Minireview

Mutation Hotspots in the β-Catenin Gene: Lessons from the Human Cancer Genome Databases

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Mutations in the β-catenin gene (CTNNB1) have been implicated in the pathogenesis of some cancers. The recent development of cancer genome databases has facilitated comprehensive and focused analyses on the mutation status of cancer-related genes. We have used these databases to analyze the CTNNB1 mutations assembled from different tumor types. High incidences of CTNNB1 mutations were detected in endometrial, liver, and colorectal cancers. This finding agrees with the oncogenic role of aberrantly activated β-catenin in epithelial cells. Elevated frequencies of missense mutations were found in the exon 3 of CTNNB1, which is responsible for encoding the regulatory amino acids at the N-terminal region of the protein. In the case of metastatic colorectal cancers, in-frame deletions were revealed in the region spanning exon 3. Thus, exon 3 of CTNNB1 can be considered to be a mutation hotspot in these cancers. Since the N-terminal region of the β-catenin protein forms a flexible structure, many questions arise regarding the structural and functional impacts of hotspot mutations. Clinical identification of hotspot mutations could provide the mechanistic basis for an oncogenic role of mutant β-catenin proteins in cancer cells. Furthermore, a systematic understanding of tumor-driving hotspot mutations could open new avenues for precision oncology.

Keywords: β-catenin, cancer genome database, hotspot mutations

INTRODUCTION

β-Catenin is an important co-activator downstream of the oncogenic Wnt signaling pathway, so mutations in the β-catenin gene (CTNNB1) have been implicated in oncogenesis (Korinek et al., 1997; Morin et al., 1997; Polakis, 2012b). Recently, large-scale cancer databases, such as The Cancer Genome Atlas (TCGA) pan-cancer analysis project, have leveraged systemic analyses on genome, exome, and transcriptome data from all types of cancers (Blum et al., 2018; Hutter and Zenklusen, 2018; Tomczak et al., 2015). Multi-dimensional cancer genome data are available on cBioPortal, an open platform for cancer genome analysis and visualization (Cerami et al., 2012; Gao et al., 2013). In this review, we have employed pan-cancer genome databases to analyze the current status of β-catenin gene (CTNNB1) mutations to identify mutation hotspots and to re-evaluate the oncogenic roles of specific β-catenin mutant proteins. An extensive review on the clinical aspects of the β-catenin protein is beyond the scope of this mini review, so we have provided a brief introduction regarding the basic biology of the β-catenin protein.

A BRIEF INTRODUCTION TO THE β-CATENIN PROTEIN

β-Catenin is a multitasking protein involved in transcription...
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Fig. 1. A schematic diagram of the Wnt signaling pathway. (A) Wnt-off. In the absence of Wnt stimulation, β-catenin is phosphorylated by CK1α and GSK3β followed by ubiquitin-proteasome mediated proteolysis. (B) Wnt-on. Upon Wnt stimulation, the destruction complex is not functional, so the β-catenin protein is translocated into the nucleus and acts as a transcriptional co-activator to regulate oncogenic target genes. APC, Adenomatous polyposis; DVL, Disheveled.

Fig. 2. The alteration frequency of CTNNB1 and APC across cancer types. Data obtained from the MSK-IMPACT pan-cancer study on cBioportal (www.cbioportal.org).

