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The Wnt Signalling Pathway: A Tailored Target in Cancer

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1759306> since 2020-10-22T15:40:30Z

Published version:

DOI:10.3390/ijms21207697

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1 *Review*

2 **The Wnt signalling pathway: a tailored target in** 3 **cancer**

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7 Received: date; Accepted: date; Published: date

8 **Abstract:** Cancer is one of the greatest public health challenges. According to the World Health
9 Organization (WHO) 9.6 million cancer deaths have been reported in 2018. The most common
10 cancers include lung, breast, colorectal, prostate, skin cancer (non-melanoma) and stomach. The
11 unbalance of physiological signalling pathways due to the acquisition of mutations in tumour cells
12 is considered the most common cancer driver. The Wntless-related integration site (Wnt)/ β -catenin
13 pathway is crucial for tissue development and homeostasis in all animal species and its
14 dysregulation is one of the most relevant events linked to cancer development and dissemination.
15 The canonical and the non-canonical Wnt/ β -catenin pathways are known to control both
16 physiological and pathological processes including cancer. Herein the impact of the Wnt/ β -catenin
17 cascade in driving cancers from different origin has been examined. Finally, based on the impact of
18 Extracellular Vesicles (EVs) on tumour growth, invasion and chemoresistance, and their role as
19 tumour diagnostic and prognostic tools, an overview of the current knowledge linking EVs to the
20 Wnt/ β -catenin pathway is also discussed.

21 **Keywords:** Wnt/ β -catenin dependent pathway; Wnt/ β -catenin independent pathway; colorectal
22 cancer; breast cancer; ovarian cancer; extracellular vesicles
23

24 **Introduction**

25 The human wingless-related integration site (Wnt) genes encode 19 evolutionarily conserved
26 glycoproteins with 22-24 Cys residues. In the endoplasmic reticulum (ER), the Wnt ligands are post-
27 translationally acetylated by porcupine, a membrane associated O-acyl transferase. Acetylation leads
28 to palmitoylation which is required for the release and binding of Wnt to the frizzled (*FZD*) receptors.
29 This, on turn, drives the biological response[1].

30 The Wnt signalling pathway regulates crucial cellular processes including cell fate
31 determination, organogenesis during embryonic development, normal adult homeostasis, motility,
32 polarity and stem cell renewal[2]. Moreover, its contribute in cancer has been extensively
33 investigated[3].

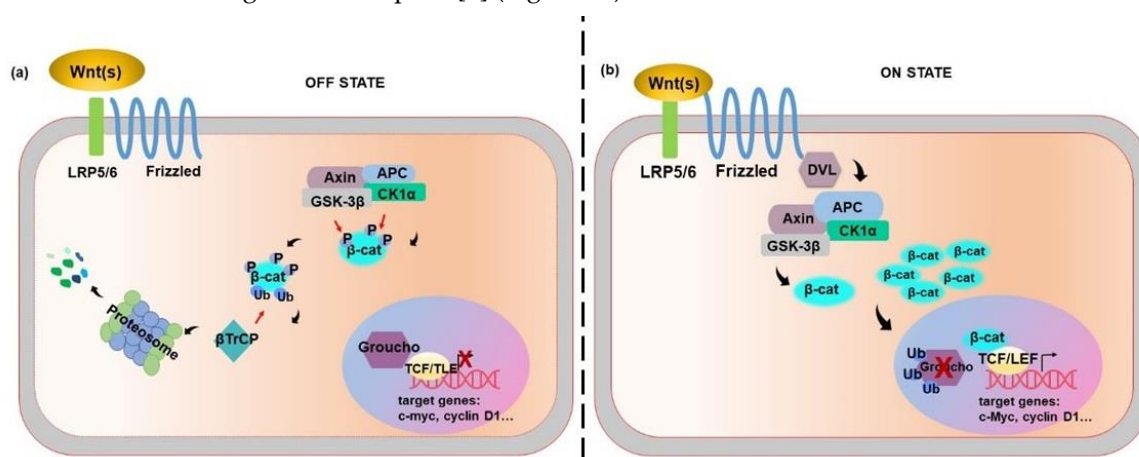
34 The Wnt pathway has been widely studied and reviewed, and a general understanding of the
35 transduction cascade has been clarified. The Wnt cascade has been subdivided into different branches
36 due to its complexity[4,5]. They include the canonical Wnt/ β -catenin (Wnt/ β -catenin dependent
37 pathway) and the non-canonical Wnt/ β -catenin pathway (β -catenin-independent pathway). The
38 latter was further allocated into two additional branches, the planar cell polarity (PCP) and the
39 Wnt/calcium pathways[2]. Both of them contribute to cancer development and dissemination.

40 The aim of the present review is to provide an overview of the current knowledge about the Wnt
41 signalling pathway in tumour development and progression. Tumours from different origin are
42 discussed. Although the canonical and the non-canonical Wnt/ β -catenin pathway work together to
43 control physiological and pathological processes[2], data related to each one are independently

44 debated. Finally, the contribute of extracellular vesicles (EVs) in triggering the Wnt/ β -catenin cascade
 45 is also analyzed.

46 Wnt canonical pathway: β -catenin dependent

47 The canonical pathway turns around the β -catenin intracellular level (Figure 1). In the absence
 48 of Wnt proteins the β -catenin “destruction complex” keeps low β -catenin in the cell. The “destruction
 49 complex” mainly consists of two kinases: casein kinase 1 α (CK1 α), glycogen synthase kinase 3 β (GSK-
 50 3 β) and two scaffolds: axis inhibition (*Axin*), and adenomatous polyposis coli (*APC*). Firstly, β -catenin
 51 undergoes phosphorylation by CK1 α at serine 45 (Ser45), Ser33, Ser37 and threonine 41 (Thr41) by
 52 GSK-3 β . Then, the E3 ubiquitin ligase, denoted as β -transducin repeat-containing protein (β TrCP),
 53 marks β -catenin ubiquitination and degradation [1]. This prevents β -catenin nuclear translocation
 54 while allows histone deacetylation and chromatin compaction by the Groucho repressor, translating
 55 into the inhibition of gene transcription[6] (Figure 1a).



56

57 **Figure 1. The Canonical Wnt signalling pathway.** (a) **OFF STATE.** In the absence of Wnt ligands β -
 58 catenin moves to the “destruction complex” consisting of casein kinase 1 α (CK1 α), glycogen synthase
 59 kinase 3 β (GSK-3 β) and two scaffolds: axis Inhibition (*Axin*), and adenomatous polyposis coli (*APC*).
 60 β -catenin undergoes phosphorylation at Ser45 residue by CK1 α and at Ser33, Ser37 and Thr41 residues
 61 by GSK-3 β . Then, the E3 ubiquitin ligase β -transducin repeat-containing protein (β TrCP), marks β -
 62 catenin ubiquitination and proteasomal degradation. This prevents β -catenin nuclear accumulation
 63 while allows chromatin compaction and Groucho-mediated promoter repression. (b) **ON STATE.**
 64 The Wnt ligands bind to frizzled (*FZD*) receptor and the low-density-lipoprotein-related protein 5/6
 65 (*LRP5/LRP6*), this results in dishevelled (*DVL*) phosphorylation and β -catenin release from the
 66 “destruction complex”, allowing β -catenin accumulation and nuclear translocation. In the nucleus,
 67 the Groucho repressor undergoes displacement allowing β -catenin to interact with T-cell
 68 factor/lymphoid enhancer factor (*TCF/LEF*), chromatin remodeling and transcription of genes such as
 69 *c-myc* and *cyclin D1*.

70 The activation of the canonical Wnt signal requires both the *FZD* family receptors and the low-
 71 density-lipoprotein-related protein 5/6 (*LRP5/LRP6*) co-receptors which phosphorylation is essential
 72 for receptor activation. Wnt binding to its receptor results in dishevelled (*DVL*) phosphorylation,
 73 leading to *Axin* de-phosphorylation and decline of its cytoplasmic content [7]. Thereby, β -catenin can
 74 be released from the “destruction complex”, and its degradation prevented while stabilization
 75 allowed. Accumulation of β -catenin turns into its nuclear translocation [7].

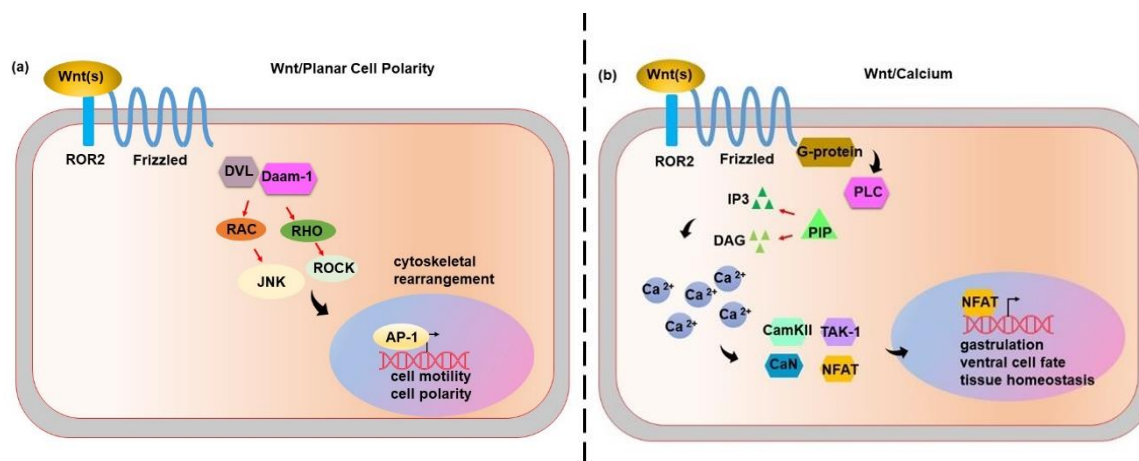
76 Although several nuclear β -catenin binding partners have been involved in the control of gene
 77 transcription, the most relevant β -catenin partners are the members of the T-cell factor/lymphoid
 78 enhancer factor (*TCF/LEF*) family of transcription factors [7]. This complex binds to the promoter
 79 region of target genes and regulates their transcription.

