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A Pan-Cancer Bioinformatic Analysis of B1-Integrin–Wnt/ B-Catenin Crosstalk and Its Potential Therapeutic Relevance

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ABSTRACT

Understanding adhesion receptor signalling dysregulation in cancer settings is vital for the effective and safe incorporation of adhesion-targeted therapeutics in the clinic. β1-integrin is a major extracellular matrix adhesion receptor that has been shown to control important processes such as proliferation, cell cycle progression, apoptosis and cell migration. β1-integrin signalling pathway is complex and can crosstalk with many tumorigenic pathways. It is therefore not surprising that enhanced β1-integrin signalling has been reported to correlate with progression and therapy resistance in many types of cancers. Therefore, a complete understanding of the pathways and genes altered in all cancer types is essential to identify novel therapeutic options specific for certain cancer types. In this study, a pan-cancer analysis was performed to identify alterations of β1-integrin and most dysregulated cancer-related genes (106 genes, Kegg map05200) using 2565 patients whole genomes data (ICGC/TCGA, 2020). OncoPrint, mutations, copy number alterations (CNA), mutual exclusivity and pathway enrichment were conducted using cBioPortal. PathwayMapper, an interactive graphical editing tool allowing collaborative curation was used to view altered genes and pathways with alteration frequencies. Pathway enrichment analyses related to genetic alterations identified the Wnt signaling was the most frequently altered pathway. Mutual exclusivity analyses showed that β1-integrin-Wnt; β1-integrin-LRP5/LRP6 and β1-integrin-FZD pairs exhibited co-occurrence, two sided fisher exact test indicates $p < 0.001$. This has shown a link between β1-integrin and Wnt/β-catenin pathways. Genetic alterations of β1-integrin receptor, whether these mutations will cause an activation of the Wnt/β-catenin pathway and their effects on overall survival and metastasis will be further examined.

Keywords: β1-integrin, Wnt signaling, Pan-cancer, Pathway enrichment

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Introduction

Cell-cell adhesion and cell-extracellular matrix interactions are critical for maintaining tissue architecture and regulating cellular functions. Integrins play a crucial role and serve as primary mediators of these interactions. The integrins comprise of a family of 24 αβ pairs of heterodimeric transmembrane adhesion receptors with a total of 18 α subunits and 8 β subunits in mammals (1). Integrin β1 is the most common subunit and the dysregulation of integrin β1-mediated signaling plays a major role in cancer by regulating multiple cellular processes. Integrins may directly regulate cellular motility, cancer cell proliferation, survival, and metastasis via binding to extracellular matrix (ECM) elements and participating in ECM reorganization (2, 3).

Integrins are capable of recognizing a wide variety of extracellular ligands, including transmembrane receptors on the surface of other cells and ECM proteins involved in cell-cell junctions. Both α and β subunits mediate adhesion and interact with extracellular matrix components such as laminin, collagen, fibronectin and vitronectin via their large extracellular domains allowing them to sense stimuli from ECM and respond them accordingly. In addition, integrins also engage with FAK, AKT, MAPK, and Src family kinases to facilitate signaling via their transmembrane and cytoplasmic domain enabling them to regulate cell survival, migration and resistance to conventional therapies (4). Integrin and integrin-linked processes have been involved in almost every step of cancer development progression from tumor initiation and proliferation to metastatic niche formation which includes intravasation, circulating cancer cell survival and extravasation (5, 6).