and cell adhesion (Hur and Jeong, 2013; Kumar and Bashyam, 2017; Valenta et al., 2012). In particular, β-catenin is an important co-activator of Wnt target genes, such as cyclin D1 and c-myc (Korinek et al., 1997; Morin et al., 1997). However, in differentiated cells, where Wnt signaling is off, the central regulatory mechanism for β-catenin is sequential phosphorylation in the N-terminal region followed by ubiquitin-mediated proteolysis (Fig. 1A). Casein Kinase-1α phosphorylates the S45 residue and primes subsequent phosphorylation on T41/S37/S33 by GSK-3β, leading to the binding of ubiquitin E3 ligase β-transducin repeats-containing proteins (β-TrCP) at the N-terminal region (D32 to S37) in a phosphorylation-dependent manner (Hart et al., 1998; Liu et al., 2002). Specific phosphorylation and ubiquitination occur in the APC/Axin complex, termed as the β-catenin destruction complex (Stamos and Weis, 2013). In contrast, the destruction complex functions no more, so the level of the β-catenin protein in the cytoplasm increases following Wnt activation (Fig. 1B). The mechanism by which Wnt signaling stabilizes β-catenin needs to be better understood in the aspect of the β-catenin destruction complex (Kim et al., 2013; 2015; Li et al., 2012; Taelman et al., 2010). Finally, Wnt-stimulated β-catenin is translocated into the nucleus, where it acts as transcriptional co-activator with DNA binding TCF/LEF proteins and activates many developmentally important, cancer-related and pathogenic genes (Nusse and Clevers, 2017).

FREQUENCY OF GENOMIC ALTERATIONS IN THE CTNNB1 GENE IN CANCERS

Small-scale targeted gene analysis demonstrates mutations in the β-catenin gene (CTNNB1) in some cancers (Polakis, 2007; 2012b). Large-scale β-catenin mutational landscape was revealed from clinical sequencing of 10,000 prospective cancer patients by the Memorial Sloan Kettering-Integrated
Table 1. The alteration frequency of CTNNB1 in endometrial, liver, and colorectal cancer

| Cancer type            | Sequencing data source                                      | No. Sequenced | No. Alteration (%) | No. Exon3-mut (%) | Reference                                      |
|------------------------|-------------------------------------------------------------|---------------|--------------------|-------------------|------------------------------------------------|
| Endometrial cancer     | Endometrial Cancer (MSK, 2018)                              | 187           | 27 (14.4)          | 25 (13.4)         | Soumerai et al., 2018                          |
|                        | Uterine Corpus Endometrial Carcinoma (TCGA, Nature 2013)    | 240           | 71 (29.6)          | 63 (26.3)         | Cancer Genome Atlas Research et al., 2013a     |
|                        | Uterine Carcinosarcoma (TCGA, PanCancer Atlas)              | 56            | 1 (1.8)            | 0 (0.0)           | Cancer Genome Atlas Research et al., 2013b     |
|                        | Uterine Clear Cell Carcinoma (NIH, Cancer 2017)             | 16            | 0 (0.0)            | 0 (0.0)           | Le Gallo et al., 2017                          |
| Liver cancer           | Liver Hepatocellular Carcinoma (TCGA, PanCancer Atlas)      | 353           | 95 (26.9)          | 78 (22.1)         | Cancer Genome Atlas Research et al., 2013b     |
|                        | Liver Hepatocellular Carcinoma (AMC, Hepatology 2014)       | 231           | 53 (22.9)          | 46 (19.9)         | Ahn et al., 2014                               |
|                        | Liver Hepatocellular Carcinoma (RIKEN, Nat Genet 2012)      | 25            | 3 (12.0)           | 3 (12.0)          | Fujimoto et al., 2012                         |
|                        | Hepatocellular Carcinomas (Inserm, Nat Genet 2015)          | 243           | 87 (35.8)          | 76 (31.3)         | Schulze et al., 2015                           |
|                        | Hepatocellular Adenoma (Inserm, Cancer Cell 2014)           | 30            | 13 (43.3)          | 11 (36.7)         | Pilati et al., 2014                            |
| Colorectal cancer      | Colorectal Adenocarcinoma (TCGA, Nature 2012)              | 212           | 11 (5.2)           | 1 (0.5)           | Cancer Genome Atlas, N. et al., 2012           |
|                        | Colorectal Adenocarcinoma (Genentech, Nature 2012)          | 72            | 5 (6.9)            | 2 (2.8)           | Seshagiri et al., 2012                         |
|                        | Colorectal Adenocarcinoma (DFCI, Cell Reports 2016)         | 619           | 31 (5.0)           | 8 (1.3)           | Giannakis et al., 2016                         |
|                        | Metastatic colorectal cancer (MSK, Cancer Cell 2018)        | 1099          | 84 (7.6)           | 19 (1.7)          | Yaeger et al., 2018                            |
|                        | Colon Adenocarcinoma (TCGA, PanCancer Atlas)                | 389           | 27 (6.9)           | 15 (3.9)          | Cancer Genome Atlas Research et al., 2013b     |
|                        | Rectum Adenocarcinoma (TCGA, PanCancer Atlas)              | 137           | 8 (5.8)            | 0 (0.0)           | Cancer Genome Atlas Research et al., 2013b     |