80 Once in the nucleus, the engagement of β -catenin transiently converts the *TCF/LEF* into
81 transcriptional activators which displace Groucho and induces chromatin remodelling and
82 transcriptional activity (Figure 1b).

83 A number of genes are targeted by Wnt- β -catenin. Among them, genes involved in positive- and
84 negative-feedback regulation, cell-cycle progression, and stem cell homeostasis are the most
85 commonly included genes.

86 Wnt non-canonical pathways: Wnt/planar cell polarity (PCP) and Wnt/Calcium

87 To date, the canonical Wnt/ β -catenin pathway is much better characterized than the non-
88 canonical one (Figure 2).



89 **Figure 2. The Wnt non-canonical signalling pathways.** (a) Wnt/planar cell polarity (PCP) pathway. Wnt
90 ligands bind to *FZD* receptors and co-receptor RAR-related orphan receptor (*ROR*) and convey the signal
91 to *DVL*. *DVL* forms the Disheveled associated activator of morphogenesis 1 (*DVL-Daam-1*) complex, which
92 triggers *RhoA*, *RHO* and *ROCK* to control cytoskeletal rearrangement. On the other hand, *DVL* triggers
93 *RAC*, *JNK* and *AP-1* involved in cell motility and polarity. (b) Wnt/Calcium pathway. Wnt ligands bind to
94 *FZD* and activate the phospholipase C (*PLC*), which hydrolyses the phosphatidylinositol (4,5)-
95 biphosphates (*PIP2*) to inositol (1,4,5)-triphosphates (*IP3*) and diacylglycerol (*DAG*). This translates into
96 intracellular calcium release and the activation of *CaN* and *CamKII*. The calmodulin activation stimulates
97 *TAK-1* and *NLK* activity. *CaN* activates the *NFAT*, which moves to the nucleus and modulates the
98 expression of genes involved in the control of gastrulation, ventral cell fate and tissue homeostasis.

99 In the non-canonical PCP pathway, Wnt ligands bind to *FZD* receptors and co-receptor protein
100 tyrosine kinase 7 (*PTK7*), RAR-related orphan receptor (*ROR*) or the receptor like tyrosine kinase
101 (*RYK*) and convey the signal to *DVL*. On the one side, *DVL* forms the disheveled associated activator
102 of morphogenesis 1 (*DVL-Daam-1*) complex, which triggers a small guanosine-5'-triphosphate (GTP)
103 GTPase, such as ras homolog gene family member A (*RhoA*), *RHO* and *RHO*-associated kinase
104 (*ROCK*). *DVL* also triggers ras-related C3 botulinum toxin substrate (*RAC*), JUN-N-terminal kinase
105 (*JNK*) and the activator protein-1 (*AP-1*). [7] The PCP pathway is involved in the cytoskeletal
106 rearrangement, cell motility and co-ordinates cell polarity. In vertebrates, the PCP pathway is also
107 required for morphology and migration of dorsal mesodermal cells undergoing gastrulation, hair
108 follicle organization, and orientation of stereocilia in the sensory epithelium of the inner ear [8]
109 (Figure 2a).

110 In the calcium-dependent pathway Wnt ligands bind to *FZD* and activate the phospholipase C
111 (*PLC*) which hydrolyses the phosphatidylinositol (4,5)-biphosphates (*PIP2*) to inositol (1,4,5)-
112 triphosphates (*IP3*) and diacylglycerol (*DAG*). This translates into the release of the intracellular
113 calcium and the activation of both calcineurin (*CaN*) and calcium/calmodulin-dependent kinase II
114 (*CamKII*). Moreover, the activation of calmodulin promotes the activation of the TGF- β -Activated
115 kinase 1 (*TAK-1*) and nemo-like kinase (*NLK*), thereby antagonizing and neutralizing the canonical
116 Wnt/ β -catenin cascade. *CaN* activates the nuclear factor of activated T-cells (*NFAT*), which moves to

117 the nucleus and regulates the expression of target genes [7] (Figure 2b). The calcium-dependent
 118 pathway plays a crucial role in several processes, including early pattern formation during
 119 gastrulation [2], ventral cell fate [9], dorsal axis formation [10], and tissue homeostasis [11].

120 COLORECTAL CANCER

121 Colorectal cancer (CRC) is one of most common cancer worldwide and represents a deep cause
 122 of cancer mortality [12] with a rapid increase in incidence and death rate [13]. Dienstmann et al. [14]
 123 established a new classification of CRCs into four consensus molecular subtypes (CMSs). Among
 124 them CMS2, CMS3, and CMS4 have a higher rate of APC mutations (over 50%) compared to CMS1.
 125 Each CMS has unique features: CMS1 (MSI Immune, 14%): hyper- mutated, microsatellite instability,
 126 strong immune activation; CMS2 (Canonical, 37%): epithelial, chromosomally unstable, marked Wnt
 127 and myc signalling activation; CMS3 (Metabolic, 13%): epithelial, metabolic dysregulation; and CMS4
 128 (Mesenchymal, 23%): a prominent transforming growth factor β ($TGF\beta$) activation, stromal invasion,
 129 and angiogenesis. Samples with combined features (13%) represent transition phenotypes or are
 130 supposed to reflect the intra-tumour heterogeneity [14].

131 The heterogeneous genetic ground underlying CRC initiation and progression mainly involves
 132 gene fusion, deletion or amplification, somatic gene mutations and epigenetic alterations. Wnt/ β -
 133 catenin signalling has emerged as one of the most significant biological pathways in both
 134 physiological setting and CRC development. Almost all CRC are characterized by a hyper-active
 135 Wnt/ β -catenin pathway, which, in many cases, is considered the most critical cancer initiating and
 136 driving event. Proteins and miRNAs guiding the Wnt/ β -catenin pathway and proposed as potential
 137 CRC therapeutic targets are discussed.

138 Canonical Wnt/ β -catenin pathway and CRC

139 Ring finger protein 6 (*RNF6*) is an oncogene frequently upregulated by gene amplification in
 140 primary CRC. Moreover, APC mutation and *RNF6* copy number amplification were commonly found
 141 in CRC patients. *RNF6* is a RING-domain E3 ubiquitin ligase and exerts its pro-metastatic effects by
 142 promoting CRC cell growth, cell-cycle progression, and epithelial to mesenchymal transition (EMT).
 143 Furthermore, *RNF6* expression and its gene amplification have been considered independent
 144 patients' prognostic factors. *RNF6* mediates the polyubiquitination of the transducin-like enhancer of
 145 split 3 (*TLE3*), a transcriptional repressor of the β -catenin/*TCF4* complex, and its proteasome
 146 degradation. The lack of *TLE3/TCF4/LEF* interaction enhances the Wnt/ β -catenin transcriptional
 147 activity, and the expression of its downstream target genes [15] (Table 1).

148 **Table 1.** Proteins/EVs involved in several tumours, their alteration, targets, and impact on tumours.

PROTEIN	RELATED CANCERS	EXPRESSION LEVEL	PATHWAY INTERACTION	IMPACT ON TUMOUR	REF.
RNF6	CRC	Upregulated	β -catenin	cell growth cell cycle progression EMT metastasis	[15]
LGR5	CRC, BC	Upregulated	β -catenin	proliferation migration	[16,65,68]
TNIK	Gastric	Upregulated	β -catenin	cell growth	[19,20]
KYA1797K	CRC	Upregulated	β -catenin	tumour growth stem cell features	[19,22]
BCL6	CRC	Upregulated	β -catenin	cellular proliferation tumour development	[22-24][25-27]

				tumour progression	
ZEB2 and ZEB1	CRC	Upregulated	β -catenin	tumour progression invasion	[27,28][30,31] [64,65] [67,68]
XIAP	CRC	Upregulated	β -catenin	proliferation chemoresistance	[27,28] [30,31]
RHBDD1	CRC	Upregulated	β -catenin	metastasis stemness EMT migration invasiveness	[31][34]
SLC35C1	CRC	Downregulated	β -catenin	cell proliferation cell progression	[32][35]
NPTX2	CRC	Upregulated	β -catenin	tumour stages lymphatic invasion metastasis	[33][36]
KLHL22	CRC	Downregulated	β -catenin	invasion migration	[37][40]
CCL2	CRC	Upregulated	Non-canonical	progression	[45][48]
LGR4	BC	Upregulated	β -catenin	tumorigenesis metastasis CSC maintenance	[63–66] [65–68]
ST7L	BC	Downregulated	GSK-3 β	proliferation invasion	[67][69]
TMED	BC	Upregulated	β -catenin	cell cycle progression colony formation migration	[68][70]
Wnt5a	BC	Downregulated	β -catenin	migration lactate production invasion	[73,74] [75,76]
Wnt5a	BC	Downregulated	β -catenin -cyclin D1 -TGF- β	cell proliferation aggressiveness	[76–78] [79–80]
Wnt5a	BC	Upregulated	ALCAM	vessel invasion tumour size migration	[79][81]
Nek2B	TNBC	Upregulated	β -catenin	chemoresistance	[89][91]
VANGL2	TNBC	Upregulated	p62/SQSTM1 (PCP)	migration anchorage-dependent and independent cell proliferation	[90][92]
HePTP	TNBC	Upregulated	-GSK-3 β	metastasis	[91][93]

