

Hypothesis of Opposite Interplay Between the Canonical WNT/beta-catenin Pathway and PPAR Gamma in Primary Central Nervous System Lymphomas

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Abstract

Primary central nervous system lymphomas (PCNSLs) are angiocentric neoplasia which present dense monoclonal lymphocyte proliferation, and occur in brain parenchyma in 90% of the cases. Activated B-cell like Diffuse Large B-cell Lymphoma (ABC-DLBCL) subtype represents more than 90% of PCNSLs and is the most aggressive subtype with a cure rate of only 40%. One of the characteristics of ABC-DLBCL subtype is neuroinflammation through the activation of NF-kappaB pathway. c-Myc alterations and protein expression have been shown in aggressive DLBCL. c-Myc is considered as a key prognostic and predictive biomarker for survival in DLBCL, its expression is associated with worst survival rates. Although mRNA of c-Myc is increased by low levels gains of c-Myc, several studies have shown that c-Myc protein expression is overexpressed without c-Myc abnormalities. These high levels of c-Myc protein in DLBCL without genetic abnormalities suggest that c-Myc protein expression may be also increased by other

mechanisms or signaling pathways which regulate its expression. In PCNSLs, the canonical WNT/beta-catenin pathway is upregulated while PPAR gamma is downregulated. The opposite interplay between WNT/beta-catenin pathway and PPAR gamma is reviewed here. Activation of WNT/beta-catenin pathway leads to the transcription of genes involved in cell proliferation, mitochondrial metabolism, protein synthesis, and tumor growth, such as c-Myc. PPAR gamma agonists induce the inhibition of several signaling pathways such as NF-kappaB, STAT, PI3K/Akt and WNT/beta-catenin pathway. Activation of PPAR gamma agonists may have a major negative key role in the regulation of PCNSLs progression.

Abbreviations

APC: Adenomatous polyposis coli
CNS: Central nervous system
DLBCL: diffuse large B cell lymphoma
DSH: Disheveled
EGFR: epidermal growth factor receptor
FZD: Frizzled
GSK-3beta: Glycogen synthase kinase-3beta
JAK: Janus Kinase
LRP 5/6: Low-density lipoprotein receptor-related protein 5/6
PI3K-Akt: Phosphatidylinositol 3-kinase-protein kinase B
PCNSL: Primary central nervous system lymphoma
PPAR gamma: Peroxisome proliferator-activated receptor gamma
STAT3: signal transducer and activator of transcription 3
TCF/LEF: T-cell factor/lymphoid enhancer factor

Introduction

Primary central nervous system lymphomas (PCNSLs) are angiocentric neoplasia which present dense monoclonal lymphocyte proliferation, and occur in brain parenchyma in 90% of the cases. PCNSLs are infiltrative and extend beyond the primary lesion. PCNSLs account for up to 1% of

Non-Hodgkin lymphomas (NHL) and 3% of primary brain tumors (Villano, Koshy, Shaikh, Dolecek, and McCarthy, 2011). Angiotropism characterizes both primary and metastatic central nervous system (CNS) lymphomas unlike malignant gliomas which are vascular tumors (Aho, Ekfors, Haltia, and Kalimo, 1993). CNS vasculature contributes to the pathogenesis of PCNSL because large B cell-lymphoma accumulates densely around brain tumor vessels. The prognosis of PCNSLs is worse than other localized extranodal lymphomas (Abrey, DeAngelis, and Yahalom, 1998; Fine and Mayer, 1993). Around 90% of PCNSL are diffuse large B cell lymphomas (DLBCL). Two molecular subtypes form DLBCL; activated B-cell like (ABC) and germinal center B-cell like (GCB) (Alizadeh et al., 2000; Georg Lenz and Staudt, 2010).

ABC-DLBCL subtype represents more than 90% of PCNSLs (Batchelor, 2016) and is the most aggressive subtype with a cure rate of only 40% (G. Lenz et al., 2008). One of the characteristics of ABC-DLBCL subtype is the activation of NF-kappaB pathway whereas GCB-DLBCL presents low levels of this signaling (Pasqualucci and Zhang, 2016). NF-kappaB is a downstream signaling of both B cell receptor (BCR) and CD40 receptors and ABC-DLBCL cells show a "chronic and active" form of BCR signaling (R. Eric Davis et al., 2010). MYD88 mediates the activity of NF-kappaB as well as type I interferon responses (S.-C. Lin, Lo, and Wu, 2010). MYD88 mutations are observed in around 30% to 40% of ABC-DLBCL. MYD88 mutations stimulates STAT3 signaling which is also a phenotypic trait of ABC-DLBCL subtype (Ngo et al., 2011).

