH1A1	TIC marker	Colorectal	Huang *et al.* (2009)
CD24	TIC marker	Colorectal	Yeung *et al.* (2010)
CD44	TIC marker	Colorectal	Zeilstra *et al.* (2008)
Lgr5	TIC marker	Colorectal	Kemper *et al.* (2012)
TERT	TIC marker	Colorectal	Hoffmeyer *et al.* (2012)
AXIN2	Chromosomal Instability	Colorectal	Hadjihannas *et al.* (2006)
PDK1	Metabolism	Colorectal	Pate *et al.* (2014)
VGEF, BCL-2 and BIRC5	Anti-apoptotic	Rat model	Kaga *et al.* (2006)
MCL1, BCL2L11 and BBC3	Anti-apoptotic	Melanoma	Zimmerman *et al.* (2013)

EMT, epithelial–mesenchymal transition; TIC, tumour-initiating cells

table 1. Small interfering RNA-mediated β-catenin knockdown restrains colon cancer cell growth in vivo and in vitro (Verma *et al.* 2003; Xu *et al.* 2010). In mouse model studies, constitutively active β-catenin was shown to promote tumour growth in prostate cancer (Pearson *et al.* 2009; Yu *et al.* 2011). Mutationally activated β-catenin causes pilomatricoma (tumour originating from hair matrix and hair germ) (Fuchs *et al.* 1999). Expression of constitutively active β-catenin provides growth enhancement to myeloma cells in vitro (Derksen *et al.* 2004). Nuclear stabilized β-catenin is associated with proliferation in hepatocellular carcinoma (Inagawa *et al.* 2002; Nhieu *et al.* 1999). The positive effect of β-catenin on tumour proliferation and growth is brought about by activation of a variety of other genes with different target genes being pivotal in different cancers. Although several previous studies had suggested possible cross-talk between Wnt/β-catenin and EGFR signalling pathways, the study by (Guturi *et al.* 2012) provided clinching evidence for β-catenin-mediated transcriptional activation of EGFR that further resulted in activation of cell proliferation in prostate cancers cells. The complex and multi-level cross-talk between these two pathways was also validated in Glioblastoma (as reviewed in Paul *et al.* 2013) as well as in epithelial tissue regeneration (Georgopoulos *et al.* 2014). Similarly, melanoma growth is brought about by microphthalmia-associated transcription factor (MITF), a β-catenin target (Widlund *et al.* 2002). Further, MITF was shown to directly interact with β-catenin resulting in transcriptional induction of specific genes involved in both melanocyte and melanoma development (Schepsky *et al.* 2006). Finally, more recent studies revealed an intricate relationship between Wnt signalling and oncogenic role of MITF in Melanocyte (and melanoma) development (Ploper *et al.* 2015). Under Wnt7A activation, β-catenin regulates ovarian tumour growth (Yoshioka *et al.* 2012) and proliferation (as reviewed in Arend *et al.* 2013). Further, β-catenin supports tumour growth by enhancing angiogenesis, through regulation of vascular endothelial growth factor (Mann *et al.* 1999). Interestingly, both Wnt signalling and oncogenic mutant KRAS were shown to transcriptionally activate VEGF in precursor colon cancer lesions (Zhang *et al.*, 2001). Similarly, β-catenin transcriptional activity could enhance VEGF expression in hepatocellular carcinoma (Qu *et al.* 2014).

2.3.2 Nuclear β-catenin and EMT and metastasis: EMT plays an essential role during cancer progression and

metastasis (as reviewed in Hay 2005; and Thiery *et al.* 2009). β-catenin-mediated EMT induction plays an important role in tumour progression in several cancers including squamous cell carcinoma (Taki *et al.* 2003) and CRC (Brabletz *et al.* 2005). A key feature of EMT is replacement of E-cadherin by N-cadherin at the cell membrane (as reviewed in Zeisberg *et al.* 2009) which in turn perturbs cadherin-catenin interaction; β-catenin can then be released from the cell membrane and translocate to nucleus, if it escapes cytosolic degradation (as reviewed in Heuberger and Birchmeier 2010). Twist (a basic helix-loop-helix transcription factor), a transcriptional target of β-catenin (Howe *et al.* 2003), downregulates E-cadherin expression to facilitate tumour metastasis (as reviewed in Kang and Massague 2004). Snail1, Snail2 (Slug) and ZEB1 are additional E-cadherin transcriptional repressors which function in a β-catenin-dependent manner (Conacci-Sorrell *et al.* 2003; as reviewed in Barrallo-Gimeno and Nieto 2005; Sanchez-Tillo *et al.* 2011). Several additional transcriptional targets of β-catenin have been identified that regulate EMT, cell migration and tumour metastasis (Table 1). p68 RNA helicase-mediated nuclear translocation of β-catenin stimulates EMT in cultured cancer cells (Yang *et al.* 2006; as reviewed in He 2006). Suppression of β-catenin signalling is also associated with differentiation of colonic epithelial cells (Mariadason *et al.* 2001). Epithelial cell polarity was restored in a colorectal cancer cell line upon repression of β-catenin-mediated gene transactivation (Naishiro *et al.* 2001). Despite increasing evidence of role of epithelial–mesenchymal transition in cancer metastasis, methods of treating same remains limited. Better understanding of exact role of β-catenin in this important process may help in development of therapy targeted against metastasis.