			β -catenin		
DLC-3	TNBC	Downregulated	β -catenin	proliferation colony formation migration invasion	[92][94]
DKK1	OC	Downregulated	β -catenin	stemness	[100][102]
SFRP1	OC	Downregulated	β -catenin	cell growth stem-like phenotype	[101][103]
AXIN2	OC	Downregulated	β -catenin	stem-like phenotype	[101][103]
LGR6	OC	Upregulated	β -catenin	stemness chemoresistance	[105,106] [107,108]
RAB14	OC	Upregulated	β -catenin	proliferation chemoresistance invasion	[97,107] [109,110]
FZD7	OC	Upregulated	Non-canonical	EMT cell cycle progression migration	[109][112]
ITGBL1	OC	Upregulated	Non-canonical	migration adhesion	[110][113]
ALPL	OC	Upregulated	Non-canonical	EMT migration invasion	[115][118]
VDR	Melanoma	Upregulated	β -catenin	tumour growth immune response	[119][122]
EVs	CRC	Upregulated	β-catenin	migration, metastasis tumour growth	{123}
14-3-3 ζ in EVs	HEK293T, COS-7, SW480, HeLa, Huh7, HEK293- EBNA- PurR and L-Wnt3a- cells	Upregulated	β-catenin GSK-3β DVL2	survival migration	[124-126]
EVs	CRC	Upregulated	β -catenin	dedifferentiation drug resistance colony formation	[127,128]
EVs	HCC	Silenced	β -catenin	proliferation tumour growth	[132,133]

DKK 1 in EVs	MM	Upregulated	β -catenin	—osteoclast activity —osteoblast differentiation	[134]
EVs	OSCC	Upregulated	β -catenin	—metastasis —stemness —cell reprogramming —chemoresistance	[136]
Wnt5b in EVs	PANC-1 Caco-2 cell lines	Upregulated	β -catenin-dependent and independent	—proliferation —migration	[138]
EVs	BC	Upregulated	Wnt-PCP	—cell growth and motility	[139]

149 The leucine-rich repeat-containing G-protein coupled receptor 5 (*LGR5*) is a Wnt/ β -catenin target
 150 gene implicated in cancer cell proliferation and migration. It has been reported that *LGR5* is highly
 151 expressed in CRC tissues compared to the healthy ones. A decline in β -catenin and *c-myc* mRNA
 152 expression were detected by knocking-down *LGR5* expression, suggesting that it may regulate the
 153 Wnt/ β -catenin activity by modulating the expression of β -catenin. Furthermore, since targeting *LGR5*
 154 improves the response to chemotherapy, *LGR5* has been proposed as a novel therapeutic target in
 155 CRC [16] (Table 1).

156 The β -catenin and RAS signalling pathways are frequently associated to the development and
 157 progression of several different cancers. They mainly act on cancer stem cell (CSC) expansion. High
 158 levels of β -catenin and RAS proteins are considered the major drivers of CSC expansion and cancer
 159 dissemination and are associated with poor patient's outcome [17].

160 Targeting the CSC pool without affecting the somatic stem cell (SSC) niche is one of the major
 161 goals of the last decades. As reported by Lenz et al. [18], the β -catenin antagonist molecule, ICG-001,
 162 effectively prevented the interplay between β -catenin and its coactivator cAMP response element
 163 binding protein (CREB)-binding protein (*CBP*). Moreover, ICG-001 effectively and without side
 164 effects abrogated drug-resistant cells. On the same line, PRI-724, a second generation of *CBP*/ β -
 165 catenin antagonist, was found safe in pre-clinical studies and displayed an acceptable toxicity profile.
 166 Yu et al. [19] investigated the *traf2*- and *nck*-interacting kinase (*TNIK*) amplification and its role
 167 in tumor progression by applying siRNA technology, while Masuda et al. [20] have generated a small
 168 molecule denoted as NCB-0846 acting as *TNIK* inhibitor. *TNIK* selectively binds both to *TCF4* and β -
 169 catenin in order to promote cancer cell growth via Wnt/ β -catenin cascade and drives colorectal CSC
 170 expansion. The NCB-0846 inhibitor was effective in interfering with *TNIK* activity tumour growth.

171 KYA1797K, a small molecule identified by Cha et al. [21], was found effective in suppressing
 172 CRC growth due to the activation of *GSK-3 β* via Axin binding and β -catenin/RAS destabilization. In
 173 line with this observation, treatment with KYA1797K abrogated CRC stem cell features both *in vitro*
 174 and *in vivo*. Mechanistically, KYA1797K pushes β -catenin and RAS towards the *Axin* binding [22]
 175 (Table 1).

176 In the last decade miRNAs have gained particular attention in cancer [23]. miRNA profiling has
 177 been linked to cancer types, stage, and invasion [24]. Moreover, oncogenic or tumour suppressive
 178 actions have been linked to miRNA expression. For these reasons, miRNAs are considered valuable
 179 tools for cancer diagnosis and prognosis and therefore useful therapeutic targets (Table 2).

180 **Table 2.** miRNAs involved in the tumours, their alteration and tumour impact.

miRNA	RELATED CANCER	EXPRESSION LEVEL	IMPACT ON TUMOUR	REF.
miR-144-3p	CRC	Downregulated	cell proliferation	[22][25-27]

miR-377-3p	CRC	Upregulated	cell expansion EMT repression of apoptosis	[25][28]
miR-377-3p	CRC	Downregulated	proliferation migration chemoresistance	[26][29]
miR-520e	CRC	Downregulated	cell proliferation colony formation invasion	[29,30][32,33]
miR106a	BC	Upregulated	cell growth cisplatin sensitivity	[58][61]
miR-5188	BC	Upregulated	tumour cell proliferation metastasis formation EMT chemoresistance	[60][63]
miR-148a	BC	Downregulated	cell migration invasion	[61][64]
miR-6838- 5p	BC	Downregulated	cell invasion migration EMT	[92][95]
miR-27a-3p	BC	Upregulated	proliferation migration.	[93][96]
miR-1207	OC	Upregulated	tumorigenicity stem cell-like traits stemness	[100][103]
miR-590-3p	OC	Upregulated	cell growth migration, invasion	[101,102][104,105]
miR-1180	OC	Upregulated	cell proliferation glycolysis	[103][106]
miR-939	PCa	Downregulated	tumour stage metastasis	[116][120]
miR-92a-3p	CRC EVs	Upregulated	cancer progression stemness EMT drug resistance	[129]
miR-1273f	HCC EVs	Upregulation	cell proliferation migration invasiveness EMT	[134]

miR-1260b	LAC EVs	Upregulation	cell invasion metastasis	[137][136]
miR-214-3p	TEC EVs	Upregulation	neovessel formation	[139][139]
miR-24-3p	TEC EVs	Downregulation	neovessel formation	[139][139]

181 Sun and co-workers [25] identified miR-144-3p as a new biomarker for CRC diagnosis and
 182 response to treatment. miR-144-3p was found downregulated and associated with CRC pathological
 183 stages in CRC patients. Interestingly, miR-144-3p overexpression reduced CRC cell proliferation by
 184 delaying G1/S phase transition in tumour cells. On the contrary, the B-cell lymphoma 6 protein
 185 (*BCL6*), a nuclear protein belonging to the BTB/POZ/zinc finger (*ZF*) family of transcription factors,
 186 was found upregulated and surprisingly post-transcriptionally regulated by miR-144-3p. Previous
 187 studies revealed that *BCL6* is involved in the control of cell cycle progression and differentiation
 188 [26,27]. Indeed, miR-144-3p/*BCL6* co-operate to inhibit cellular proliferation, development, and
 189 progression of CRC by interfering with *c-myc* and *cyclin D1* expression [25] (Table 1).

190 miR-377-3p displays an ambiguous role in CRC. Liu and colleagues [28] uncovered that
 191 upregulation of miR-377-3p promotes G1-S phase transition, cell expansion and EMT, while represses
 192 apoptosis in CRC patients. Moreover, *GSK-3 β* , a direct miR-377-3p target, was found upregulated
 193 upon miR-377-3p overexpression. These data suggest that a complex regulatory network boosting
 194 tumour progression is associated with the expression of miR-377-3p in CRC.

195 Conversely, in a recent study, Huang et al. [29] have shown that miR-377-3p, significantly
 196 reduced in CRC patients, is involved in the control of proliferation, migration and chemo resistance,
 197 particularly at advanced tumour stage. The authors investigated miR-377 functions and mechanism
 198 of action in CRC cells. The zinc finger E-box binding homeobox 2 (*ZEB2*) and the X-linked inhibitor
 199 of apoptosis protein (*XIAP*) are two positive regulators of the Wnt/ β -catenin cascade [30,31]. In CRC,
 200 *ZEB2* enables tumour progression and invasion, whereas *XIAP* promotes cell proliferation and
 201 chemoresistance. De facto, miR-377-3p overexpression was found to suppress the malignant CRC
 202 phenotype, as well as cell proliferation, invasion and drug resistance by directly targeting the 3' UTR
 203 sequence of both *ZEB2* and *XIAP* mRNAs. Since miR-377-3p/*ZEB2-XIAP* inhibited CRC progression
 204 by reducing Wnt/ β -catenin-associated gene expression (e.i. *cyclin D1*, *Axin2*, *TCF1*, *SOX2*, *c-myc*,
 205 matrix metalloproteinase-2 (*MMP-2*), *MMP-9*, *CD44*, vascular endothelial growth factor (*VEGF*), and
 206 Twist) approaches increasing its expression have been proposed for novel therapeutic options (Table
 207 1).

