

Wnt Signaling Pathway Is among the Drivers of Liver Metastasis

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Abstract: Liver metastasis, originating either from a primary liver or other cancer types, represent a large cancer-related burden. Therefore, studies that add to better understanding of its molecular basis are needed. Herein, the role of the Wnt signaling pathway in liver metastasis is outlined. Its role in hepatocellular carcinoma (HCC) epithelial-mesenchymal transition (EMT), motility, migration, metastasis formation, and other steps of the metastatic cascade are presented. Additionally, the roles of the Wnt signaling pathway in the liver metastasis formation of colorectal, breast, gastric, lung, melanoma, pancreatic, and prostate cancer are explored. The special emphasis is given to the role of the Wnt signaling pathway in the communication between the many of the components of the primary and secondary cancer microenvironment that contribute to the metastatic outgrowth in the liver. The data presented herein are a review of the most recent publications and advances in the field that add to the idea that the Wnt pathway is among the drivers of liver metastasis and that its targeting could potentially relieve liver metastasis-related complications.

Keywords: Wnt signaling pathway; liver metastasis; hepatocellular carcinoma; colorectal cancer; breast cancer; gastric cancer; lung cancer; melanoma; pancreatic cancer; prostate cancer



Citation: Samaržija, I. Wnt Signaling Pathway Is among the Drivers of Liver Metastasis. *Livers* **2021**, *1*, 180–200. <https://doi.org/10.3390/livers1040015>

Academic Editor: Gian Luca Grazi

Received: 28 August 2021

Accepted: 27 September 2021

Published: 4 October 2021

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1. Introduction

Malignant primary and secondary liver cancers account for the vast part of cancer-related negative burdens. The most common primary liver cancer is hepatocellular carcinoma (HCC), which is among the top cancers according to the incidence and mortality. It represents approximately 90% of all liver cancers and has an incidence of 850,000 new cases per year [1]. HCC usually occurs in the setting of chronic liver inflammation and is often linked to chronic viral hepatitis infection (hepatitis B or C) or exposure to toxins (e.g., alcohol). Another type of common liver cancer is intrahepatic cholangiocarcinoma (ICC). ICC is an aggressive epithelial malignancy of the bile ducts within the liver that is often locally advanced to metastatic disease and has an extremely poor prognosis. The recurrence of liver cancer after hepatic resection remains a major complication with no adjuvant therapies able to prevent it. Recurrence rates are as high as 70% at 5 years and are divided into either early (<2 years) or late (>2 years) [2]. Recurrence that takes place earlier is usually due to micro-metastases that remained and progressed after resection, while the late onset recurrence results from de novo tumors arising in a microenvironment that is primed for their development. Although metastasis originating from HCC and ICC can be detected in other organs, the most common site of metastasis of the primary HCC and ICC is the liver itself, which contributes to the above-mentioned recurrence scenarios.

Another frequent cancer-related liver malignancy includes metastasis from the colorectal cancer (CRC) accounting for the most common primary cancer that metastasizes to the liver. The percentage of CRC that metastasize to the liver is 30–50% [3]. Liver metastasis is a leading cause of death for CRC patients and, given the fact that CRC is among the top five cancers by incidence and mortality [4], it is evident that this type of disease progression represents large cancer-related burden. Other common primary cancers that metastasize to

the liver include lung, melanoma, breast, pancreatic, and gastric cancer, each with high incidences for this type of disease progression [3].

It is evident from these introductory lines that liver metastasis, originating either from primary liver or other cancer types (Figure 1), represents a significant cancer-related complication. Therefore, efforts are being made in understanding their biology and finding the targets for the effective treatment. In this paper, the role of the Wnt signaling pathway as a driving force in liver metastasis originating from primary liver cancer and from other cancer types is explored.