2.3.3 Nuclear β-catenin and tumour-initiating cells (TICs) and tumour micro-environment (TME): TICs (previously called as cancer stem cells) are a sub-population of tumour cells having capacity of self-renewal (to generate tumour) and to differentiate into any cell type within tumour to promote growth and metastasis (as reviewed in Jordan *et al.* 2006; and Reya *et al.* 2001). β-Catenin-mediated signalling is associated with TICs in multiple malignancies, including breast (Lamb *et al.* 2013), colon (Shenoy *et al.* 2012), gastric (Yong *et al.* 2016), and glioblastoma (Kaur *et al.* 2013). Several β-catenin target genes, listed in Table 1, serve as prominent markers for TICs. PCNA-associated factor (PAF) activates β-catenin transcriptional target (Jung *et al.* 2013) and regulates cell plasticity to maintain breast cancer cell stemness (Wang *et al.* 2016). β-Catenin mediates drug resistance in Mixed Lineage Leukemia TICs (J. Yeung *et al.* 2010) and its loss impairs renewal of Chronic myelogenous leukemia stem cells (Zhao *et al.* 2007). c-Kit-mediated β-catenin regulation enhances self-renewal and expansion of TICs to promote ovarian tumorigenesis (Chau *et al.* 2013). β-catenin was shown to maintain ovarian cancer spheroid culture and promote tumour formation via ALDH1A1 (Condello *et al.* 2015). In hepatocellular carcinoma, TGFβ-activated β-catenin induces an early liver progenitor phenotype and promotes tumour recurrence (Zulehner *et al.* 2010). WNT16B-mediated β-catenin signalling in prostate TME promotes prostate cancer cell survival and tumour progression (Sun *et al.* 2012); whereas miR-320-mediated β-catenin downregulation supresses stem-cell-like properties (Hsieh *et al.* 2013). By regulating Telomerase (*TERT*, a direct target of β-catenin) expression, β-catenin may help in maintaining telomere length of TICs, thus promoting their maintenance (Hoffmeyer *et al.* 2012).

Generally, cancer cells are surrounded by stromal cells which include various immune cells, endothelial cells, fibroblasts, and mesenchymal stem cells (MSCs) (as reviewed in Friedl and Alexander 2011). Interplay between cancer and stromal cells creates the TME, which plays an essential role during all stages of tumorigenesis (as reviewed in Mbeunkui and Johann 2009). In oesophageal cancer, tumour-associated fibroblasts secrete Wnt2 into the tumour milieu, to promote β-catenin-mediated signalling in adjacent malignant cells for tumour progression (Fu *et al.* 2011). Ectopic expression of β-catenin in breast-cancer-associated fibroblasts increases proliferation of co-cultured cancer cells (Verghese *et al.* 2011). β-Catenin secreted via exosomes from tumour cells regulates genes in the neighbouring fibroblasts to inhibit differentiation and promote TIC expansion in their niche (Klapholz-Brown *et al.* 2007). Altogether, these studies underscore the role of β-catenin signalling in regulating TICs and TME to promote tumour growth. With the advent of organoid cultures, upcoming studies may provide more insight into role of β-catenin in regulating TME and its interplay in tumorigenesis.