208 Functional experiments showed that miR-520e plays a pivotal role in regulating CRC cell
 209 proliferation, colony formation and invasion [32]. Moreover, it has been reported that low miR-520e
 210 expression is associated with the increased CRC growth and migration. The astrocyte elevated gene-
 211 1 (*AEG-1*), which acts as an oncogene [33], is a direct miR-520e target in CRC. Cells overexpressing
 212 miR-520e displayed lower *GSK-3 β* phosphorylation and β -catenin expression. Mechanistically, it was
 213 found that miR-520e regulates cancer cell behaviour by targeting *AEG-1* which on turn inactivate the
 214 Wnt/ β -catenin signalling and the transcription of its downstream genes. Hence, miR-520e
 215 overexpression could represent a promising therapeutic target in CRC by *AEG-1* suppression.

216 Approximately 40–50% of CRC patients develop metastasis, mostly to the liver and lung. In
 217 cancer patients, metastases are associated with 90% of all cancer-related death, thereby the
 218 mechanisms accounting for the metastatic spread have been deeply investigated. Zhang et al. [34]
 219 demonstrated that the rhomboid domain containing 1 (*RHBDD1*) plays a crucial role in driving
 220 metastasis formation in CRC patients, via the Wnt/ β -catenin pathway. It has been shown that
 221 *RHBDD1* is able to influence the Wnt/ β -catenin cascade by increasing the phosphorylation of β -
 222 catenin at the Ser552 and Ser675 residue without affecting its nuclear translocation. Moreover, it
 223 promotes EMT, stemness, migration and invasiveness. *RHBDD1* also improves the expression of the
 224 β -catenin target gene, *ZEB1*. Furthermore, the protein level of *RHBDD1* positively correlated with
 225 *ZEB1*. Thereby, *RHBDD1* has been proposed as a novel therapeutic target and/or a clinically useful
 226 biomarker for metastatic CRC (Table 1).

227 *SLC35C1*, or GDP-fucose transporter 1, is a member of the solute carrier (*SLC*) superfamily of
228 solute carriers. The Deng's group [35] explored the mechanism throughout *SLC35C1* regulates the
229 canonical Wnt/ β -catenin pathway in CRC. They demonstrated a reduction of *SLC35C1* and an
230 increase of β -catenin at all tumour stages. Indeed, silencing *SLC35C1* resulted in the increased release
231 of Wnt3a and *c-myc*, *Axin2* and *cyclin-D1* expression. This suggests that *SLC35C1* is involved in the
232 control of the canonical Wnt/ β -catenin pathway, and thereby in tumour cell proliferation and tumour
233 progression (Table 1).

234 Neuronal pentraxin 2 (*NPTX2*) is a member of the neuronal pentraxin family and is essential for
235 the formation of synapsis. *NPTX2* was found overexpressed at both mRNA and protein level in CRC,
236 particularly in metastatic lesions [36]. *NPTX2*, which was found to positively correlate with tumour
237 stages, lymphatic invasion, distant metastasis, and poor patients' outcome, promotes β -catenin
238 nuclear translocation and the expression of *c-myc*, *cyclin D1*, *Snail*, and *N-cadherin*. No *NPTX2*
239 receptors have been identified in CRC, however, its cellular internalization was found mediated by
240 the Wnt/ β -catenin receptor, *FZD6*. Additionally, it has been reported that *NPTX2/FZD6* interaction
241 translates in cancer cell proliferation and metastasis formation by triggering the Wnt/ β -catenin
242 pathway [36] (Table 1).

243 Aberrant gene expression and DNA methylation profiles are considered hallmarks of CRC
244 initiation and progression [37]. Due to the *APC* inactivating mutations, the Wnt/ β -catenin pathway
245 plays a key role in CRC metastatic spread [35][38]. Bruschi et al. [39] investigated the early
246 transcriptional and epigenetic changes resulting from *APC* inactivation in intestinal crypts in crypt
247 base columnar (*CBC*) cells. The authors have found that *APC* disruption rapidly induces changes in
248 DNA methylation, indicating that focal remodelling of the DNA methylation profile occurs early and
249 concomitantly with the first oncogenic event. Moreover, it has been demonstrated that the hyper-
250 activation of the Wnt/ β -catenin pathway associated with the *APC* loss-of-function turns out in a rapid
251 increase of intestinal stem cell commitment towards differentiation. Again, it was correlated with the
252 remodelling of the DNA methylation profile. This study unveils that early changes in DNA
253 methylation are crucial for the impaired fate decision program associated with *APC* loss-of-function.

254 The kelch-like family member 22 (*KLHL22*) is a tumour suppressor protein involved in the
255 development/progression of several cancers [40]. Low expression of *KLHL22* was found in CRC
256 tissues. *KLHL22* overexpression was associated with decreased migration, invasion and reduced
257 expression of the EMT markers, vimentin, N-cadherin, Twist1 and Snail1. Intriguingly, *KLHL22*
258 knockdown led to β -catenin and *LEF* increased expression, while *KLHL22* overexpression translates
259 into *GSK-3 β* upregulation and β -catenin downregulation [40] (Table 1).

260 Non-canonical Wnt pathway and CRC

261 The canonical and non-canonical Wnt family members play discrete roles in CRC. The activation
262 of the Wnt/calcium pathway turns into stimulation of sensitive proteins such as *CamKII* and *PKC*
263 [38][41]. A Ror family of receptor tyrosine kinases, the *ROR2* has been shown to act as a Wnt5a
264 receptor or co-receptor [42]. Wnt5a has different roles in CRC. It can act as antagonist or agonist of
265 the canonical Wnt/ β -catenin pathway, depending on the cellular context. Lee et al. [43] noticed that
266 the antagonism between the canonical and the non-canonical Wnt/ β -catenin signalling pathways is
267 linked to Wnt5a. Mechanistically, Wnt5a suppressed the canonical Wnt/ β -catenin cascade by acting
268 as ligand on the *ROR α* [42]. After *PKC α* -mediated phosphorylation, *ROR α* modifies its affinity and
269 interacts with the armadillo repeat domains of β -catenin, thus suppressing its transcriptional activity.

270 Three relevant goals have been recently achieved by Voloshanenko et al. [44] supporting the role
271 of Wnt5a/b in cell growth, via the non-canonical β -catenin pathway. First, they identified the
272 procollagen-lysine,2-oxoglutarate 5-dioxygenase 2 (*PLOD2*), the hydroxyacyl-CoA dehydrogenase
273 (*HADH*), ligand-dependent corepressor (*LCOR*) and the receptor expression-enhancing protein 1
274 (*REEP1*) as candidate genes regulated by the non-canonical Wnt/ β -catenin pathway. Second, these
275 genes were found regulated by Wnt5a/b, as well as by *ROR2*, the *DVL2*, the activating transcription
276 factor 2 (*ATF2*) and *ATF4* in a non-canonical Wnt/ β -catenin independent manner. Lastly, Wnt5a/b
277 silencing was found to impair cancer cell proliferation.

278 Among several soluble Wnt proteins, Wnt11 was found upregulated in CRC patients [45].
279 Recently, Gorroño-Etxebarria and colleagues [46] have shown that increased Wnt11 and its *FZD6*,
280 *RYK*, *PTK7* receptors, positively correlate with poor prognosis. Additionally, Wnt11 downregulated
281 β -catenin transcriptional activity and increased *ATF2* via the non-canonical Wnt signalling pathway.
282 Thereby, Wnt11 has been proposed as a prognostic biomarker and therapeutic target in CRC patients.

283 Tumour micro environment (TME) has a pivotal role in cancer development [47]. Liu et al.[48]
284 reported that, unlike CRC cells, tumour associate macrophages (TAMs), and in particular M2-like
285 cells express Wnt5a. Furthermore, it has been shown that Wnt5a positive TAMs regulate
286 macrophages infiltration, tumour cell proliferation and migration. Wnt5a pro-tumour activity was
287 found associated with the overexpression of the C-C motif chemokine ligand 2 (*CCL2*) in Wnt5a-
288 treated macrophages. Consistently, Wnt5a knockdown reduced *CCL2* expression in TAMs and their
289 cancer-promoting activity. In Wnt5a-treated macrophages both *CaMKII* and ERK1/2 undergo
290 phosphorylation and lead to *CCL2* secretion. This study provided evidence for a new role of Wnt5a
291 in CRC and describes a potential novel therapeutic target (Table 1).

292 BREAST CANCER

293 Breast cancer (BC) is the most diagnosed cancer in women [46][49], the first cause of cancer death
294 in women worldwide [47][50], and one of the most expensive health care cost [46][49]. Both the
295 canonical and non-canonical Wnt/ β -catenin pathways are essential for mammary gland development
296 [51] and for BC growth and dissemination [52]. Hyper-active Wnt/ β -catenin was reported in breast
297 tumours [50][53]. In human BC, elevated intracellular β -catenin level has been associated with high
298 tumour grade [54] and poor prognosis. Moreover, up to 90% of metaplastic carcinomas and non-
299 metastasizing fibromatosis have been associated with the highest β -catenin expression level [55].
300 Moreover, proteins such as Wnt3a [56] and xenopus frizzled 7 (*Xfz7*) [57] have been involved in the
301 activation of both the canonical and the non-canonical Wnt signalling pathways.