c-Myc alterations and protein expression have been shown in aggressive DLBCL (Karube and Campo, 2015). These alterations are frequently associated with oncogenic abnormalities, as B-cell lymphoma 2 (Bcl-2) and B-cell lymphoma 6 (Bcl-6) genes translocation and overexpression (Karube and Campo, 2015). c-Myc rearrangements appear similarly expressed in both GCB and ABC-DLBCL (Johnson et al., 2012). Although mRNA of c-Myc is increased by low levels gains of c-Myc, several studies have shown that c-Myc protein expression is overexpressed without c-Myc abnormalities (Horn et al., 2013; Johnson et al., 2012; Stasik et al., 2010; Valera et al., 2013). These high levels of c-Myc protein in DLBCL without genetic abnormalities suggest that c-Myc protein expression may be also increased by other mechanisms or signaling pathways which regulate its expression (Meyer and Penn, 2008).

In numerous tissues, canonical WNT/beta-catenin pathway activation induces inactivation of peroxisome proliferator-activated receptor gamma (PPAR gamma), while PPAR gamma activation induces inhibition of canonical WNT/beta-catenin pathway (Lecarpentier, Claes, Duthoit, and Hébert, 2014). WNT/beta-catenin pathway, a determining factor in the evolution of numerous cancers (Gruetter, 2003; Thompson, 2014; Warburg, 1956), is increased in DLBCL (Walker et al., 2015; Yan Zhang et al., 2014). Inflammation and WNT/beta-catenin pathway act in a positive interplay (Ma and Hottiger, 2016). c-Myc is a WNT target gene (Angers and Moon, 2009). PPAR gamma is low expressed in CNS and observed in several cell types such as neurons, astrocytes, oligodendrocytes and microglia (Lambiv et al., 2011; Sarin and Bernath, 2008; J. Wu et al., 2012; Z. Yang et al., 2010). In many pathophysiological states, PPAR gamma activation induces repression of the WNT/beta-catenin pathway (J. Liu, Wang, Zuo, and Farmer, 2006; Moldes et al., 2003; Sharma, Pradeep, Wong, Rana, and Rana, 2004). PPAR gamma agonists show benefic roles in DLBCL (X. Li, Du, Xu, Lin, and Ling, 2013). Anti-inflammatory properties of PPAR gamma agonists may partly explain their beneficial therapeutic effects. PPAR gamma agonists can decrease the activation of WNT/beta-catenin pathway and represent a promising therapeutic target for PCNSL patients.

We focus this review on the hypothesis of an opposite interplay between the canonical WNT/beta-catenin pathway and PPAR gamma in regulating the molecular mechanisms underlying the PCNSLs.

1. Canonical WNT/beta-catenin pathway

Wingless and integration site (named WNT) pathway is a cascade of several signaling which is involved in development, metabolism, cellular growth, and maintain of stem cells (van Amerongen and Nusse, 2009). WNT pathway is composed by secreted lipid-modified glycoproteins (Al-Harthi, 2012). Dysregulation of the WNT pathway is involved in several pathways (Lecarpentier et al., 2014). Aberrant WNT/beta-catenin pathway is observed in cancer development (Sumithra, Saxena, and Das, 2016). WNT extracellular ligands bind Frizzled (FZD) receptors and low density lipoprotein receptor-related protein 5 and 6 (LRP 5/6) and disheveled (DSH), which induce beta-catenin accumulation and then beta-catenin nuclear translocation for binding T-cell factor/lymphoid enhancer factor (TCF/LEF). (Logan and Nusse,

2004). Nuclear beta-catenin associated with TCF/LEF activates several target genes expression such as c-Myc, cyclin D1 (Angers and Moon, 2009). Downregulation of the WNT pathway is characterized by the absence of binding between WNT extracellular ligands and the complex FZD/LRP 5/6. Thus, the beta-catenin destruction complex composed by adenomatous polyposis coli (APC), AXIN and glycogen synthase kinase-3 (GSK-3 β) is activated and mediates proteasomal degradation of beta-catenin (Clevers and Nusse, 2012). GSK-3 β inhibits cytosolic beta-catenin accumulation and nuclear translocation (Aberle, Bauer, Stappert, Kispeert, and Kemler, 1997; Clevers and Nusse, 2012).

In non-Hodgkin lymphoma patients, MMP-2 and MMP-9 have a major role in ECM degradation (Kossakowska et al., 1999). Beta-catenin promotes MMP-2 and MMP-9 expressions by regulating COX-2 activity to increase invasion and metastasis of tumors (H. Kim et al., 2013; Z.-H. Peng et al., 2011).