2.3.4 Nuclear β-catenin and chromosomal instability: Chromosomal instability (CIN) is an early event in tumorigenesis (Nowak *et al.* 2002; as reviewed in Grady 2004) characterized by structural abnormalities in chromosomes and/or change in their dosage (aneuploidy) (Geigl *et al.* 2008; as reviewed in Pikor *et al.* 2013). CIN is an important hallmark of cancer (as reviewed in Negrini *et al.* 2010; Lengauer *et al.* 1997). Accumulation of genomic alterations is suggested to be an important cause of clonal heterogeneity (as reviewed in Sieber *et al.* 2003 and Janssen and Medema 2013). Several studies have highlighted nuclear transcriptionally active β-catenin to be an important driver of CIN. Wnt-signalling-mediated aberrant activation of β-catenin causes CIN in colon cancer (Hadjihannas *et al.* 2006; Mårtensson *et al.* 2007) and T cell lymphomas (Dose *et al.* 2014). In cancer cells, the β-catenin target AXIN2 modulates mitotic spindle check point by interacting with spindle check point regulator Polo-like kinase 1 (PLK1) to induce gain or loss of chromosomes, thus generating CIN (as reviewed in Hadjihannas and Behrens 2006). In gastric tumours, anaphase bridge index (an indicator of CIN) is in concordance

with nuclear β-catenin expression; β-catenin signalling deregulates G2/M progression and promotes escape from mitotic arrest and apoptosis to generate CIN (Aoki *et al.* 2007). The β-catenin target c-Myc generates CIN via ROS-mediated DNA damage and promotes aneuploidy through its targets Mad2 and BubR1 (as reviewed in Prochownik and Li 2016 and Schvartzman *et al.* 2010). Activated c-Myc also induces chromosomal structural aberrations like fusion of centromere and telomere, chromosome breaks, deletion and translocation to trigger CIN via c-*myc* activation (as reviewed in Kuzyk and Mai 2014). Altogether, β-catenin appears to promote CIN by modulating target gene expression. Although the importance of CIN in tumour progression in solid tumours is well established, the role of β-catenin in generating CIN is not understood in detail.

2.3.5 Nuclear β-catenin and cancer cell metabolism: A cancer cell reprograms its metabolism in order to facilitate growth and survival (as reviewed in Pavlova *et al.* 2016; Warburg 1956). The most well-studied metabolic process in cancer cell is the manifestation of increased aerobic glycolysis ('Warburg effect') (as reviewed in Vander Heiden *et al.* 2009). The Warburg effect describes an oft-noted observation in a cancer cell wherein generation of energy in the form of ATP is achieved predominantly using aerobic glycolysis followed by fermentation of lactic acid in the cytosol rather than through the 'time-consuming' TCA cycle in the mitochondria; the latter being the norm in normal cells. Several β-catenin transcriptional targets that regulate cancer cell metabolism are listed in Table 1. β-Catenin along with its co-activator Pyruvate kinase M2 (PKM2) induces *myc* expression, which in turn promotes the Warburg effect (Yang *et al.* 2012). In breast cancer, β-catenin regulates mitochondrial respiration and glucose metabolism by inducing expression of pyruvate carboxylase (a key enzyme of anaplerosis) and by suppressing cytochrome C oxidase (an integral enzyme of electron transport chain, essential for oxidative phosphorylation) activity (Lee *et al.* 2012). β-Catenin transcriptional target Pyruvate dehydrogenase kinase 1 promotes aerobic glycolysis in colon cancer cells (Pate *et al.* 2014). β-catenin targets are also involved in fatty acid and glutamine metabolism in ovarian adenocarcinoma (as reviewed in Sherwood 2015). There is also evidence of β-catenin itself being regulated by oxidative stress. In breast cancer cells, reactive oxygen species (ROS) were shown to promote β-catenin-FOXO3a interaction resulting in decrease of TICs and tumorigenicity (Dong *et al.* 2013). Furthermore, specific nutrients are reported to modulate β-catenin signalling in cancer cells; glucose enhances β-catenin signalling through its acetylation (Chocarro-Calvo *et al.* 2013). Taken together, above studies give insight into the different modes of β-catenin signalling integration with cancer cell metabolism. Future studies on β-catenin signalling will shed light on the manipulation process of altered tumour cell metabolism to support cancer progression.