302 Canonical Wnt pathway and BC

303 Dysregulation of the Wnt/ β -catenin cascade has been associated with cancer initiation and
304 metastasis formation [56][58]. Moreover, high β -catenin expression has been reported in basal-like
305 BC subtype [50][53]. Additionally, it has been demonstrated that loss of secreted frizzled-related
306 protein 1 (*sFRP1*) is an early event in BC patients and is associated with poor prognosis [59].
307 Furthermore, the activation of the Wnt/ β -catenin cascade has been associated with radio resistance
308 of progenitor cells. Thereby, the Wnt/ β -catenin pathway has been proposed as a target to harm the
309 self-renewal potential of stem/progenitors [60].

310 A recent study demonstrated that high β -catenin level is associated with miR106a
311 overexpression and involved in BC cell growth. Additionally, high level of miR106a was reported to
312 reduce cisplatin sensitivity. Major results were obtained exploiting the Wnt inhibitor, FH535. In fact,
313 FH535 treatment reduced the expression of β -catenin, *cyclin D1*, *c-myc* and *Ki67*, impaired tumour
314 growth and induced apoptosis [61].

315 In a different study [62], the impact of the Wnt/ β -catenin canonical pathway in cisplatin
316 resistance was investigated by silencing β -catenin via small interfering RNA (siRNA). The authors
317 demonstrated that upon β -catenin silencing, the cells become more sensitive to cisplatin treatment.
318 These effects were associated with the increased expression of the apoptotic proteins caspase 3/9.

319 A recent study demonstrated that miR-5188, aberrantly expressed in breast cancer patients,
320 positively correlates with poor prognosis. The molecular analyses revealed that miR-5188 directly
321 targets the forkhead box protein O1 (*FOXO1*). In physiological setting, *FOXO1* binds β -catenin and
322 induces its degradation. This implies that miR-5188 overexpression leads to β -catenin nuclear
323 accumulation and transcription of its downstream target genes, mainly involved in EMT, tumour cell
324 proliferation, metastasis formation and chemo resistance. Moreover, the authors elegantly showed
325 that miR-5188 expression is under the control of c-Jun, which directly binds to its promoter region.
326 This on turn generates a positive loop accelerating tumour progression. Clinically, miR-5188 has been
327 proposed as a diagnostic or prognostic factor and/or a direct target for anti-cancer therapy [63].

328 The upregulation of the lncRNA *hoxa* transcript at the distal tip (*HOTTIP*) has been also linked
329 to poor prognosis in BC patients. Overexpression of *HOTTIP* correlates with the expansion of breast
330 CSCs (BCSCs) and the expression of the stem cell markers, *OCT4* and *SOX2*. Han et al. [64]
331 demonstrated a reduced expression of differentiation markers, such as *CK18* and *CK14* and that miR-
332 148a inhibits BC cell migration and invasion by directly targeting *Wnt1*. Moreover, it has been
333 reported that *HOTTIP* controls miR-148a-3p by acting as a competing endogenous RNA (ceRNA).
334 Thereby, *HOTTIP* promotes expansion of CSCs *in vitro* and tumorigenesis *in vivo* by regulating the
335 miR-148a-3p/*Wnt1*/ β -catenin axis [64]. These data are summarized in Table 2.

336 The *LGR4* was identified as a prognostic marker in breast tumours displaying poor prognosis
337 [65]. A tight molecular interplay between *LGR4* and *Wnt*/ β -catenin signalling has been reported to
338 control stemness. Indeed, *LGR4* binding to the soluble R-spondin proteins eases the *Wnt*/ β -catenin
339 cascade [64][66]. Previous studies have proven that upregulation of *ZEB1* by *SLUG* (the protein
340 product of *SNAI2*), increased EMT [67]. As a matter of fact, *LGR4* knockdown leads to *SLUG* and
341 *ZEB1* downregulation, thereby impairs invasion and metastasis [68]. A correlation with poor
342 outcome and the expression of the *LGR4* homolog *LGR5* was also reported. *LGR5* maintains the pool
343 of BCSCs and promotes tumour progression and invasiveness by activating the *Wnt*/ β -catenin
344 canonical pathway [68] (Table 1).

345 Wang et al. [69] first demonstrated that the expression of the suppression of tumorigenicity 7
346 like (*ST7L*) is downregulated in BC cells, and more importantly, that *ST7L* acts as an antitumor
347 supervisor by reducing *GSK-3 β* phosphorylation and inducing β -catenin degradation. However, the
348 mechanisms through which *ST7L* controls *GSK-3 β* phosphorylation is still missing (Table 1).

349 A recent study [70] reported the overexpression of the transmembrane emp24 domain (*TMED*)
350 in BC and its correlation to poor prognosis. Aberrant level of *TMED* boosts cell cycle progression,
351 colony formation, migration and invasion and the expression of *CDK2*, *CDK4*, *CDK6*, cyclin E, β -
352 catenin, *cyclin D1*, *c-myc*, *MMP-7* and *TCF4*. Conversely, silencing *TMED3* drastically reduced
353 migration and invasion. Moreover, the observation that β -catenin knockdown translates in the
354 reduction of its regulated genes supports the notion that the oncogenic effect of *TMED* goes through
355 the *Wnt*/ β -catenin pathway (Table 1).

356 Cryptotanshinone (CTS) is an herbal medicine derived from roots of *salvia miltiorrhiza* which
357 displays anti-tumour properties. It has been shown that *in vitro* CTS reduces tumour cell growth,
358 migration and invasion by downregulating the pyruvate kinase muscle isozyme M2 (*PKM2*), a
359 protein involved in glycolysis, and more importantly in β -catenin activation [71].

360 **Wnt non-canonical pathway and BC**

361 Among the *Wnt* ligands, the most extensively studied ligand, activating the β -catenin
362 independent pathway, is *Wnt5a*. However, its different biological actions are enlightened by the
363 observation that it can also initiate the canonical β -catenin signalling cascade [70][72].

364 *Wnt5a* is an evolutionarily conserved *Wnt* ligand, which plays an important role in
365 developmental processes. *Wnt5a*^{-/-} knockout mice showed perinatal lethality, due to developmental
366 defects [73].

367 In tumorigenesis, *Wnt5a* signalling is central and displays multiple intriguing and opposite roles
368 mainly acting as a β -catenin antagonist. These data are discussed.

369 The *Wnt5a* suppressive properties detected in tumours connoted by β -catenin hyper-activation
370 has been linked to the shift towards the stimulation of the β -catenin independent signalling pathway.

371 Foxy5 is a *Wnt5a* mimicking hexapeptide able to decrease BC cell migration and invasion [74].
372 More recently Prasad et al. [75] confirmed these data and added new information on the role of *Wnt5a*
373 in the regulation of the expression of the phosphofructokinase platelet-type (*PFKP*). They have shown
374 that low *PFKP* level correlates to cancer cell migration and poor patients' survival. The growth and
375 expansion of tumour cells also rely on glucose consumption resulting in the accumulation of lactate.
376 Cancer cell metabolism was also associated with β -catenin activation [76]. At this regard, it has been
377 shown that *Wnt5a* affects the aerobic glycolysis by inhibiting the activation of β -catenin. Therefore,
378 an onco-suppressive role was proposed for *PFKP*.

379 According to the study of Borcherding et al. [77], Serra Roarty et al. [76][78] demonstrated that
380 the paracrine activity of Wnt5a suppresses the expression of both β -catenin and *cyclin D1*. The authors
381 have shown that Wnt5a supports TGF- β -mediated tumour suppressive functions by antagonising
382 Wnt/ β -catenin signalling and limiting tumour cell proliferation.

383 Moreover, Leris and colleagues [79] proved that Wnt5a mRNA level was significantly lower in
384 tumour than in normal tissues, particularly in those displaying a more aggressive behaviour. Again,
385 this observation has suggested a suppressive role of Wnt5a in cancers. It has been also reported that
386 loss of Wnt5a associates with a higher histological tumour grade, increased risk of recurrence, and a
387 shorter recurrence-free survival in invasive BC [80] (Table 1).

388 On the contrary, Kobayashi et al. [81] reported that Wnt5a is expressed in ER-positive BC cells
389 and positively associates to vessel invasion, tumour size and migration. Mechanistically, Wnt5a
390 induces the expression of the activated leukocyte cell adhesion molecule (*ALCAM*), a protein
391 involved in migration and invasion. Knockdown of either Wnt5a or *ALCAM* inhibited tumour cell
392 migration, confirming the role of the Wnt5a/*ALCAM* axis in the migratory phenotype of ER-positive
393 BC (Table 1).

394 A relevant role of Wnt5a in reprogramming the TME was also described [82]. It has been shown
395 that under pro-inflammatory conditions the non-canonical Wnt protein induces the expansion of the
396 CD163(+) immunosuppressive macrophages translating in the release of IL-10 and the inhibition of
397 the classical TLR4-NF- κ B signalling pathway [82].