*Data obtained from the listed cancer studies on cBioportal (www.cbioportal.org)

Table 2. Status of mutations in cancer cell lines harboring activating mutations of CTNNB1

| Cancer type            | Cell Line | CTNNB1       | APC        | TP53       | BRAF   | KRAS   |
|------------------------|-----------|--------------|------------|------------|--------|--------|
| Colorectal cancer      | SW48      | S33Y         | R2714C     |            |        |        |
|                        | CCK81     | T41A         | Y159C      | P278H      | S273N  |        |
|                        | SNU407    | T41A         |            |            | R726C  |        |
|                        | HCT116    | S45del       |            |            |        | G13D   |
|                        | LS180     | S45F         | R1788C     |            |        |        |
|                        | LS180     | S45F         |            |            |        |        |
| Gastric cancer         | KE39      | D32N         | V272L      |            | G12D   |        |
|                        | AGS       | G34E         |            |            |        | G12D   |
|                        | SNU719    | G34V         |            |            |        |        |
|                        | OCUM1     | S45C         |            |            |        |        |
| Endometrial cancer     | HEC265    | D32V, X561_splice | P1233L   |            |        |        |
|                        | HEC6      | D32V         |            |            | V160A  |        |
|                        | HEC108    | S37P, D207G  | S678G, A2388V, T2514I | P151H |        |
|                        | JHUEM2    | S37C         |            |            | A2V    |        |
|                        | SNGM      | S37P         |            |            |        | G12V   |
| Lung cancer            | MORCPR    | S33L         | P865L, A2122dup | P152R5+18 | G13C   |        |
|                        | SW1573    | S33F         |            |            |        | G12C   |
|                        | LXF289    | T41A         |            |            | R248W  |        |
|                        | HCC15     | S45F, Y670*  | D2796G     |            | D259V  |        |
| Liver cancer           | HUH6      | G34V         |            |            | N239D, A159D |        |
|                        | SNU398    | S37C         |            |            |        |        |
| Melanoma               | SKMEL1    | S33C         |            |            |        | V600E  |
|                        | COL0783   | S45del       |            |            |        | P27L   |
|                        |           |              |            |            |        | V600E  |

*Mutation data obtained from Cancer Cell Line Encyclopedia (Novartis/Broad, Nature, 2012) on cBioportal (www.cbioportal.org).
#Abbreviation: del, deletion; dup, duplication; Ts, frame shift; splice, splice site mutation; *, stop codon
Mutations in the β-catenin gene are common in colorectal cancer and can have diverse functional consequences. The β-catenin protein is composed of three domains: an N-terminal domain (~100 aa), a central domain (residue 141-664) made of 12 Armadillo (Arm) repeats and a C-terminal domain (~100 aa) (Fig. 3A). The central domain of the protein, the Arm repeats domain, forms a rigid rod-like structure and interacts with many binding proteins (Xu and Kimelman, 2007). However, it has been difficult to determine the structure of the terminal regions (N- and C-terminals) of β-catenin, so they are likely to be flexible and could be intrinsically disordered (Xing et al., 2008). Interestingly, the N-terminal region of the β-catenin protein is encoded by exon 3 (amino acid residues 5-80) of CTNNB1, so the N-terminal mutations can also be referred to as exon 3 mutations.