β1-integrin expression is considerably altered in many types of cancer including breast, prostate, pancreatic cancer (7). Genes related β1-integrin pathways were found significantly dysregulated in hepatocellular carcinoma (HCC) as well. These altered genes has also been found to associate with Ras/Raf/MAPK and mTOR pathways which enhances proliferative signals and facilitates metastasis (8). Knockdown of integrin β1 inhibited invasion and also enhanced radiosensitivity, via suppression of the downstream focal adhesion kinase (FAK)/cortactin signaling pathway in laryngeal cancer cells (9). Recent findings suggest that integrins are master regulators of oncogenic processes and also play a central role in contributing to drug resistance (10). Ahmed et al. have shown that inactivating β1-integrin leads to selective apoptosis and cytostasis in breast cancer cells, indicating its involvement in DNA repair mechanisms through pathways regulating survival signaling in response to DNA damage (11). β1-integrin could serve as potential therapeutic targets. Dysregulated β1-integrin signaling plays an important and multifactorial role in cancer. Its involvement in processes such as proliferation, migration and therapy resistance makes it as a valuable therapeutic target. However, due to its complex, context-dependent behavior of β1-integrin linked pathways and sometimes antagonistic roles in cancer cells, therapeutic targeting of integrin β1 still presents a challenge despite decades of research. Therefore further elucidation of β1-integrin signaling is required for the development of new treatment strategies in order to improve patient outcomes. As mentioned earlier, β1-integrin can interact with a wide range of intracellular partners and crosstalk with tumorigenic pathways and complete understanding of the pathways and genes altered in all cancer types is essential to identify tumor-specific therapeutic approaches. In this study, a pan-cancer analysis was performed to identify alterations of β1-integrin and their association with key dysregulated cancer-related genes. We aimed to explore a potential link at the genomic level across multiple cancer types to provide insight into its clinical relevance.

Materials and Methods

Whole-genome data from 2,565 patients were obtained through TCGA and ICGC databases (12). A curated set of 106 cancer-associated genes was selected based on the KEGG "Pathways in cancer" (map05200). Data were analyzed via cBioPortal, employing tools such as OncoPrint visualization, mutation profiling, copy number alterations (CNAs), mutual exclusivity analysis, and enrichment mapping. The cBio Cancer Genomics Portal (http://cbioportal.org) is an open-access resource for interactive exploration of multidimensional cancer genomics data sets (13, 14). The cBioPortal for Cancer Genomics, established by the Memorial Sloan Kettering Cancer Center, serves as an intuitive platform designed to facilitate the integration and

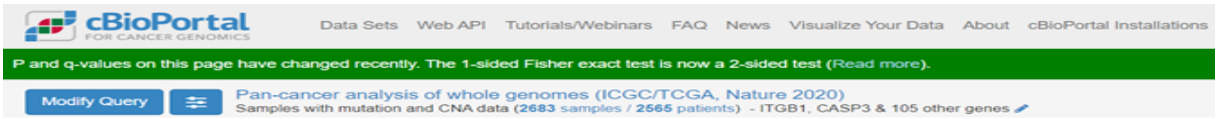
interpretation of complex datasets generated by large-scale cancer genomics initiatives. It facilitates the direct exploration and analysis of genomic alterations within expansive cancer datasets, thereby supporting data-driven discoveries across the oncology community. A pan-cancer analysis was performed to identify alterations of β1-integrin and most dysregulated cancer-related genes (106 genes, Kegg map05200) using whole genome data. To explore genomic alterations across the selected gene set, OncoPrint plots were generated using the cBioPortal platform. These visualizations enabled the detection of alteration patterns—particularly mutual exclusivity and co-occurrence among key genes within the pathway of interest. Co-occurrence and exclusivity analyses were conducted using Fisher's exact test ($p < 0.001$ considered significant).

To visualize and annotate cancer-related signaling pathways, we employed PathwayMapper, a web-based collaborative platform specifically designed for the visualization and real-time editing of curated cancer pathways (15). The PathwayMapper tool is accessible at http://pathwaymapper.org and the code is available on Github (https://github.com/iVis-at-Bilkent/pathway-mapper). PathwayMapper is based on the Cytoscape.js (16) graph library, uses backbone.js in the frontend, and node.js and the Google Realtime API in the backend. This tool enables the integration of genomic alteration data retrieved from cBioPortal, and supports both individual and multi-user curation environments with concurrent editing capabilities and conflict resolution. Pre-curated pathways were overlaid with mutation and copy number alteration data using a bidirectional color scheme: positive values, indicating activating alterations, were represented with a white-to-red gradient, while negative values, corresponding to inactivating events, were shown in a white-to-blue gradient. Exported pathway maps, generated in scalable vector graphics (SVG) format, included alteration frequencies for potential use in publication-quality figures. This approach allowed intuitive identification of frequently altered nodes and facilitated the contextual interpretation of pathway-level perturbations.