398 Moreover, higher level of Wnt5a was found in human monocyte-derived myeloid dendritic cells
399 (Mo-mDCs) than in normal monocytes and macrophages. Wnt5a was found to inhibit the generation
400 of Mo-mDCs by stimulating BC cells to produce IL-6. In addition, the presence of IL-6 in the
401 conditioned media of Wnt5a stimulated BC cells was found involved in the inhibition of Mo-mDC
402 differentiation [83]. Consistently, overexpression of Wnt5a mRNA was detected in metastases
403 derived from primary BC cells and in BC cell lines [84].

404 Wnt5a signalling is also able to modify the CD44-AKT signalling pathway, leading to a reduced
405 BC cell migration and invasion. In epithelial BC cells, silencing of Wnt5a drives EMT-like changes
406 without altering the expression of common EMT markers. On the contrary, it interferes with CD44
407 expression and induces pAKT downregulation, thereby acting via a EMT-independent mechanism
408 [85].

409 The dual activity of Wnt5a has been also ascribed to the Wnt5a isoforms. Bauer et al. [86] have
410 shown that the Wnt5a gene encodes for two distinct isoforms: the Wnt5a-long (*Wnt5a-L*) and Wnt5a-
411 short (*Wnt5a-S*) isoform. When analysed in several cell lines *Wnt5a-L* reduced tumour progression,
412 while *Wnt5a-S* promoted tumour growth.

413 Overall, Wnt5a may play multiple roles. Whether it acts as a tumour suppressor or a tumour
414 promoter remains elusive and depends on the availability of essential receptors, the TME, and the
415 activation of discrete signalling pathways.

416 TRIPLE-NEGATIVE BREAST CANCER

417 Triple-Negative Breast Cancer (TNBC) is an invasive type of breast carcinoma that lacks the
418 expression of estrogen and progesterone receptor as well of the human epidermal growth factor
419 receptor 2 (HER2) [87] and accounts from 10 to 15% of all BC [88].

420 TNBC patients have poor outcome due to the high grade of proliferation, early tumour
421 dissemination, and the lack of targeting approaches [89,90]. The malignancy is associated with earlier
422 age of onset, aggressive clinical course, and dismal prognosis [88]. TNBC gained attention due to the
423 aggressiveness and the lack of effective treatment options. Therefore, the most relevant data on this
424 breast cancer subtype are independently discussed.

425 Gene expression omnibus (GEO) databases were applied by Shen et al. [91] to gather gene
426 expression data in TNBC patients who underwent chemotherapy. They reported that co-expression
427 of NIMA-related kinase 2 (*Nek2*) and β -catenin correlated with patients' poor prognosis. β -catenin
428 binds to and is phosphorylates by the *Nek2B* isomer. Thereby, in TNBC, *Nek2B* functions as a β -
429 catenin regulator by activating the Wnt signalling pathway and its downstream target genes. In

430 addition, it has been suggested that *Nek2B* and β -catenin may synergize to promote resistance to
431 chemotherapy. However, further studies are required to better elucidate the relationship between β -
432 catenin and *Nek2* and its possible implications in cancer development (Table 1).

433 TNBC aggressiveness also relies on the activation of the non-canonical Wnt/PCP pathway.
434 Indeed, the aberrant activation of downstream genes activated by the non-canonical Wnt/PCP
435 pathway has been implicated in tumour growth and poor prognosis. Results from Puvirajesinghe
436 and colleagues [92] revealed that van gogh-like 2 (*VANGL2*), a core Wnt/PCP component, plays a
437 crucial role in cancer cell migration, anchorage-dependent and independent cell proliferation, as well
438 as in tumour growth. Since, the scaffold p62/SQSTM1 protein, a *VANGL2*-binding partner, has a key
439 role in *VANGL2*-p62/SQSTM1-*JNK* pathway, the possibility to exploit p62/SQSTM1 as a potential
440 therapeutic target has been proposed. This would be of particular relevance since the *JNK* targeting
441 approaches are associated with major side effects in clinical setting (Table 1).

442 Yu and colleagues [93] demonstrated that the hematopoietic protein tyrosine phosphatase
443 (*HePTP*) stabilizes β -catenin in the cytoplasm and allows its nuclear translocation by regulating the
444 phosphorylation of *GSK-3 β* . This results in the transcriptional activation of target genes leading to
445 cell migration and invasion. Since knockdown of *HePTP* significantly suppresses metastases formed
446 by TNBC cells, *HePTP* has been also proposed for therapeutic approaches in TNBC (Table 1).

447 Recently, Kong et al. [94] have shown that a Rho-GTPase-activating protein, the deleted in liver
448 cancer gene 3 (*DLC-3*), is downregulated in TNBC and its expression is linked to lymphatic
449 metastases. *DLC-3* overexpression leads to β -catenin and *c-myc* downregulation as well as in reduced
450 *in vitro* cell proliferation, colony formation, migration, and invasion. Hence, a tumour-suppressor
451 role related to the inhibition of the Wnt/ β -catenin signalling pathway has been postulated (Table 1).

452 Liu and colleagues [95] have reported a low expression of miR-6838-5p in TNBC compared to
453 normal cells. miR-6838-5p overexpression reduced cell invasion, migration, EMT, β -catenin, *c-myc*
454 and *cyclin D1* expression by post-transcriptionally controlling Wnt3a expression.

455 Recently, miR-27a-3p was found overexpressed in tumour cells and linked to poor prognosis in
456 TNBC patients. miR-27a-3p leads to the activation of Wnt/ β -catenin cascade and enhances cell
457 proliferation and migration by directly targeting the 3'-UTR region of *GSK-3 β* [96] (Table 2).

458 OVARIAN CANCER

459 Ovarian Cancer (OC) is a global issue representing the fourth most common cancer in the female
460 population, particularly in developed countries [97]. The poor survival rate is mainly due to the lack
461 of screening methods at the early stages along with the absence of effective treatment options for
462 advanced stages [96][98]. Among different OC subtypes, the epithelial subtype (EOC) holds about
463 90% of the overall ovarian malignancies [97][99].

464 Canonical Wnt pathway and OC

465 Wnt/ β -catenin signalling pathway play a crucial role in carcinogenesis of all OC subtypes
466 [98][100]. In particular, several transcription factors, proteins and miRNAs acting on this pathway
467 have been explored [99][101].

468 Chen and co-workers [102] investigated the role of the Wnt/ β -catenin pathway antagonist
469 dickkopf-related protein 1 (*DKK1*). They showed that *DKK1* is involved in the control of OC stemness.
470 Mechanistically, it has been shown that STAT3 directly activates the transcription of miRNA-92a,
471 translating in *DKK1* downregulation [102]. Moreover, overexpression of miR-1207 was found to
472 correlate with high nuclear β -catenin level [103]. Wu et al. [103] investigated the effects of miR-1207
473 on the expression of the *SFRP1*-*AXIN2* and the inhibitor of β -catenin and T cell factor 4 (*ICAT*). They
474 found that miR-1207 overexpression was associated with a reduced *SFRP1*-*AXIN2* and *ICAT*
475 expression and the appearance of a stem-like phenotype (Table 1).

476 Salem et al. [104] proved that miR-590-3p promotes OC growth and metastasis, by targeting
477 *FOXA2*. Moreover, it has been shown that miR-590-3p upregulation significantly increase cell
478 growth, migration, and invasion in EOC cells, both *in vitro* and *in vivo* [105]. Similarly, *FOXA2*, which
479 exhibits suppressive activity on EOC cells, has been identified as a miR-590-3p target [105]. The cyclin

480 G2 gene (*CCNG2*) has been also reported to display several repressive actions on EOC-derived
481 tumour cell lines. It inhibits cell proliferation, migration, invasion and EMT. Thereby, since miR-590-
482 3p post-transcriptionally regulates *FOXA2*, *FOXO3*, *CCNG2* and *DDK1* expression, miR-590-3p has
483 been proposed as a potential target in EOC patients [105]. A crucial role of *SFRP1* in OC growth has
484 been also proposed. Since miR-1180 is highly expressed in neoplastic tissues, Hu et al. [106] explored
485 the relationship between miR-1180 and the *SFRP1*/Wnt/ β -catenin signalling pathway in this context,
486 demonstrating that miR-1180 triggers the activation of the Wnt/ β -catenin cascade by targeting *SFRP1*.

487 The members of the R-spondin ligand family have been reported as positive effectors of the
488 Wnt/ β -catenin signalling [107]. *LGR4-6* plays crucial roles in the activation of the Wnt/ β -catenin
489 cascade [107,108]. Moreover, Ruan et al. [107] have reported that LGR6 induces stemness and chemo
490 resistance via the Wnt/ β -catenin pathway in OC cells. Restrain of the stem phenotype and increased
491 sensitivity to chemotherapy have been proved by *LGR6* silencing (Table 1).

492 A recent study established that the overexpression of the Rab GTPase family member, *Rab14*,
493 regulates *GSK-3 β* phosphorylation and β -catenin nuclear accumulation [109,110]. Moreover, high
494 level of *Rab14* was found associated with higher expression of Wnt/ β -catenin target genes including
495 *MMP-7* and *c-myc* [110](Table 1).

496 Jiang et al. [97] have demonstrated that tetrandrine (TET) enhances the anti-tumour effect of
497 paclitaxel (PTX) by decreasing *c-myc* and *cyclin D1* and increasing p21 expression, resulting in cell
498 cycle arrest. The pro-apoptotic effects of PTX+TET have been also investigated. TET was found to
499 inhibit β -catenin downstream target genes by enhancing PTX activity and conferring sensitivity to
500 PTX in resistant cells [97].