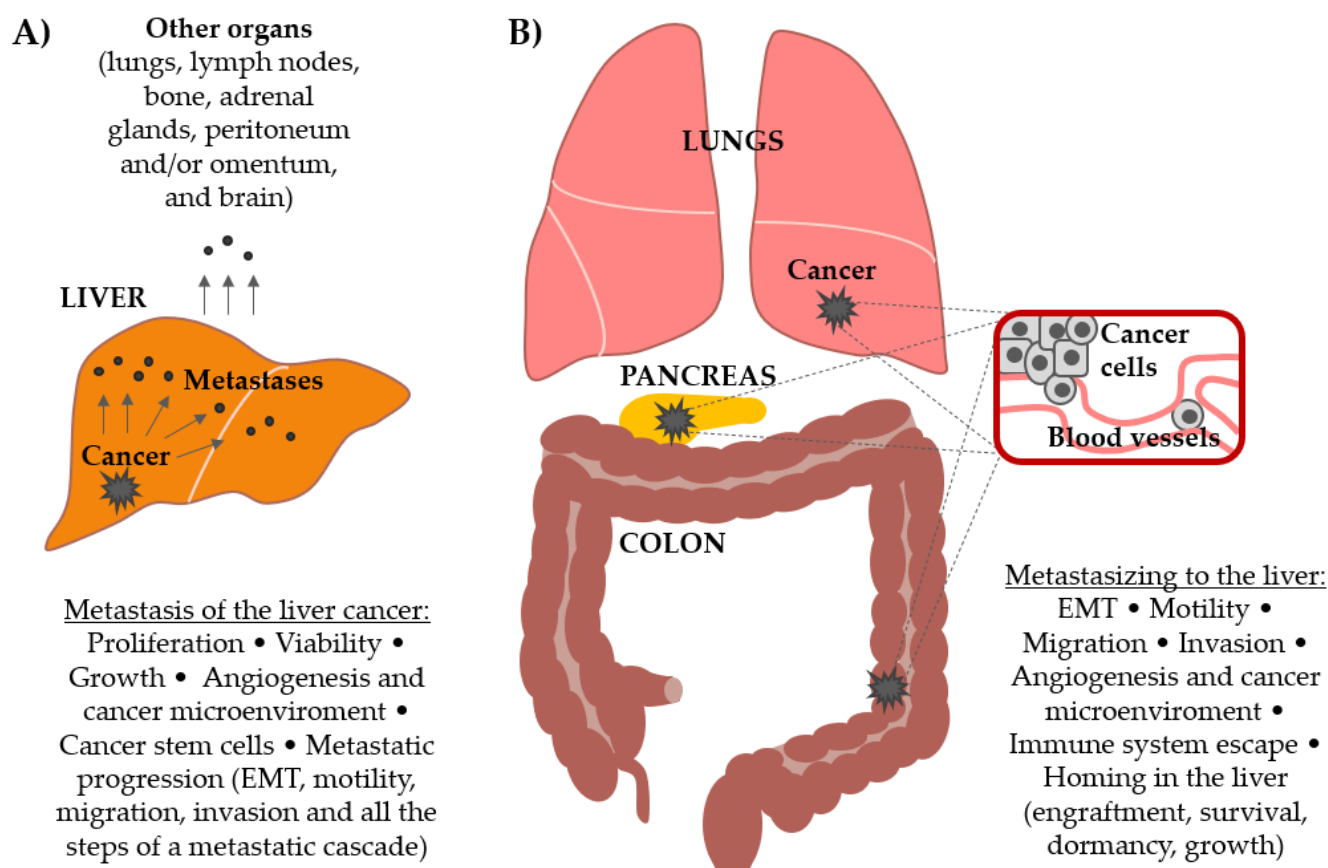


Figure 1. Involvement of the Wnt signaling pathway in (A) the progression and metastasis formation by primary liver cancer and in (B) the formation of secondary cancers in the liver (metastasis from other primary tumors, most commonly colorectal, pancreatic, melanoma, lung, breast, gastric, and prostate). Different processes that lead to metastatic outgrowth in both scenarios are delineated.

2. Wnt Signaling Pathways

Wnt signaling is initiated by Wnt-secreted glycoproteins that bind to the seven trans-membrane spanning domains containing receptors from the Frizzled family. There are 19 Wnt and 10 Frizzled genes in humans. Specificity of the Wnt signaling is possibly achieved through cell-specific expression of Frizzled receptors, or additionally, through the association of Frizzled receptors with different co-receptors. Several different pathways downstream of Wnt binding to Frizzled could be initiated, like outlined below.

2.1. 'Canonical' Wnt Signaling Pathway

Among the Wnt signaling pathways, Wnt/ β -catenin is the best studied and, therefore, denoted as the Wnt 'canonical' pathway. In the absence of Wnt 'canonical' pathway activation, cytoplasmic β -catenin is destined for a destruction in a so-called β -catenin destruction complex. This complex includes axin, adenomatous polyposis coli (APC), and

diversin. In this complex, β -catenin becomes phosphorylated by the serine/threonine kinases casein kinase 1 (CK1) and glycogen synthase kinase 3 beta (GSK3 β). Subsequently, β -catenin is targeted for ubiquitination by the beta-transducin repeat-containing protein (β -TrCP) and is then degraded by the proteasome. Activation of the Wnt/ β -catenin pathway results in the recruitment of a cytoplasmic mediator Dishevelled (Dvl) which leads to the stabilization of a transcription co-factor β -catenin which accumulates in the cytoplasm and enters the nucleus. In the nucleus, β -catenin acts as a co-activator of the T-cell factor/lymphoid enhancer factor-1 (TCF/LEF) transcription factors and contributes to the expression of different target genes. Among other genes with similar function, B-cell CLL/lymphoma 9 protein (BCL9) has been shown to promote β -catenin's transcriptional activity. The common Wnt/ β -catenin target genes include c-Myc, cyclin D1 (CCND1), c-Jun, Axin-2, etc. In the absence of a Wnt signal, TCF/LEF family members interact with transcriptional inhibitors which serve to repress Wnt signaling. The Wnt/ β -catenin pathway is essential during development, cell proliferation, differentiation, migration, and survival and is frequently deregulated in different pathological states [5].

2.2. 'Non-Canonical' Wnt Signaling Pathways

Several 'non-canonical' Wnt pathways have also been described. Among them, the Wnt/planar cell polarity (PCP) and Wnt/calcium pathways are the best understood. Common theme for both pathways is Dvl activation upon ligand binding to the receptor, but these pathways diverge further downstream. The PCP pathway is characterized by the activation of the Rho/Rac GTPases. When this pathway is activated, Wnt binding to Frizzled receptors mediates asymmetric cytoskeletal organization and the polarization of cells by influencing the actin cytoskeleton [6]. The Wnt/calcium pathway leads to the release of intracellular calcium and activates calcium-activated protein kinase C (PKC) and calcium/calmodulin-dependent protein kinase II (CamKII). Frizzled co-receptors involved in this pathway include Knypek and receptor tyrosine kinase like orphan receptor 2 (Ror2). The Wnt/calcium pathway is important for cell adhesion and cell movements during gastrulation [7].

For easier comprehension, Wnt signaling pathways are usually described as individual pathways, but reported crosstalk and shared components between the Wnt signaling branches suggest that Wnts act through a complex intracellular signaling network [8].

2.3. Proteins That Modulate Wnt Signaling Pathways

Some of the proteins that influence Wnt signaling include Wntless (Wls). Wls is a highly conserved transmembrane protein located in compartments of the secretory pathway that shuttles palmitoylated Wnt proteins from the endoplasmic reticulum to the plasma membrane and acts as a Wnt cargo receptor [9].

Wnt antagonists are divided into the secreted Frizzled related proteins (sFRP class) and the Dickkopf (DKK) class. sFRP class includes the sFRP family (sFRP1-5), Wnt inhibitory factor-1 (WIF-1), and Cerberus. These antagonists act by binding directly to Wnt, disturbing their ability to bind to the receptor. Members of the Dickkopf class (DKK1-4) inhibit Wnt signaling by binding to co-receptor LDL receptor related protein (LRP) 5/LRP6 of the Wnt/ β -catenin pathway. Therefore, while sFRP class of the antagonists may inhibit both canonical and noncanonical Wnt signaling pathways, those of the DKK class specifically inhibit Wnt/ β -catenin pathway [10].

3. Wnt Signaling Pathway Drives Hepatocellular Carcinoma Metastasis

The role of Wnt signaling pathway in HCC primary growth and treatment is well described and has been reviewed elsewhere [11,12]. Briefly, most liver tumors have mutations in genes encoding key components of the Wnt/ β -catenin signaling pathway. This pathway has been suggested to have an important role in the pathogenesis of HCC and especially in the transition from chronic liver diseases, including viral hepatitis, to hepatocellular adenomas and further, from adenomas to HCC [12]. β -catenin activation has also been

linked to immunotherapy resistance in HCC [13]. For these reasons, the Wnt/ β -catenin pathway has been suggested to be a mechanism by which cells evade anti-tumor drugs and the immune system [14]. Consequently, the components of the Wnt pathway are considered to be the targets in HCC treatment [15,16].