Results

Mutual exclusivity and co-occurrence analyses revealed a significant pattern of co-occurrence between β1-integrin (ITGB1**)** and multiple members of the Wnt signaling family, suggesting a potential functional relationship. The two-sided Fisher's exact test demonstrated statistically significant co-occurrence between β1-integrin and several Wnt pathway genes, with p values < 0.001. Among the top-correlated genes, WNT9A showed the highest positive association with β1-integrin alterations (Spearman's $\rho = 0.181$, $p = 8.92 \times 10^{-9}$, $q = 4.94 \times 10^{-8}$), followed by WNT2B ($\rho = 0.174$, $p = 3.47 \times 10^{-8}$) and WNT2 ($\rho = 0.139$, $p = 1.08 \times 10^{-5}$). These genes are known to be involved in canonical and non-canonical Wnt/β-catenin signaling, reinforcing the notion of integrin-Wnt crosstalk in cancer (Table1).

Table 1. Correlation of β1-integrin (ITGB1) alterations with Wnt pathway gene alterations in pan-cancer analysis.



Correlated Gene	Cytoband	Spearman's Correlation	p-Value	q-Value
WNT9A	1q42.13	0.181	8.92e-9	**4.94e-8**
WNT2B	1p13.2	0.174	3.47e-8	**1.79e-7**
WNT2	7q31.2	0.139	1.080e-5	**3.907e-5**
WNT5A-AS1	3p14.3	0.126	7.288e-5	**2.309e-4**
WNT7B	22q13.31	0.125	7.626e-5	**2.409e-4**
WNT3A	1q42.13	0.125	8.377e-5	**2.627e-4**
WNT5A	3p14.3	0.121	1.267e-4	**3.851e-4**
WNT9B	17q21.32	0.0977	2.085e-3	**5.050e-3**
WNT3	17q21.31-q21.32	0.0951	2.729e-3	**6.453e-3**
WNT4	1p36.12	0.0927	3.497e-3	**8.074e-3**
WNT5B	12p13.33	0.0846	7.725e-3	**0.0165**
WNT11	11q13.5	0.0303	0.340	0.436

Mutual exclusivity analysis revealed statistically significant co-occurrence patterns between β1-integrin (ITGB1) and key upstream components of the Wnt/β-catenin signaling pathway**,** including LRP5, LRP6, and multiple Frizzled (FZD**)** receptors. Specifically, β1-integrin–LRP5, β1-integrin–LRP6, and β1-integrin–FZD gene pairs showed strong co-alteration signals, with *p*-values less than 0.001 based on the two-sided Fisher's exact test, indicating non-random co-occurrence across cancer types (Table 2).

Table 2. Co-occurrence between β1-integrin and Wnt pathway co-receptors (LRP5, LRP6, FZD) identified by mutual exclusivity analysis.

cBioPortal FOR CANCER GENOMICS — Data Sets | Web API | Tutorials/Webinars | FAQ | News | Visualize Your Data | About | cBioPortal Installations

P and q-values on this page have changed recently. The 1-sided Fisher exact test is now a 2-sided test (Read more).

Modify Query

Pan-cancer analysis of whole genomes (ICGC/TCGA, Nature 2020)
Samples with mutation and CNA data (2683 samples / 2565 patients) - ITGB1, CASP3 & 105 other genes

Correlated Gene	Cytoband	Spearman's Correlation	p-Value	q-Value
FZD1	7q21.13	0.337	9.81e-28	**3.45e-26**
FZD6	8q22.3	0.249	2.02e-15	**2.35e-14**
FZD7	2q33.1	0.209	2.85e-11	**2.14e-10**
FZD4	11q14.2	0.196	4.42e-10	**2.89e-9**
FZD8	10p11.21	0.193	9.73e-10	**6.07e-9**
FZD5	2q33.3	0.189	1.86e-9	**1.12e-8**
FZD10	12q24.33	0.0465	0.144	0.214
FZD9	7q11.23	0.0144	0.652	0.729

Correlated Gene	Cytoband	Spearman's Correlation	p-Value	q-Value
CTNNB1	3p22.1	0.340	2.74e-28	**1.01e-26**

Correlated Gene	Cytoband	Spearman's Correlation	p-Value	q-Value
LRP5	11q13.2	0.210	2.37e-11	**1.79e-10**

Correlated Gene	Cytoband	Spearman's Correlation	p-Value	q-Value
LRP6	12p13.2	0.334	2.60e-27	**8.81e-26**

These findings suggest a potential functional interaction or coordinated dysregulation between β1-integrin and Wnt co-receptors, reinforcing the hypothesis that integrin-mediated adhesion signaling may converge on or modulate canonical Wnt pathway activity. The observed co-alteration supports the proposed crosstalk between β1-integrin and Wnt/β-catenin signaling in the context of tumor progression.