501 Barghout and co-workers [111] demonstrated a more active Wnt/ β -catenin signalling in
502 carboplatin-resistant cells than in sensitive ones. Unlike the Wnt ligands, the negative Wnt regulators
503 *DKK1*, *SFRP1*, and the *FRZB* have been found downregulated in cisplatin-resistant cells. These
504 findings suggest that Wnt/ β -catenin blockade may be effective on resistant EOC.

505 Non-canonical Wnt pathway and OC

506 The *FZD7* is highly expressed in OC [112] and its overexpression in mesenchymal (Mes) and
507 Stem-A OC subtypes, has been associated with the induction of EMT. The PCP pathway, which
508 activates the *Rho-ROCK* axis, was found involved in the activation of actomyosin contractility,
509 cadherin-based cell-cell adhesion and migration, while the Wnt/calcium pathway in the metastatic
510 spread and cytoskeleton changes in this clinical setting [112]. Therefore, it has been proposed that the
511 *FZD7* controls both cell cycle progression and cell migration via the non-canonical Wnt/PCP pathway
512 (Table 1).

513 The integrin beta like 1 subunit (*ITGBL1*) was found highly overexpressed in OC [113]. It has
514 been shown that *ITGBL1* promotes cell migration and adhesion via Wnt/PCP, *RhoA*, the focal
515 adhesion kinase, and the steroid receptor coactivator (*FAK/src*) pathway (Table 1).

516 The *PTK7* which interacts with *Wnt5A*, *LRP6* and *FZD7* [114,115] may act as tumour suppressor
517 or oncogene [116,117]. In EOC, *PTK7* downregulation is indeed associated with a poor prognosis
518 [116].

519 Luo and colleagues [118] have investigated the role of the alkaline phosphatase (*ALPL*) in OC.
520 They demonstrated that *ALPL* overexpression inhibits EMT, migration and invasion of high grade
521 serous OCs (HGSOC) and *FZD2* correlates with a poor survival rate [118]. Mechanistically they have
522 shown that *ALPL* overexpression represses *Wnt5a/FZD2*-mediated EMT activation possibly by
523 interfering with *STAT3* activation [118] (Table 1).

524 WNT PATHWAY AND OTHER CANCERS

525 Glioma is an aggressive tumour of the nervous system displaying rapid progression and poor
526 prognosis. Zhao et al. [119] have found that overexpression of β -catenin and *cyclin D1* is associated
527 with high level of the long noncoding RNA, *FGD5* antisense RNA 1 (lncRNA *FGD5-AS1*). A close
528 relationship between them was straitened by the observations that inhibition of *FGD5-AS1* reduced

529 β -catenin and *cyclin D1* expression while β -catenin downregulation decrease lncRNA FGD5-AS1
 530 expression. This results in the impaired tumour cell migration and invasion.

531 Prostate cancer (PCa) is among the most common tumour in male. A recent study by Situ et al.
 532 [120] provided evidence for the involvement of the microRNA-939 (miR-939) in PCa. Downregulation
 533 of miR-939 was found in tumour tissues at advanced tumour stage, in distant lesions as well as
 534 associated with poor prognosis. Molecularly, it was demonstrated that miR-939 upregulation
 535 interferes with the Wnt/ β -catenin cascade by directly targeting the hepatoma-derived growth factor
 536 (HDGF).

537 Osteosarcoma (OS) is a common bone paediatric tumour displaying high rate of lung metastasis.
 538 The inhibition of β -catenin activation, metastasis formation and chemo-resistance were found
 539 modulated by tegavivint (a Wnt/ β -catenin inhibitor) which has been proposed as an alternative
 540 therapeutic option in OS [121].

541 Melanoma is among the most immunogenic tumours displaying increased lymphocytic
 542 infiltration. Low $1\alpha,25$ -dihydroxyvitamin D3 and vitamin D receptor (VDR) level correlates to
 543 increased cancer incidence and melanoma progression, respectively. Recently, it has been shown that
 544 high VDR expression correlated with the inhibition of tumour growth, low Wnt/ β -catenin activation
 545 and the induction of the immune response [122] (Table 1).

546 The long non-coding RNA00261 (Linc00261) has been shown to display onco-suppressor
 547 properties in Pancreatic Cancer (PC). Linc00261 overexpression inhibits PC cell proliferation,
 548 invasion, EMT and metastasis. Bioinformatics analysis revealed that Linc00261 inhibits the activation
 549 of the β -catenin/TCF4 cascade and the metastatic spread by regulating the miR-552 5p/FOXO3 axis
 550 [123].

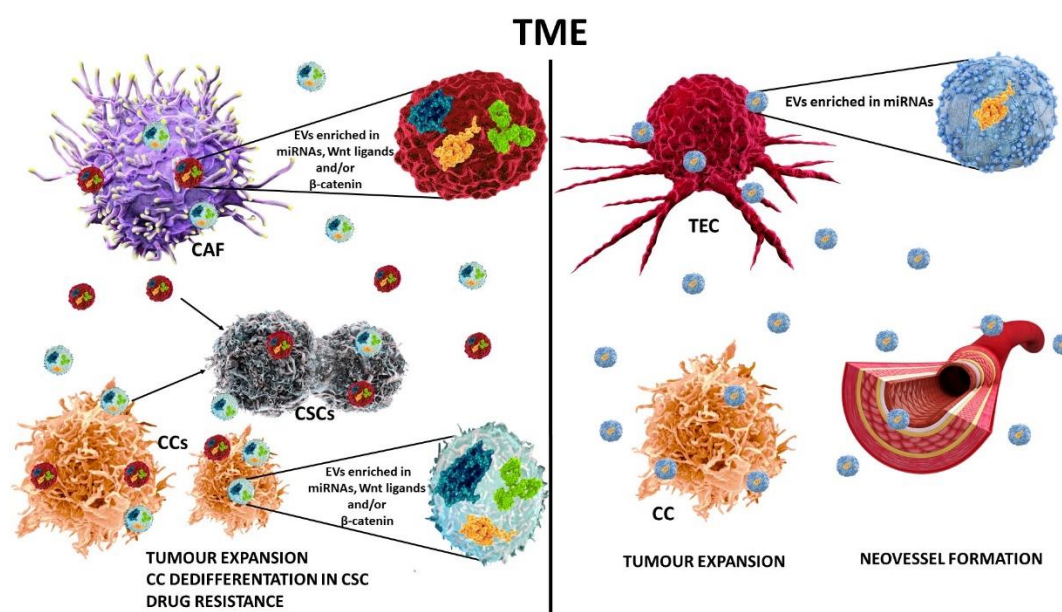
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552 EXTRACELLULAR VESICLES AND THE WNT PATHWAY

553 EVs are heterogeneous small membrane-bound carriers with complex cargoes released under
 554 both physiological and pathological conditions. Almost any cell can release EVs, which act as inter-
 555 cellular mediators modifying target cell fate at closed or distant sites [121][124].

556 Based on the biogenesis, size, content, mechanisms of release and function, three discrete EV
 557 subtypes are recognized: microvesicles (MVs), exosomes, and apoptotic bodies [121][124].

558 EVs-mediated transfer of specific molecules are known to dictate the phenotype of the recipient
 559 cell. They can act on proliferation, motility, EMT, migration, invasion, immune evasion, chemo-
 560 resistance, and TME reprogramming (Figure 3).



561

562 **Figure 3. Schematic representation of cell-to-cell communication in the TME by EVs.** EVs are
 563 released by almost all cell types in the TME. EVs serve as inter-cellular mediators transferring specific
 564 molecules (proteins including Wnt ligands and β -catenin, and miRNAs) to recipient cell thus
 565 promoting tumour expansion, cancer cell dedifferentiation in CSCs, chemo-resistance, and neovessel
 566 formation. CCs: cancer cells; CSCs: cancer stem cells; TEC: tumour-derived endothelial cell; CAF:
 567 cancer associated fibroblasts.

568 Moreover, EVs derived from serum or other biological fluids have been proposed as tumour
 569 biomarkers. More importantly, EVs have gained attention as anti-cancer tools. Indeed, EVs can be
 570 used as drug delivery systems or potential cancer vaccines. Moreover, the transfer of Wnt ligands or
 571 β -catenin via EVs has been proposed as a Wnt signalling activation mechanism.

572 Kalra et al. [125] have shown that EVs released by CRC cells and containing the mutant β -catenin
 573 and high Wnt/ β -catenin activity boost the expression of target genes as *c-myc* and *cyclin D1* when
 574 transferred to recipient cell (Table 43).
 575

576 **Table 3. EVs involved in several tumours, their alteration, targets, and impact on tumours**

EV CARGO	EV SOURCE	TARGET CELLS	RELATED CANCERS	EXPRESSION LEVEL	PATHWAY INTERACTION	IMPACT ON TUMOUR CELLS	REF.
Mutant β -catenin in EVs	LIM1215	RKO	CRC	Upregulated	β -catenin	migration, metastasis tumour growth	[125]
14-3-3 ζ in EVs	HEK293T	COS-7, SW480	CRC	Upregulated	β -catenin GSK-3 β DVL2	survival migration	[126]
Wnt ligands in EVs	CAFs	CRC	CRC	Upregulated	β -catenin	dedifferentiation drug resistance colony formation	[127, 128]
β -catenin in EVs	milk	HCC	HCC	Silenced	β -catenin	proliferation tumour growth	[131, 132]

DKK-1 in EVs	MM	MM	MM	Upregulated	β -catenin	osteoclast activity osteoblast differentiation	[133]
EVs	OSCC	OSCC	OSCC	Upregulated	β -catenin	metastasis stemness chemoresistance	[135]
Wnt5b in EVs	Caco-2 and PANC-1	A549	Lung cancer	Upregulated	β -catenin dependent and independent pathways	proliferation migration	[137]
EVs	CAFs	BC	BC	Upregulated	Wnt-PCP	cell growth and motility	[138]

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The 14-3-3 are conserved molecules displaying regulatory functions and promoting cancer progression [126]. The 14-3-3 ζ isoform which binds both β -catenin and GSK-3 β , leads to the nuclear translocation and accumulation of β -catenin and enhance cell motility. Moreover, EVs enriched in 14-3-3 ζ and β -catenin, after internalization, promote cell survival and migration by activating the Wnt/ β -catenin cascade [126] (Table 43).