This chapter explores another important role for Wnt signaling pathway in HCC and that is in their regional (intrahepatic) and systemic (other sites) metastatic progression.

3.1. Aberrant Expression of Wnt Signaling Pathway Components Correlates with the Ability of Liver Cancers to Metastasize

Early studies have noted that the expression of the genes that are implicated in the Wnt signaling pathway correlates with metastatic abilities of HCC. For example, nuclear accumulation combined with cytoplasmic accumulation of β -catenin tended to be associated with metastasis and vascular invasion in HCC [17]. High Wnt3a expression in HCC was related to poorly differentiated grade, liver cirrhosis, hepatitis B virus infection, higher tumor-node metastasis stage, and 5-year survival rate [18]. In addition, overexpression of Dvl2 correlated with histological grade, metastasis, and vein invasion in patients with HCC, and the knockdown of Dvl2 reduced cell migration and invasion in HepG2 cells. [19]. Further to this, the TCF4 gene expression was closely associated with intrahepatic metastasis of HCC [20] and BCL9 expression was significantly associated with microvascular invasion and intrahepatic metastasis [21]. Wls is highly expressed in advanced-stage ICC. The intensity of Wls expression was positively associated with tumor stage, tumor-node-metastasis stage, and lymphatic invasion in ICC [22]. These studies indicate that metastatic progression of HCC and ICC include higher expression of some of the components that positively regulate the Wnt signaling pathway.

3.2. Mechanisms of Action of the Wnt Signaling Pathway in Liver Cancers Metastasis Process: The Roles in EMT, Migration, Invasion, and Metastasis Formation

Mechanistically, one of the first steps in metastatic cancer progression is epithelial-mesenchymal transition (EMT) by which epithelial cells gain migratory and invasive properties and become mesenchymal cells. It has been shown that crosstalk between β -catenin and Snail induces EMT in HCC [23]. Additionally, Wnt/ β -catenin signaling enhances hypoxia-induced EMT in HCC by increasing the EMT-associated activity of HIF-1 α [24]. Hypoxia, on the other hand, activates Wnt/ β -catenin signaling by inducing the expression of BCL9 in human HCC [25]. The importance of the Wnt pathway activation for EMT in HCC cells was further confirmed by the study that showed that TGF β signaling in HCC EMT includes joint activation of the Sonic hedgehog and Wnt signaling pathways [26]. These studies have described that Wnt pathway is an important part of the network of signaling pathways that induce complex EMT process. To delineate components of the Wnt pathway that are involved in HCC EMT, it was shown, for example, by pharmacologic and genetic interventions, that Fzd2 expression induces EMT and enhances cell migration and invasiveness through a previously unknown, non-canonical pathway that includes Fyn and Stat3 [27,28].

Further mechanistic insights into Wnt pathways' role in HCC metastasis came from the study that has shown that deletion of Wnt3a inhibits migration and invasion by downregulating matrix metalloproteinases (MMP) -2/-7/-9 expression via the MAPK pathway [29]. MMPs stimulate the degradation of extracellular matrix components and promote the migration of cancer cells into the surrounding tissue. The involvement of miRNAs downstream of Wnt signaling has been shown in the work that described that the β -catenin/TCF-4-LINC01278-miR-1258-Smad2/3 axis promotes HCC lung metastasis [30]. Taken together, these publications are delineating the events downstream of Wnt signaling pathway activation that induce HCC metastasis formation.

While the above studies interrogated mainly the role of Wnt/ β -catenin pathway, a recent study has shown that downregulation of VANGL1 inhibits cellular invasion and only slightly affects motility in HCC cells. The VANGL1 protein is one of the core components of the Wnt/PCP pathway and this work suggests that the Wnt/PCP pathway may play

a role in progression of HCC affecting cellular invasion but its role in cell motility is less prominent [31].

Since the discovery of the positive role of Wnt signaling in HCC metastasis formation, several studies have explored the expression and the ability of re-introduction of its antagonists into HCC cell lines and a consecutive role in metastasis formation. In this way, it has been shown that reconstitution of Wnt pathway antagonist, sFRP-1, suppresses tumor growth, angiogenesis, and lung metastasis in HCC cell line MHCC97-H xenografts [32]. Furthermore, the expression of another antagonist, WIF1, in HCC cell lines negatively correlated with their metastatic potential. The up-regulation of WIF1 expression inhibited the invasion of HepG2 and SMMC-7721 HCC cell lines possibly through the Wnt/ β -catenin signaling pathway [33]. Although DKK1 is a well-described antagonist that suppresses Wnt/ β -catenin signaling, studies have shown that it might promote HCC cell migration and invasion through the β -catenin/MMP7 signaling pathway [34–36]. However, DKK4 suppresses cell invasion in human hepatoma cells [37]. These studies remind of the complexity of the Wnt signaling pathways and multitude of players that are involved and whose specificity of action most probably depends on a cell type, as seen with DKK1 [38].

Proteins That Converge to Wnt Signaling Pathway to Influence Liver Cancer Metastasis Formation

The studies mentioned above clearly indicate a role for Wnt signaling in HCC metastasis formation. Numerous other studies that analyze the roles of single proteins in HCC metastasis formation have shown that many of these proteins converge to the Wnt signaling pathway. Such a network of proteins is briefly outlined in the Table 1, establishing firmly the role of the Wnt pathway in HCC EMT, motility, migration, invasion, and metastasis formation. Additionally, the involvement of several miRNAs and lncRNAs into signaling that leads to Wnt pathway activation has been shown. Those are either downstream of the Wnt signaling pathway like miR-25 [39] and miR-1258 [30] or converge to its activation or inhibition like, for example, miR-885-5p [40], miR-148b [41], miR-429 [42], miR-197 [43], miR-212 [44], miR-3194-3p [45], and miR-186 [46].

Table 1. Proteins that converge to the Wnt signaling pathway and in that way influence epithelial-mesenchymal transition (EMT), motility, migration, invasion, and metastasis of hepatocellular carcinoma (HCC). The publications are listed in chronological order.