The β-catenin protein has been found to have diverse functions, including regulation of cell adhesion, cell fate, and cell proliferation. Mutations in the β-catenin gene are associated with worse recurrence-free survival. The β-catenin protein has been shown to be a direct driver mutation in colorectal cancer cell lines with mutations in CTNNB1. Furthermore, the β-catenin protein has been shown to be a direct driver mutation in colorectal cancer cell lines with mutations in CTNNB1. Additionally, in liver cancer, hotspot mutations in CTNNB1 were deeply analyzed in a large cohort of patients from HCA to carcinoma (HCC). S45, K335, and N387 mutations result in weak activation of β-catenin, while LxxQ, S33, G42, and G43 mutations result in strong activation of β-catenin. These mutations are associated with worse recurrence-free survival (Kim et al., 2009).
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Fig. 3. Diagram of β-catenin protein domains and hotspot mutations. (A) A schematic diagram of the β-catenin protein and mRNA. UTR, untranslated region; CDS, coding sequence; ATG, translation start codon; TAA, translation stop codon. (B) Exon 3 hotspot mutations of CTNNB1 are marked on the lollipop plot downloaded from the MSK-IMPACT pan-cancer study on cBioportal. Deep deletions near Exon 3 of CTNNB1 pre-mRNA are indicated as red lines. Deletion data were obtained from metastatic colorectal cancer study (MSK) on cBioportal.

β-catenin and are frequently found in HCA. T41 mutations show relatively moderate activation. Exon 3 deletion and β-TrCP binding site (D32-S37) mutations show strong activation and are enriched in HCA/HCC borderline and HCC, respectively. Highly activated β-catenin is associated with malignant tumors, as evaluated by glutamine synthase staining. Although S45 mutations show weak activation, most S45 mutant alleles in HCC are duplicated, resulting in strong activation of β-catenin. This study suggests that HCA harboring high/moderate mutants or S45 mutants may be associated with malignant transformation (Rebouissou et al., 2016). Accelerated liver regeneration and hepatocarcinogenesis was also observed in mouse overexpressing S45 mutant β-catenin (Nejak-Bowen et al., 2010). In colorectal cancers, most somatic mutations are observed at D32, S33, G34, S37, T41, and S45 in exon 3 of β-catenin mRNA. These hotspot mutations have been shown to stabilize β-catenin by disturbing the phosphorylation-dependent ubiquitination, leading to tumorigenesis. S45 is a priming-phosphorylation site for Casein Kinase I alpha (CK1α) (Liu et al., 2002). S33, S37, and T41 are further phosphorylated by GSK3β. D32 and G34 is required to bind with β-TrCP, a component of ubiquitin E3 ligase for phosphorylated β-catenin (Aberle et al., 1997; Hart et al., 1998).

Exon 3-spanning in-frame deletion in metastatic colorectal cancers
Recently, prospective targeted sequencing was reported with metastatic and early-stage colorectal cancer patients of a large cohort study (Yaeger et al., 2018). In this MSK study, the frequency of CTNNB1 alterations (8%) is slightly higher than that in TCGA cohort (5% of TCGA pan-cancer atlas), but in-frame deletion is highly enriched in the MSK cohort. This difference may be due to the distinct features between MSK and TCGA cohorts. The MSK cohort includes 47% of metastases that were not included in TCGA cohort, representing more aggressive and advanced disease. Activating hotspot mutations of β-catenin are more frequently occurred in microsatellite instability-high (MSI-H) tumors than in microsatellite stable (MSS) tumors (25% of MSI-H, 6% of MSS). Interestingly, however, exon 3-spanning in-frame deletions were identified only in MSS tumors and the nuclear staining of β-catenin was observed in tumors harboring in-frame deletions in CTNNB1 (Yaeger et al., 2018).