Pathway enrichment analysis of genomic alterations across the pan-cancer dataset identified the Wnt signaling pathway as one of the most frequently altered biological networks. To visualize these alterations in a structured and pathway-centric context, we used PathwayMapper, an interactive web-based tool designed for collaborative pathway curation. The platform enabled the mapping of mutation and copy number alteration frequencies onto a curated Wnt signaling pathway diagram. As illustrated in Figure 1, numerous components of the Wnt/β-catenin pathway exhibited notable alteration frequencies. Key structural genes such as APC (8.5%), CTNNB1 (6.4%), and AXIN2 (7.1%) were among the most frequently altered. Upstream receptor elements, including LRP5 (4.8%), LRP6 (5.7%), and Frizzled (FZD)-associated components, also showed appreciable alteration levels. These results highlight both core and peripheral dysregulation within the Wnt signaling axis, suggesting widespread perturbation of this pathway across various cancer types.

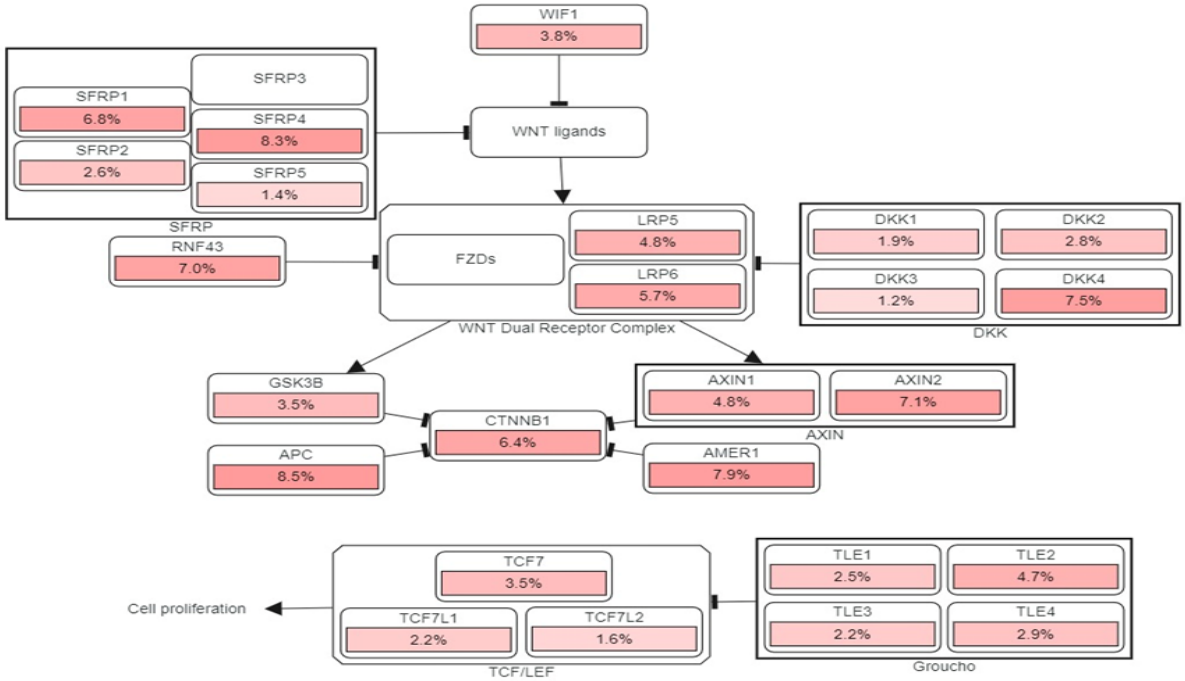


Figure 1. Alteration frequencies of genes involved in the Wnt/β-catenin signaling pathway, visualized using PathwayMapper. Red intensity reflects the percentage of cases with genomic alterations for each gene across 2,565 samples.