Protein	Mechanism	Effect	Ref.
HGF	Activates Wnt pathway by transcriptional activation of LEF1	Facilitates in vitro tumor migration and invasion	[47]
CTHRC1	Activates the PCP pathway of Wnt signaling	Promotes in vitro tumor migration and invasion and cell-matrix adhesion	[48]
CAV1	Induces Wnt/ β -catenin pathway through nuclear accumulation of β -catenin	Enhances EMT, invasiveness, and lung metastasis in vitro and in vivo	[49]
CLDN3	Inactivates the Wnt/ β -catenin-EMT axis through downregulation of GSK3B, CTNNB1, SNAI2, and CDH2	Inhibits cell motility and invasiveness in vitro and in vivo	[50]
AEG-1	Transcriptionally regulated by c-Myc and induces c-Myc by activating the Wnt/ β -catenin pathway	Activates prosurvival and EMT-signaling pathways and induces in vivo lung metastasis	[51]
GAL1	Promotes β -catenin nuclear translocation, TCF4/LEF1 transcriptional activity and CCND1 and c-Myc expression	Triggers EMT in vitro	[52]
TRIM37	Activates the Wnt/ β -catenin pathway	Promotes in vitro and in vivo cell migration and metastasis by inducing EMT	[53]
HKDC1	Downregulation represses β -catenin and c-Myc expression	Associated with aggressive phenotype	[54]

Table 1. Cont.

Protein	Mechanism	Effect	Ref.
FRAT1	Knockdown suppresses Wnt/ β -catenin pathway by partially suppressing the expression levels of β -catenin, CCND1, and c-Myc	Knockdown inhibits in vitro hypoxia-induced EMT, migration, and invasion	[55]
NTR1	NTS/NTR1 co-expression correlates with the activation of the Wnt/ β -catenin signaling pathway	NTS/NTR1 co-expression enhances EMT, invasion, and in vivo metastasis formation	[56]
CTNND1	Acts, at least in part, by indirectly enhancing Wnt/ β -catenin signaling	Promotes in vitro migration, invasion, and in vivo metastasis formation	[57]
PRC1	Inhibits APC stability, and promotes β -catenin release from the APC complex	Promotes in vitro migration and invasion	[58]
CX32	Its inhibition enhances Snail expression through activation of Wnt/ β -catenin signaling	Regulates EMT, migration, and invasion in vitro and inhibits tumor metastasis in vivo	[59]
FERMT2	Activates Wnt/ β -catenin signaling and increases β -catenin expression (especially non-phosphorylated form)	Promotes in vitro invasion and metastasis	[60]
OCT4	Upregulates LEF1, a key component of the WNT signaling pathway	Induces EMT in vitro	[61]
DDX39	Activates Wnt/ β -catenin pathway by increasing β -catenin levels in the nucleus	Promotes tumor growth, migration, invasion, and in vivo metastasis	[62]
PCL3	Inhibits β -catenin degradation, and activates β -catenin/TCF signaling	Positively regulates the migration, invasion, and in vivo metastasis formation	[63]
ITGB5	Directly interacts with β -catenin and inhibits its degradation, thus leading to Wnt/ β -catenin activity	Elevated ITGB5 facilitates in vitro cell migration	[64]
JUB	Activates β -catenin in the nuclei	Induces in vitro EMT and migration	[65]
LRP16	Its overexpression could prevent β -catenin from entering the nucleus	Attenuates cell migration, and invasion in vitro, and metastasis in vivo	[66]
ZIC5	Increases the expression of β -catenin and CCND1 and promotes β -catenin to enter the nucleus	Promotes proliferation, migration, and invasion in vitro and in vivo	[67]
SOX9	SOX9-AS1/miR-5590-3p/SOX9 positive feedback acts through the Wnt/ β -catenin pathway	Aggravates HCC progression and metastasis in vitro and in vivo	[68]
AKIP1	Interacts with and sustains β -catenin in the nucleus by blocking its interaction with APC; enhances phosphorylation of β -catenin	Promotes invasion and increases intrahepatic and lung metastasis in vivo	[69]
FBXO17	Its silencing might function through downregulating the expression of proteins in Wnt/ β -catenin pathway	In vitro metastasis ability in the anti-FBXO17 group is decreased	[70]
FOXG1	Activates Wnt signaling through forming TCF4/ β -catenin/FOXG1 complex	Promotes EMT and aggressiveness in vitro and enhances metastasis in vivo	[71]
GATA5	Co-localizes with β -catenin in the cytoplasm, preventing β -catenin from entering the nucleus	Inhibits in vitro cell growth, colony formation, migration, and invasion	[72]
GRP78	Activates the Wnt/HOXB9 pathway by chaperoning LRP6	Promotes in vitro and in vivo invasion and metastasis	[73]
HEG1	Promotes β -catenin expression and maintains its stability, leading to its accumulation and nuclear translocation	Promotes EMT and in vitro and in vivo invasion and metastasis	[74]
NDRG3	Promotes nuclear translocation of β -catenin	Enhances metastasis and angiogenesis in vitro and in vivo	[75]
MSI1	Activates Wnt/ β -catenin signaling pathway (downregulation reduces the expression of phospho- β -catenin and CCND1 and elevates the protein expression of DKK1 and APC)	Affects in vitro cancer cell viability, migration, and invasiveness	[76]
p62/IMP2	Activates Wnt/ β -catenin pathway	Promotes in vitro EMT and migration	[77]
RICH2	Overexpression positively correlates with the expression of WNT5a and inversely correlates with β -catenin	Inhibits formation of filopodia and invasion and proliferation in vitro	[78]

Table 1. Cont.