CONCLUSION
Large-scale analysis of pan-cancer genomic database revealed a high frequency of CTNNB1 mutations in endometrial, liver, and colorectal cancers. In addition, mutations are frequently located near exon 3 of CTNNB1, which encode for the regulatory amino acids (D32, S33, G34, S37, T41, and S45) at the N-terminal region of the protein. Since the N-terminal region is highly unstructured and flexible, the contributions of N-terminal hotspot mutations from a structural perspective are not easy to comprehend (Dar et al.,
FUTURE PERSPECTIVES

Re-evaluating hotspot mutations

The high frequency of mutations affecting the GSK3β and β-TrCP-binding sites (D32, S33, G34, S37) can be explained by their roles in the β-catenin destruction complex (Megy et al., 2005; Stamos and Weis, 2013). However, higher frequencies of S45 and T41 mutations cannot be easily explained in terms of the residues for priming and relay kinases, respectively. In fact, recent study suggested the uncoupling of CK1ε phosphorylation on S45 residue to GSK3β phosphorylation on S37/S33 residues. The phosphorylations on the T41/S45 residues of β-catenin were spatially uncoupled from the phosphorylated S33/S37/T41 (Maher et al., 2010). In addition, a previous study reported that the phosphorylations on S33/S37/T41 can occur in the absence of the phospho-S45 in colon cancer cells (Wang et al., 2003). In desmoid-type fibromatosis, protein stability and target genes for the S45F mutant are different from those of the wild-type β-catenin (Colombo et al., 2017). Moreover, the S45F mutation is associated with low efficacy of a cyclooxygenase-2 inhibitor in desmoid tumors (Hamada et al., 2014). It will be important to determine the oncogenic role of the S45F mutant β-catenin protein, as a type of mutation distinct from other mutant β-catenin proteins.

β-catenin in multiple protein complexes

β-Catenin protein was first discovered as a component of the adherens junction (Ozawa et al., 1989). Later, it is considered as a multitasking protein involved in transcription as well as in cell adhesion (Hur and Jeong, 2013; Kumar and Bashyam, 2017; Valenta et al., 2012). However, it should be noted that most β-catenin proteins reside in the adhesion complex near the plasma membrane in which it interacts with E-cadherin and α-catenin with high affinities (Huber and Weis, 2001). Multiple roles of β-catenin protein may come from multiprotein assembly forming distinct complexes in different intracellular locations (Xu and Kimelman, 2007). In the nucleus, β-catenin associates with DNA binding proteins, such as TCF/LEF and BCL9 (Graham et al., 2001; Sampietro et al., 2006). Collectively, the N-terminal region of β-catenin is critical for regulating the adhesion and transcription functions of the protein. Thus, the regulatory mechanism of phosphorylation may differ in distinct β-catenin complexes (Dar et al., 2016). Therefore, many questions arise as to whether the specific mutant β-catenin proteins can form a previously unknown complex, in addition to the adhesion, destruction, and transcription complexes (Fig. 4). We hope that the clinical information gained from the large cancer genome databases could facilitate the study of novel functions of β-catenin in RNA metabolism as an RNA-binding protein (Hur and Jeong, 2013; Kim et al., 2009; Kim et al., 2012; Lee and Jeong, 2006). To enhance our understanding of such novel functions, a systematic mutant β-catenin library could be developed to link the differential functional impacts to specific mutations in cancer. More functional studies on specific mutant β-catenin proteins will open up new avenues for elucidating the mechanisms underlying mutant β-catenin-mediated oncogenesis.

Novel therapeutic approach for mutant β-catenin proteins

β-Catenin protein has been a prime target for anti-cancer drug development, but some limitations may suspend successful drug development. In most cases, wild-type β-catenin protein have been utilized as a target protein and Wnt signaling activated transcription is used as a screening read-out (Cui et al., 2018; Krishnamurthy and Kurzrock, 2018; Polakis, 2012a). As a novel strategy, the information obtained for mutant β-catenin can be implemented for mutant-specific anti-cancer therapeutics, as utilized for mutant p53 proteins (Bykov et al., 2018; Kotler et al., 2018). Large-scale clinical analysis could provide important information on the functions of cancer-related proteins and cancer signaling, as shown here (Hyman et al., 2017). Therefore, future research should be directed toward a precision oncology strategy by identifying the molecular signature of cancer-related genes and exploiting cancer genome databases (Zehir et al., 2017).

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