2.3.5 Nuclear β-catenin and programmed cell death and autophagy Evading programmed cell death (apoptosis) is an essential process during malignant transformation (Hanahan and Weinberg 2011). Nuclear β-catenin increases cancer cell proliferation and protects it against apoptosis (He *et al.* 1998; Tetsu *et al.* 1999). In a rat myocardial infarction model, β-catenin was shown to promote anti-apoptotic signalling via induction of VGEF, BCL-2 and BIRC5 (Kaga *et al.* 2006). β-catenin signalling has been shown to block cytochrome c release to inhibit apoptosis in colorectal cancer cells (Chen *et al.* 2001). In contrast, knockdown of β-catenin disrupts mitochondrial membrane potential to induce apoptosis (Hsu *et al.* 2014). In metastatic melanoma cell lines, downregulation of β-catenin induces apoptosis via reduction in the expression of anti-apoptotic genes (Bcl-2, Mcl-1) and the cell cycle regulator Cyclin D1 (Sinnberg *et al.* 2011). However, contradictory studies also exist, where β-catenin was shown to promote apoptosis. In melanoma cells, Wnt-mediated β-catenin activation promotes TRAIL-dependent apoptosis through increased pro-apoptotic (BCL2L11 and BBC3) and decreased anti-apoptotic (MCL1) protein levels (Zimmerman *et al.* 2013). Activation of β-catenin promotes apoptosis in hematopoietic progenitor cells through the intrinsic mitochondrial pathway (Ming *et al.* 2012). Upon overexpression, β-catenin induces apoptosis in colon cancer cell lines, independent of its LEF1 (transcriptional cofactor)-dependent function (Kim *et al.* 2000; Lu *et al.* 2012). The β-catenin target c-*myc* enhances mitochondrial-dependent apoptotic signal (as reviewed in Hoffman *et al.* 2008) and induces apoptosis (as reviewed in McMahon 2014) through activation of *cdc25A* in growth-factor-depleted cells (Galaktionov *et al.* 1996). It is not surprising that β-catenin, being an oncogene, exhibits a contradictory role in regulating apoptosis. It is a normal cellular defence mechanism to induce apoptosis upon aberrant, un-timely or very high level activation of an oncogene, as is already known for other oncogenes such as c-Myc (as reviewed in Hoffman *et al.* 2008); this could explain the positive effect of β-catenin on apoptosis. However, transcriptional targets of β-catenin have specific roles in inhibiting apoptosis in a context-dependent manner. Thus, β-catenin functions as both pro-apoptotic and anti-apoptotic factor.

Autophagy is a catabolic process that maintains cellular homeostasis and is known to both promote and suppress tumour growth (as reviewed in Yang *et al.* 2011 and Mathew *et al.* 2007). β-Catenin appears to negatively regulate autophagy in cancer. It regulates basal and stress induced autophagy by suppressing autophagosome (a key structure in autophagy) formation. However, in a negative feedback-loop, autophagy induces proteasome-independent β-catenin degradation to inhibit its signalling (Petherick *et al.* 2013). Suppression of β-catenin pathway induces autophagy in breast TICs (Fu *et al.* 2014) as well as in prostate cancer cells (Lin *et al.* 2015). The role of β-catenin in cellular

autophagy has not been explored in detail thus far. Given the importance of autophagy in tumorigenesis and the preliminary results from work done during past few years, the link between β-catenin and autophagy is worth exploring.

2.3.6 Nuclear β-catenin and anti-tumour immunity: β-Catenin signalling plays a significant role in immune cell biology (as reviewed in Staal *et al.* 2008). Growing literature supports role of tumour intrinsic β-catenin signalling in anti-tumour immunity (Spranger *et al.* 2015; Sweis *et al.* 2016). Intrinsic β-catenin signalling positively correlates with T-cell exclusion in cutaneous melanoma (Spranger *et al.* 2015). In addition, constitutively active β-catenin excludes T-cell infiltration response against tumour antigens in mouse model of melanoma (Spranger *et al.* 2015). Overexpression of β-catenin inhibits melanoma-specific cytotoxic T-cell-mediated IFN-γ production in an IL-10-dependent manner and suppresses dendritic cell activity in vivo (Yaguchi *et al.* 2012). These studies suggest the involvement of β-catenin signalling in suppression of anti-tumour immunoresponse. In muscle-invasive urothelial bladder cancer, β-catenin signalling is present in non-T-cell-inflamed tumours, an immunotherapy-resistant type (Sweis *et al.* 2016). Further studies on tumour intrinsic β-catenin signalling and immune response interplay may provide more insight into this emerging and exciting area of β-catenin biology.

3. Conclusion

In this review, we have summarized the important role of nucleus-restricted β-catenin in tumour biology. Nuclear β-catenin appears to function in a dosage- and context-dependent manner. As a multifunctional protein, it regulates distinct biological processes by activating transcription of a plethora of genes in a context-dependent manner, based on interaction with a wide range of partners. Our understanding of role of β-catenin in cancer has improved considerably. As described above, it appears to regulate several pro-tumorigenic process within the cell including cell cycle, apoptosis, metabolism, etc. The importance of β-catenin signalling is not only limited to tumour cells, but studies have suggested a possible role in microenvironment and tumour-immunity as well. However, knowledge of its coordination across complex function(s) is still rudimentary. Therefore, a more meticulous perception of molecular mechanisms is needed to understand the full potential of the varied β-catenin-dependent impact on tumorigenesis.

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