Protein	Mechanism	Effect	Ref.
AQP9	Overexpression reduces the levels of DVL2, GSK-3 β , CCND1, and β -catenin	Overexpression suppresses in vitro migration, invasion, and EMT	[79]
ARHGEF11	Induces β -catenin nuclear translocation and upregulates ZEB1	Promotes EMT and migration in vitro	[80]
GAL3	Activates the PI3K-Akt-GSK-3 β - β -catenin signaling cascade	Regulates in vitro angiogenesis and EMT and favors tumor lung metastasis in vivo	[81]
KIF2C	Direct target of the Wnt/ β -catenin pathway that mediates the crosstalk between Wnt/ β -catenin and mTORC1 signaling	Promotes migration, invasion, and metastasis both in vitro and in vivo	[82]
KIF18B	The knockdown downregulates the expression of c-Myc, CCND1, β -catenin, and p-GSK-3 β Its overexpression induces PRMT5 translocation from the nucleus to the cytoplasm and translocation of β -catenin from the cytoplasm to the nucleus which upregulates WNT/ β -catenin signaling pathway	Knockdown might suppress proliferation, migration, and invasion in vitro	[83]
MTDH	PRMT5 and β -catenin play a pivotal role in MTDH-mediated HCC in vivo metastasis		[84]
NRF1	Enhances ubiquitination of β -catenin for targeting proteasomal degradation	Promotes invasion and metastasis to the lung and liver in in vivo models	[85]
FXR	Decreases expression of β -catenin target genes and reduces nuclear translocation of β -catenin proteins in vitro and in vivo	Suppresses migration and invasion in vitro and inhibits local invasion and lung metastasis in vivo	[86]
USP1	Its knockout impairs expression of Wnt target genes	Frequently upregulated in liver circulating tumor cells and expression correlates with metastasis	[87]
ATE1	Accelerates degradation of β -catenin and inhibits Wnt signaling by regulating turnover of RGS5	Knockdown promotes cancer growth, migration, and disease progression in vitro and in vivo	[88]
PGC1 α	Inhibits Warburg effect by PPAR γ -dependent WNT/ β -catenin/PDK1 axis	Suppresses in vitro and in vivo metastasis	[89]
RAD54B	Increases nuclear β -catenin and up-regulates Wnt/ β -catenin downstream target genes (c-Myc, CCND1, MMP7, CD44, VEGF, c-Jun)	Increases in vitro cell viability and motility, and in vivo intrahepatic metastasis	[90]
ZEB1	Could activate the Wnt/ β -catenin signaling pathway by upregulating the protein expression levels of β -catenin, c-Myc, and CCND1	Promotes in vitro cell proliferation and migration and inhibits apoptosis	[91]

Abbreviations: HGF, hepatocyte growth factor; CTHRC1, collagen triple helix repeat containing 1; CAV1, caveolin 1; CLDN3, claudin 3; AEG-1, astrocyte elevated gene-1; GAL1, galectin-1; TRIM37, tripartite motif containing 37; HKDC1, hexokinase domain containing 1; FRAT1, frequently rearranged in advanced T-cell lymphomas 1; NTR1, neurotensin receptor 1; CTNND1, catenin delta 1; PRC1, protein regulator of cytokinesis 1; CX32, connexin 32; FERMT2, FERM domain containing kindlin 2; OCT4, octamer-binding transcription factor 4; DDX39, DExD-box helicase 39A; PCL3, polycomb-like protein 3; ITGB5, integrin beta 5; JUB, LIM domain-containing protein ajuba; LRP16, LDL receptor related protein 16; ZIC5, zic family member 5; SOX9, SRY-box transcription factor 9; AKIP1, A-kinase interacting protein 1; FBXO17, F-box protein 17; FOXG1, forkhead box G1; GATA5, GATA binding protein 5; GRP78, endoplasmic reticulum chaperone BiP; HEG1, heart development protein with EGF like domains 1; NDRG3, NDRG (n-myc downstream-regulated gene) family member 3; MSI1, musashi RNA binding protein 1; p62/IMP2, insulin-like growth factor 2 mRNA binding protein 2; RICH2, ARHGAP44 Rho GTPase activating protein 44; AQP9, aquaporin 9; ARHGEF11, Rho guanine nucleotide exchange factor 11; GAL3, galectin-3; KIF2C, kinesin family member 2C; KIF18B, kinesin family member 18B; MTDH, metadherin; NRF1, NF-E2-related factor 1; FXR, farnesoid X receptor; USP1, ubiquitin specific protease 1; ATE1, arginyltransferase 1; PGC1 α , peroxisome proliferator-activated receptor gamma coactivator 1-alpha; RAD54B, RAD54 (DNA repair and recombination protein) homolog B; ZEB1, zinc finger E-box binding homeobox 1.

3.3. Wnt Signaling Pathway in Liver Cancer Stem Cell and Mesenchymal Stem Cell Biology

Besides its roles in the above-mentioned processes that endow cancer cells with increased metastatic abilities, the Wnt signaling pathway is also active and contributes to the biology of other cells that are implicated in the metastatic outgrowth. For example, metastatic cancer spread is potentiated by cancer stem cells (CSC) which possess qualities that are characteristic of embryonic or adult stem cells. Those include self-renewal, differentiation, dormancy, and cellular plasticity which enables their adaptation to new environments. These abilities are needed for the successful establishment of metastasis [92]. The roles of Wnt signaling in CSCs biology is well described and has been a subject of several reviews [93,94]. In HCC, it was shown that deacetylation of β -catenin by SIRT1

increases its protein stability and regulates self-renewal and oncogenesis of liver CSCs through promoting the transcription of Nanog [95]. Additionally, a small molecule inhibitor that inhibits Wnt/ β -catenin signaling targets and depletes CD133+ /ALDH+ liver CSCs, which decreases their tumorigenicity in vitro and in vivo [96]. Sox9 is a member of the Sox proteins that are involved in human development by regulating lineage restriction, cell differentiation, and stem cell properties. It was shown that Sox9 confers stemness properties in HCC and suppresses HCC cell migration, invasion, and in vivo lung metastasis through Frizzled-7 mediated Wnt/ β -catenin signaling [97]. In the mentioned publication, Frizzled-7 was identified to be the direct transcriptional target of Sox9. A further paper confirmed the role of the above-mentioned signaling axis that includes Sox9 and Wnt/ β -catenin in the self-renewal of liver CSCs [98]. Additionally, several miRNAs and lncRNAs have been shown to influence liver CSCs through the Wnt pathway [99]. These include miR-612 [100], miR-452 [101], miR-5188 [102], lncAPC [103], lncSAMMSON [104], and lncFZD6 [105].

Mesenchymal stem cells (MSCs) are multipotent adult stem cells that are present in multiple tissues. MSCs promote hepatocarcinogenesis and metastasis formation via signaling that includes activated Wnt/ β -catenin pathway and EMT [106]. Further to this, irradiated mesenchymal stem cells have been shown to increase the ratio of CD133+ HCC cells and support stemness maintenance of HCC stem cells through the Wnt/ β -catenin signaling pathway. This was reflected when liver CSCs were co-cultured with irradiated MSCs, which resulted in increased colony and tumor formation abilities via increased activity of the Wnt/ β -catenin signaling pathway [107]. In another study, it was also shown that overexpression of hepatocyte nuclear factor 4 alpha (HNF4a) in human MSCs inhibits HCC progression by reducing hepatoma cell growth, migration, and invasion through downregulation of the Wnt/ β -catenin signaling pathway [108].