Hu et al. [127] have investigated the mechanism of drug resistance in CRC and have proven that EVs released by fibroblasts drive dedifferentiation of CRC cells towards CSCs (Figure 3a). Additionally, they found that EVs derived from fibroblasts contain the Wnt ligands which activate the Wnt/ β -catenin pathway in target cells, induce transdifferentiation of CRC cells into CSCs and increase drug resistance. Furthermore, it has been reported that collagen accumulation and the APC mutation in CRC cells stimulate the release of EVs and, under hypoxia conditions, fibroblast derived EVs boost CRC colony formation [128] (Table 43).

Accumulating evidence shows that EVs enriched in miRNAs are key determinants of human cancer cell growth, invasion and metastasis [129][129]. CAF-derived EVs enclose miR-92a-3p which contribute to cancer progression, stemness, EMT, and drug resistance. Moreover, miR-92a-3p enriched EVs correlated with the activation of the Wnt/ β -catenin pathway [129] (Figure 3a).

Long non-coding RNA-APC1 (lncRNA-APC1) is a negative regulator of CRC. Low level of lncRNA-APC1 correlates with metastasis, advanced clinical stage and poor prognosis in CRC patients. APC, via lncRNA-APC1 promotes cell-cycle arrest and suppresses angiogenesis by lowering the release of CRC cell-derived EVs. Finally, it has been shown that EV-derived from CRC are enriched in Wnt1 and enhance CRC cell proliferation and migration via the non-canonical Wnt/PCP signalling [130].

Hepatocellular carcinoma (HCC) is one of the most common cause of cancer-related deaths worldwide. Constitutive activation of the Wnt/ β -catenin pathway turns into the expression of the epithelial cell adhesion molecule (*EpCAM*) [131]. Ishiguro et al. [132] provided evidence that loss in β -catenin and reduced proliferation and invasion can be obtained by *EpCAM* positive liver cancer stem cells (LCSC) targeted by EVs engineered with a β -catenin specific siRNA (Table 43).

Multiple myeloma (MM) is a hematopoietic malignancy associated with an altered homeostasis of bone formation/resorption. MM-derived EVs enriched in *DKK-1* were found to boost the Wnt/ β -catenin signalling and contribute to the abnormal osteogenesis. The inhibition of EV shedding

608 combined to chemotherapy were found to impair tumour load, angiogenesis and osteolysis [133]
609 (Table 43).

610 Furthermore, a recent study noticed that the release of EVs from HCC cells is increased in
611 hypoxic conditions and linked to cancer cell proliferation, migration, invasiveness and EMT.
612 Mechanistically they have shown that miR-1273f enriched in EVs activates the Wnt/ β -catenin
613 signalling cascade by targeting the Wnt/ β -catenin inhibitor LHX6 [134].

614 Chen et al. [135] proved that EVs released from oral squamous cell carcinoma (OSCC) cells
615 correlate with the increased level of β -catenin, the expression of several oncogenic markers, the
616 reprogramming of normal gingival fibroblasts into CAFs, the increased metastasis, stemness
617 reprogramming, chemoresistance, and patients' poor survival (Table 43).

618 Xia et al. [136] have demonstrated the uptake of EVs and the delivery of functional miRNAs in
619 different cell lines. The exosomal-miR-1260b was found crucial for the activation of the Wnt/ β -catenin
620 signalling and the invasiveness of lung adenocarcinoma cells.

621 Harada et al. [137] purified and characterized Wnt5b-associated EVs. In pancreatic PANC-1 and
622 colorectal Caco-2 cell lines Wnt5a carried by EVs displays the ability to enhance cancer progression
623 (Table 43).

624 Luga et al. [138] demonstrated that EV shedding by fibroblasts boosts BC cell growth and
625 motility via the Wnt/PCP signalling. CAF-derived EVs were found crucial drivers of cell migration
626 during metastasis formation. Moreover, they found that EVs secreted from fibroblast L cells promote
627 the autocrine Wnt11-PCP cascade in tumour cells increasing their motility and metastatic properties
628 (Table 43).

629 Lombardo et al. [139] provided evidence that EVs released by tumour-derived endothelial cells
630 (TECs-EVs) boost *in vivo* TEC-derived neovessels. Mechanistically they showed that EV released by
631 naive TECs-EVs regulate the expression of *APC*, *GSK-3 β* and drive β -catenin nuclear accumulation
632 via miR-214-3p and miR-24-3p (Figure 3b). Overall, this study revealed a key role of the Wnt/ β -
633 catenin cascade in TEC-derived neovessel formation. Moreover, they recently showed that naive
634 TEC-EVs were also able to boost TNBC metastatic spread and lung metastasis formation when
635 injected intravenously [140] (Table 2).

636 Overall these data indicate a crucial contribute of EVs released by different cell sources in
637 driving tumor development and dissemination. Several data suggest that these effects mainly rely on
638 the transfer of their specific cargo into target cells. Therefore, approaches able to modify their cargo,
639 particularly miRs and proteins involved in their tumor promoting action, have been proposed as
640 useful therapeutic options. EV engineering by using siRNA for mutated protein has been tested and
641 their effectiveness demonstrated in pancreatic cancer [141]. This suggests that using siRNA for
642 mutant β catenin should be considered as an alternative option for CRC. Likewise, siRNA for
643 different Wnt proteins or rearrangement of dysregulated EV miRs can be used to targeting the Wnt/ β
644 catenin cascade. Alternatively, EVs loaded with Wnt/ β catenin inhibitors can be used as naturally
645 delivery tools.

646 CONCLUSIONS

647 Cell-to cell communication is part of the evolutionary processes. Wnt ligands are essential for the
648 homeostasis and in the last 30 years genetic, biochemical, and molecular investigations have
649 uncovered several Wnt signalling components [2,3]. Driving interest on this topic mainly relies on
650 dysregulation of the Wnt/ β -catenin signalling and cancer development/progression [3]. Moreover,
651 Wnt/ β -catenin cascade seems to contribute to the TME shape, which play a crucial role in the control
652 of tumour progression and immune regulation. Many different Wnt proteins have been described,
653 and among them Wnt5a, plays a critical role taking part in both the canonical and the non-canonical
654 Wnt/ β -catenin pathway [77,78].

655 The identification of specific tools able to interfere with the Wnt/ β -catenin cascade has been a
656 hotspot for many years. This is particularly true for CRC, in which almost 70% of CRC patients
657 display *APC* mutations [15]. Apart from CRC, the Wnt/ β -catenin pathway is gaining attention in
658 several malignancies, such as breast, ovarian, melanoma, prostate and paediatric osteosarcoma [117–

659 119]. At this regard, BC and in particular TNBC are featured by the abnormal activation of both the
660 canonical and non-canonical Wnt/ β -catenin pathway [89,90]. Likewise, a hyper-active Wnt/ β -catenin
661 cascade has been shown to play a crucial role in the progression, stemness, and drug resistance in OC
662 [101,105]. Several miRNAs have been identified to modulate this cascade and thereby widely studied
663 as screening markers or targets in different tumour settings [142].

664 In the TME, intercellular communication has been recently reported as mediated by the transfer
665 of EV molecular cargo and revised in [143]. Their cargo also includes a number of Wnt components.
666 Of note, wild-type and mutant β -catenin able to promote survival and proliferation of recipient cell
667 and, in several instance dedifferentiation towards a CSC phenotype, have been detected in EVs
668 (Figure 3a). Moreover, their role in mediating drug resistance has been reported. Furthermore, since
669 EVs are released within the TME their contribute in cancer growth and progression has been
670 extensively investigated [144]. EV shedding, blockade, or engineering have been proposed as
671 innovative anti-tumour instrument to fine-tuning the Wnt/ β catenin pathway [142,145].

672 In the last decades several efforts have been directed to the development of Wnt/ β catenin
673 targeting approaches in order to interfere with tumour progression. However, these efforts have been
674 limited by the crucial role of the Wnt/ β catenin pathway in preserving tissue homeostasis. Therefore,
675 future energies should be directed to clearly dissect the mechanisms driving the unbalanced Wnt/ β
676 catenin pathway in cancer, and EV mechanism of action should be considered amid them. Should
677 identified, targeting approaches would become a suitable anti-cancer option.

678 **Acknowledgments:** This work has been supported by grants obtained by MFB from the Associazione Italiana
679 per la Ricerca sul Cancro (AIRC) project IG 2015.17630, and by grants obtained by MFB from Ministero
680 dell'Istruzione, Università e Ricerca (MIUR) ex 60%.

681 **Author Contributions:** MK: contributes to data curation and writing the original draft; VP: contributes to data
682 curation and writing the original draft; MFB: contributes to writing, visualization, founding and editing the Ms.

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