Furthermore, OncoPrint plots supported the presence of co-alteration patterns rather than mutual exclusivity among these gene pairs. Collectively, these findings suggest that β1-integrin may contribute to oncogenic processes in part through its association with Wnt pathway activation**,** potentially promoting tumor progression.

Discussion

The Wnt signaling pathway was found to be the most notable alteration observed across the cohort. Co-occurrence analysis showed significant associations between β1-integrin and Wnt pathway members, including LRP5, LRP6 and FZD receptors. Alterations of β1-integrin were co-detected with alterations of Wnt pathway genes which indicates a potential functional crosstalk. It was found that β1-integrin–Wnt interaction was consistent across various cancer types. These findings suggest that β1-integrin have a potential role in regulating Wnt signalling activity.

The Wnt protein family consists of 19 secreted glycoproteins which activates various signalling mechanisms and plays an important role in cell proliferation, cell adhesion, differentiation and migration (17). The Wnt signalling pathway include canonical and noncanonical pathways. The canonical Wnt signaling pathway is activated by the binding of Frizzled and LRP5/6 receptors. This interaction prevents the degradation of β-catenin so β-catenin accumulates in the cell. The accumulated β-catenin is then transported to the nucleus, initiating transcription of target genes. Non-canonical Wnt pathway is independent of β-catenin and generally regulate processes such as cellular polarity, motility, and calcium signaling. While the canonical Wnt pathway primarily regulates cell proliferation, the noncanonical Wnt pathway is involved in regulating cell polarity and migration (18).

Previous studies have shown that integrin activation can amplify Wnt signals. Du et al. found that integrin upon activation on a stiff extracellular matrix, phosphorylates downstream molecules and this results in GSK3β-phosphorylation. Consequently, degradation of β-catenin is inhibited, catenin accumulates and stabilized catenin enters the nucleus to initiate β-catenin/Wnt1 feedback via binding wnt1-promoter (17). Another study showed that integrin activation leads to cisplatinresistance in melanoma cells via integrin-driven PI3K/AKT signalling and activation of canonical Wnt pathway by phosphorylation and deactivation of Gsk3-β (19). Additionally, another study showed that loss of β1-integrin downregulates Wnt signaling, which can be rescued by reactivating downstream effectors like Rac1 (20). Taken

together, these findings supports β1-integrin–induced Wnt pathway activation.

We discussed in previous sections that integrins can directly regulate the proliferation and cell migration of cancer cells by binding to ECM elements. Monoclonal antibodies have been developed to prevent the transmission of integrin-related mechanical and biochemical signals from the cancer microenvironment. As a result strong preclinical results have been obtained. While preclinical experiments demonstrate the potent antitumor effects of integrin-targeted therapies, including monoclonal antibodies and synthetic molecules, unfortunately, the same effect has not been observed in patients in clinical trials, and they have largely failed to halt tumor progression (21-23). The disappointing results regarding patient survival, disease stabilization, and metastasis formation may be due to the complexity of integrin mechanisms, the development of anoikis resistance, and their ability to compensate for each other. Therefore, more comprehensive investigation of integrin and related mechanisms is necessary to improve the efficacy of integrin-targeted therapies.

Conclusion

This study highlights a significant genomic correlation between β1-integrin and Wnt/β-catenin pathways across multiple cancers. Although these findings support a functional interaction between Wnt/β-catenin and β1-integrin, this relationship needs to be further confirmed with functional studies. Understanding this relationship may uncover new therapeutic targets, especially in tumors showing resistance to conventional treatments.

The Ethics Committee

Ethical approval was not required for this study as it did not involve human or animal subjects.

Conflict of Interest

The author declares that there is no conflict of interest.

Authorship Contributions

Conceptualization: SE, SO
Collection of data and analysis: SE, SO, ÖBE
Writing, review and editing: SE, SO, ÖBE
All authors have read and agreed to the published version of the manuscript.

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