3.4. Wnt Signaling Pathway Affects the Communication between Different Components of the Liver Cancer Microenvironment That Promote Metastasis

The activation of Wnt signaling in other components of a liver cancer microenvironment that promote metastasis has been documented. These include crosstalk between hepatic tumor cells and macrophages, which takes place via Wnt/ β -catenin signaling. This communication promotes M2-like macrophage polarization and tumor growth, migration, metastasis, and immunosuppression in HCC [109]. To confirm the role of Wnt signaling in this process, it was shown that lncRNA LINC00662 promotes M2 macrophage polarization and HCC progression via Wnt/ β -catenin signaling pathway [110]. Another component of a liver cancer microenvironment, hepatic stellate cells, have been shown to promote EMT, proliferation, invasiveness, and metastatic abilities of HCC in vitro and in vivo through microRNA-1246-ROR α -Wnt/ β -catenin axis [111].

Angiogenesis is another important prerequisite for cancer cells to grow and metastasize. Wnt signaling is involved in vasculature formation [112] and in endothelial cell proliferation and migration [113]. Recently, angiocrine Tie-Wnt signaling axis in the liver controlling hepatocyte function during liver regeneration was described [114]. Moreover, angiocrine Wnt signaling controls liver growth and development of metabolic liver zonation in mice [115]. In HCC, miR-1301 was shown to inhibit angiogenesis, cell migration, and invasion in vitro and in vivo by decreasing Wnt/ β -catenin signaling through downregulation of BCL9, β -catenin, and VEGF expression in tumor cells. [116]. These papers add to the evidence that show that Wnt signaling affects many of the processes required for metastatic expansion, including vasculature formation.

3.5. Wnt Signaling Pathway Is Activated in Residual HCC Cells after Incomplete Radiofrequency Ablation

Some therapeutic approaches in HCC, like incomplete radiofrequency ablation (RFA), leave residual cancer cells behind. It was shown that incomplete RFA enhances invasiveness and metastasis of residual HCC cells by stimulating EMT-like phenotype changes through activation of the β -catenin signaling in HCCLM3 cells [117]. Another study has shown that insufficient radiofrequency ablation promotes the metastasis of residual hepato-

cellular carcinoma cells via upregulating flotillin proteins which altered the EMT status and metastatic potential of heat-treated HCCLM3 cells by activating the Akt/Wnt/ β -catenin signaling pathway [118].

Taken together, the data presented in Section 3 confirm that the expression of the components of the Wnt pathway is de-regulated during HCC metastatic progression. Further, the Wnt pathway has been shown to strongly influence HCC EMT, motility, migration, invasion, and metastasis. It has a key role in CSCs, too, as well as in the biology of other components of the HCC microenvironment that potentiate the metastatic spread. Finally, after the treatment of HCC, the residual cancer cells, which are usually more aggressive and have higher metastatic abilities, show the activation of the Wnt pathway. Since the treatment options in advanced liver cancer are limited, the data presented here point to the possibility that targeting Wnt signaling pathways in liver cancers could alleviate metastasis related complications.

4. Wnt Signaling Pathway Drives Secondary Liver Cancers

Secondary liver cancers denote metastasis in the liver that originate from primary cancers from tissues other than the liver. Common primary cancers that metastasize to the liver include colorectal, lung, melanoma, breast, pancreatic, gastric, and prostate cancer.

4.1. Colorectal Cancer Liver Metastasis

Like mentioned above, colorectal cancer liver metastases represent a large cancer-related burden and are, therefore, the most studied. In the colon, the Wnt signaling pathway is an essential mediator of tissue homeostasis and repair and is frequently de-regulated during cancer development. Almost all CRCs show hyperactivation of the WNT pathway, which is believed to be the initiating and driving event [119]. The most common mutation in CRC is inactivation of APC and in carriers of an APC inactivating mutations, the risk of CRC by the age of 40 is almost 100% [120]. For these reasons, the Wnt signaling pathway is an important target in anti-CRC treatment [121,122].

4.1.1. Aberrant Expression of Wnt Signaling Pathway Components Correlates with the Ability of CRC to Metastasize to the Liver

In the CRC metastasis to the liver, the expression of the Wnt signaling pathway components is highly de-regulated. Early on, it was noted that Wnt2 mRNA is frequently up regulated in colorectal polyps, primary CRC, and also in liver metastasis from CRC [123]. High Wnt6 expression in CRC tissue indicates unfavorable survival outcome for patients with CRC liver metastasis after liver resection suggesting that detection of Wnt6 expression may be valuable marker for guiding postoperative treatment [124]. On the other hand, nuclear β -catenin expression at the invasive front and in the vasculature predicts liver metastasis in CRC [125] and its overexpression in metastatic sentinel lymph node is strongly associated with synchronous liver metastasis and may contribute to predict liver metastasis [126]. Further, deregulated expression of nuclear β -catenin was associated with the development of liver metastasis, but not of CNS metastasis [127]. Co-expression of CD166/ β -catenin, CD44/ β -catenin, and CD44/CD166/ β -catenin were significant factors associated with liver metastasis, suggesting that specific combinations of CSC markers and β -catenin and additional analyzed proteins could be a significant predictor of poor survival in stage II CRC [128]. Finally, a recent study analyzing liver metastasis from different origins found that β -catenin overexpression was frequent in metastasis from CRC patients (27 out of 30 samples), but also breast (3/5), lungs (1/2), and some other sites [129]. Another study analyzed the expression of β -catenin, APC, and Wnt1 in the primary tumor and corresponding metastasis of patients with CRC. In accordance with the above-mentioned results, the authors found a higher expression of nuclear β -catenin at the tumor invasion front, in the primary tumor, and the corresponding hepatic and lymphatic metastases. By contrast, APC expression was significantly lower in all analyzed tumor compartments compared with normal colonic mucosa. The same study found that Wnt1 protein expression was significantly lower in liver metastases but not in the primary tumor

or lymphatic metastases compared with normal colonic mucosa [130]. An additional study adding to the hypothesis that the suppression of Wnt signaling pathway is a favorable event in CRC patients with metastasis, showed that high preoperative levels of circulating sFRP-5 predict better prognosis in those patients, and its levels are significantly lower in patients with either vascular invasion or liver metastasis [131].

4.1.2. Mechanisms of Action of the Wnt Signaling Pathway in CRC Metastasis Process

Mechanistically, Frizzled-7 expression has been suggested to promote survival, invasion, and metastatic characteristics of CRC cells through non-canonical and the canonical Wnt signaling pathways [132]. Among the downstream Wnt pathway events that lead to metastasis, new direct Wnt/ β -catenin target genes, BOP1, CKS2 and NFIL3, were identified and shown to induce EMT, cell migration, and experimental metastasis of CRC cells [133]. Further, it was shown that the SOX17/miR-371-5p/SOX2 axis suppresses EMT at least in part by inhibiting Wnt/ β -catenin signaling which leads to the inhibition of CRC metastasis [134]. Like with HCC metastasis, for CRC liver metastasis, numerous studies have shown that single protein or miRNA manipulation leads to the regulation of the Wnt pathway and in this way influences the CRC liver metastasis formation. These include cyclin dependent kinase 8 (CDK8) [135,136], HNF4a [137], sciellin (SCEL) [138], R-spondin 2 (RSPO2) [139], DNA methyltransferase 1 (DNMT) [140], the E2A gene (encodes two basic helix-loop-helix transcription factors, E12 and E47) [141], paired related homeobox 2 (PRRX2) [142], neuronal pentraxin 2 (NPTX2) [143], forkhead box P3 (FOXP3) [144], mitochondrial pyruvate carrier 1 (MPC1) [145], thyroid hormone receptor interactor 13 (TRIP13) [146], NUMB endocytic adaptor protein (NUMB) [147], ATM interactor (ATMIN) [148], FOS like 1, AP-1 transcription factor subunit (FOSL1) [149], arrestin beta 1 (ARRB1) [150], far upstream element binding protein 1 (FUBP1) [151], CK1 δ / ϵ -AES axis [152], etc.

Combined mutations of APC, KRAS, and TGFBR2 were shown to govern metastasis of intestinal cancer illustrating how key driver mutations in CRC cooperatively influence the development of a metastatic disease [153]. Adding to this data, it was shown by whole exome sequencing of CRC liver metastasis that the top three genes with the highest mutation frequency were TP53, APC, and KRAS [154]. This suggests that APC mutations are not only important during CRC development but are also playing an essential role in its metastasis formation.

Colon cancer metastases are often associated with activation of the Wnt/ β -catenin signaling pathway and high expression of the metastasis mediator S100A4. Studies have shown that inhibiting Wnt/ β -catenin signaling suppresses S100A4-dependent CRC liver metastasis, and, therefore, has a therapeutic potential [155,156]. Another protein frequently involved in positive regulation of CRC metastasis formation is the neural cell adhesion molecule L1 [157]. Gene coding for L1 is a target gene of β -catenin/TCF in CRC cells. L1 localizes preferentially to the invasive front of tumors and its forced expression confers increased cell motility, invasion, and tumorigenesis, and the induction of human CRC cell metastasis to the liver but does not require changes in EMT and CSCs markers [158]. This type of CRC cell metastasis formation is gaining attention recently and it is a subject of several studies that are trying to widen the knowledge on this process [157].

Regarding CRC CSCs, it was shown that those CSCs that express CD110, the thrombopoietin (TPO)-binding receptor, mediate liver metastasis. Further, TPO promotes metastasis of CD110+ CSCs to the liver by activating lysine degradation which generates acetyl-CoA that is subsequently used in p300-dependent LRP6 acetylation. This triggers tyrosine phosphorylation of LRP6, which activates Wnt signaling to promote self-renewal of CD110+ CSCs [159]. The importance of the Wnt pathway in CRC CSCs biology was also shown by the study that documented the significance of leucine-rich repeat-containing G-protein-coupled receptor 5 (Lgr5) in cancer stem cells in the colon and rectum [160]. Lgr5 is a Wnt target gene and is widely used as a marker of organ stem cells with self-renewal capacity [161].

4.1.3. Wnt Signaling Pathway Affects the Communication between Different Components of the CRC Microenvironment That Promote Metastasis

Metastasis formation is a process involving a multitude of different cells that act in concert in the primary tumor microenvironment, but also at the secondary site. In a microenvironment of a CRC primary tumor, it was shown that cancer-associated fibroblasts (CAFs) play an important role in metastasis formation. For example, CAF secreted exosomes promote metastasis and chemotherapy resistance by enhancing cell stemness and EMT. Mechanistically, CAFs promote the transferring of exosomes to CRC cells, leading to an increase of miR-92a-3p level in CRC cells, which activates the Wnt/ β -catenin pathway and inhibits mitochondrial apoptosis contributing to cell stemness, EMT, metastasis, and 5-FU/L-OHP resistance [162]. In a study where conditioned medium (CM) from normal colonic fibroblasts, CAFs from primary tumor (CAF-PT) or liver metastasis (CAF-LM) were used the influence of each CM on CRC cell lines was tested. In this way, it was shown that the liver microenvironment induces more efficiently the aggressiveness of CRC cells but secondarily evokes cell death. The transcriptomic profile of CRC cells treated with CAF-LM CM was associated with Wnt and MAPK pathways activation in gene set enrichment analysis [163]. Another study showed that intervention with BCL9 activity and expression modulates the cellular landscape of CAFs in the tumor-immune microenvironment of CRC. Moreover, CAFs affect cancer-associated immune surveillance by inhibition of the Wnt signaling pathway [164]. CAF-derived Wnt2 increases tumor angiogenesis in colon cancer both in vitro and in vivo [165]. In regard to angiogenesis, it was shown that lncRNA GAS5 inhibits angiogenesis, invasion, and metastasis of CRC through the Wnt/ β -catenin signaling pathway [166]. Additionally, Wnt/ β -catenin signaling was shown to influence many of the processes involved in vasculature formation in CRC, like sprouting and nonsprouting angiogenesis, vasculogenic mimicry, and the formation of mosaic vessels [167].

In the light of involvement of other cells in the metastasis process, single-cell transcriptome analysis revealed granulocytes enrichment and tumor-immune microenvironment heterogeneity in CRC liver metastases. In this context, the Wnt signaling pathway was found to be activated and promote granulocytes migration [168].

4.2. Breast Cancer Liver Metastasis

Like mentioned above, several cancers other than CRC frequently metastasize to the liver. Studies have shown the importance of the Wnt signaling in those processes. For example, it was shown that AF1q is a novel TCF7 co-factor that specifically binds to TCF7 in the Wnt signaling pathway and results in transcriptional activation of CD44 as well as transcription of multiple downstream targets of the TCF7/LEF1. In this way, AF1q promotes breast cancer metastasis including those to the liver [169]. Ablation of Frizzled-6 expression in mammary cancer cell lines inhibited motility and invasion, induced a more symmetrical shape of organoid three-dimensional cultures, and inhibited bone and liver metastasis. Further to this, multivariate analysis suggested an independent prognostic significance of Frizzled-6 expression in triple-negative breast cancer (TNBC), predicting distant relapse [170]. Another study has shown that β -catenin-independent Wnt signaling and Ki67 are associated with poor prognosis in patients with breast cancer liver metastases [171]. Moreover, simultaneous metastases in liver, ovaries, and bone from chemo-resistant TNBC are prevented by interfering with the Wnt signaling pathway, suggesting that inhibition of the Wnt pathway treats multi-organ metastases of TNBC [172].

4.3. Gastric Cancer Liver Metastasis

In gastric cancer, it was shown that β -catenin expression is lost in a subgroup of primary gastric cancers. It is also frequently absent in metastases, and exhibits nuclear localization in cancers with either β -catenin or APC gene mutations [173]. In contrast with this, the paper showed that Twist promotes gastric cancer cell migration, invasion, and metastasis. The same paper suggests that Twist may play an important role in Wnt/TCF4 signaling because overexpression of Twist in MKN28 cells increased TCF4/LEF DNA

binding activity, and promoted expression of TCF4's downstream target genes, CCND1 and MMP-2 [174]. Supporting the positive role of Wnt signaling in gastric cell metastasis, a study has shown that blocking Wnt5a by antibody suppresses in vitro migration and invasion and in vivo metastasis formation of gastric cancer cells by inhibiting its receptor-mediated endocytosis [175]. In addition, RYK, a receptor of noncanonical Wnt ligand Wnt5a, is positively correlated with gastric cancer tumorigenesis and, specifically, the potential of liver metastasis [176]. Further to this, Dvl-associating protein with a high frequency of leucine residues (Daple) was shown to mediate Wnt5a-induced Rac and JNK activation, laminin α 2 expression, and cell migration and invasion. According to these in vitro-obtained results, Daple depletion suppressed liver metastasis in a mouse xenograft model of gastric cancer, suggesting that the non-canonical Wnt signaling pathway contributes to gastric cancer progression at least partly via Daple [177].

4.4. Lung Cancer Liver Metastasis

In lung cancer, it was shown that Glypican-5 suppresses EMT of the lung adenocarcinoma by competitively binding to Wnt3a and inactivating the Wnt/ β -catenin signaling pathway [178]. Besides Wnt3a, Wnt5a was also found to enhance EMT, invasion, migration, and metastasis in vitro and in vivo in non-small-cell lung cancer [179]. Further, Destrin (DSTN), a member of ADF/cofilin family of proteins, was shown to contribute to lung adenocarcinoma progression, including liver metastasis. Mechanistically, DSTN facilitates nuclear translocation of β -catenin, which promotes EMT [180].

4.5. Melanoma Liver Metastasis

The studies on the role of Wnt signaling in melanoma progression are scarce. However, recent study has shown that Wnt signaling enhances neural crest migration of melanoma cells and induces an invasive phenotype, emphasizing the essential role of embryonic EMT-inducing neural crest signaling for the spreading of malignant melanoma [181].

4.6. Pancreatic Cancer Liver Metastasis

As shown in Figure 1, pancreatic cancer often progresses to form liver metastasis. An early study has shown that aberrant expression of β -catenin and E-cadherin correlated strongly with lymph node spread and liver metastases in pancreatic endocrine tumors [182]. In further studies, it has been shown that BCL9L plays an important role in TGF- β -induced EMT and metastasis of pancreatic cancer through its effects on E-cadherin and β -catenin [183]. Several other studies investigated the roles of molecules that converge to Wnt signaling pathway and influence pancreatic cell metastasis. These include semaphorin 5a (SEMA5A) [184], lncRNA DLX6-AS1 [185], activator of transcription and developmental regulator (AUTS2) [186], cadherin 13 (CDH13) [187], and lncRNA 00261 [188].

4.7. Prostate Cancer Liver Metastasis

Prostate cancer is another cancer type with frequent liver metastasis. The results from my recent work [189], which is a meta-analysis of the gene expression data, show that many of the genes whose expression changes specifically in liver metastasis in comparison to primary prostate cancer belong to the enriched term of the Wnt signaling. Those include genes coding for sFRP-1, Frizzled related protein (FRZB), Frizzled-6, Frizzled-7, ROR1, LRP1, LRP6, GSK3B, TCF7, BCL9, CCND2, CAMK2G, Dishevelled associated activator of morphogenesis 2 (DAAM2), and Ras homolog family member A (RHOA). Although some of the antagonists of Wnt pathway are significantly down-regulated, also, some of the positive regulators of the pathway are slightly down-regulated, so it would be hard to conclude on the status of the Wnt signaling pathway in these samples. However, considering the number of the components with changed expression, Wnt pathway deregulation in prostate cancer liver metastasis is recognized and could serve as an initial point for further studies. For example, a study has shown that DKK1 expression increases early in prostate cancer development and decreases during progression from primary tumor

to metastasis, which would indicate the activation of the Wnt pathway [190]. Additionally, a recent study presented a new model of multi-visceral and bone metastatic prostate cancer with activation of Notch and Wnt pathways [191] adding to the complexity of Wnt signaling in contribution to a metastatic process in prostate cancer.

In conclusion, the data presented in Section 4 point to the de-regulated Wnt signaling pathway in liver metastasis from different primary tumors. They also confirm involvement of the Wnt pathway in the many of the steps that are required for the metastatic outgrowth and that are schematically outlined in Figure 1.

5. Conclusions

Liver metastasis, originating either from primary liver or other cancer types, represents a large cancer-related complication. Wnt signaling pathway is considered in the treatment of HCC and primary cancers, like CRC, that often metastasize to the liver [15,16,121,122]. Herein, the data that show critical involvement of Wnt pathway in many of the steps that are required for liver metastasis in different scenarios are presented. Therefore, the information outlined in these chapters contributes to the idea that Wnt pathway is among the drivers of liver metastasis and that its targeting could potentially relieve the liver metastasis-related burdens. To that end, selective inhibitors of Wnt pathway could be used alone or in combination to treat patients with advanced liver metastasis. Future studies that will describe their efficacy and toxicity are needed. This is especially important, because the vast majority of cancer-related deaths are caused by metastasis formation and the current anti-cancer therapies mainly target primary cancers. Therefore, therapies that effectively target metastasis should significantly contribute to the success of anti-cancer treatments.

Funding: This research was funded by My Zaba Start 2019 donation from Zagrebačka banka.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The author declares no conflict of interest.

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