WNT pathway in DLBCLs (Figure 1)

The Forkhead box protein P1 (FOXP1) is a transcription factor which participates to tissue homeostasis, development and regeneration (Kato, Igarashi, Fukuda, Nakagama, and Kato, 2013; Koon, Ippolito, Banham, and Tucker, 2007). Proper B-cell development needs FOXP1 expression, FOXP1 deficient lymphoid stem cells fail to differentiate and overexpression of FOXP1 decreases B-cell maturation (Hu et al., 2006; Sagardoy et al., 2013). FOXP1 has anti-apoptotic activity and is considered as an oncogene in B-cell lymphomas (van Keimpema et al., 2014). FOXP1 is an enhancer of WNT/beta-catenin pathway transduction (Walker et al., 2015). Several studies have shown that WNT/beta-catenin pathway is increased in DLBCLs (Ge, Lv, Feng, Liu, and Wang, 2012; Koch et al., 2014; Qiang, Endo, Rubin, and Rudikoff, 2003; Reya et al., 2000; Staal et al., 2001).

Interactions between WNT pathway and PI3K/Akt pathway

Phosphatidylinositol 3-kinase/serine/threonine kinase (protein kinase B)/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway is present in cell growth, proliferation, protein synthesis and energetic metabolism (Brazil, Yang, and Hemmings, 2004; Ciuffreda, Di Sanza, Incani, and Milella, 2010; Heras-Sandoval, Pérez-Rojas, Hernández-Damián, and Pedraza-Chaverri, 2014; Yu and Cui, 2016).

WNT/ β -catenin pathway is considered as an upstream activator of PI3K/Akt/mTOR pathway (J. Chen, Alberts, and Li, 2014) through the inhibition of GSK-3 β (Huang, Nguyen-McCarty, Hexner, Danet-Desnoyers, and Klein, 2012). In addition, decrease of beta-catenin signaling downregulates the expression of PI3K/Akt/mTOR pathway (K. S. Park et al., 2004; Yue et al., 2010). Moreover, in adipocyte differentiation, activated PI3K/Akt pathway can induce inhibition of GSK-3 β (Ross, Erickson, Hemati, and MacDougald, 1999; Tang et al., 2005). PTEN is a PI3K inhibitor, and PTEN deletions are often observed in DLBCLs (Knittel, Liedgens, Korovkina, Pallasch, and Reinhardt, 2016).

2. c-Myc

c-Myc expression is observed in 30% to 50% DLBCL (Chisholm et al., 2015; Karube and Campo, 2015). c-Myc expression is concomitant to Bcl-2 rearrangement in 60% to 80% of DLBCL (Pedersen et al., 2014; Pillai, Sathanoori, Van Oss, and Swerdlow, 2013; Valera et al., 2013) and to Bcl-6 rearrangements but in a lower frequency (Pillai et al., 2013). c-Myc expression is more frequent in GCB-DLBCLs but also found in ABC-DLBCL (David et al., 2017; Valera et al., 2013). c-Myc is involved in human cancers and its expression participates to the development of B-cell lymphomas (Sheiness, Fanshier, and Bishop, 1978). c-Myc controls several functions, such as cell cycle, cell growth, cellular metabolism, protein synthesis, adhesion and mitochondrial function (Dang et al., 2006). c-Myc is considered as a key prognostic and predictive biomarker for survival in DLBCL, its expression is associated with worst survival rates (Johnson et al., 2012; Kluk et al., 2012; Perry et al., 2014; Valera et al., 2013; Zhou et al., 2014). c-Myc rearrangement is correlated with poor progression-free survival and overall survival in R-CHOP chemotherapy patients (Delmore et al., 2011; Kluk et al., 2012). Bcl-2, Bcl-6 and BLIMP1 rearrangements are largely associated with c-Myc expression (Boi et al., 2015; Hnisz et al., 2013; Whyte et al., 2013). In normal conditions, c-Myc is not expressed because Bcl-6 and BLIMP1 physiologically repress its expression (Karube and Campo, 2015; Y. Lin, Wong, and Calame, 1997; A. L. Shaffer et al., 2000). BCL6 expression suppresses c-Myc transcription by directly binding to its promoter (Basso et al., 2010; Ci et al., 2009, p. 6; Nahar et al., 2011). In DLBCLs, BLIMP1 disruption increases c-Myc expression (Wierstra and Alves, 2008). Activation of B-cell receptor (BCR), CD40 (cluster designation 40) and interleukin-2 (IL-2) receptors suppresses Bcl-6

activity and then prevents the inhibition of c-Myc by Bcl-6 to allowing cell division (De Silva and Klein, 2015; Oestreich, Mohn, and Weinmann, 2012).

3. NF-kappaB pathway in ABC-DLBCL

NF-kappaB signaling is a main effector of inflammation (Ben-Neriah and Karin, 2011; Karin, 2009; Pasparakis, 2009), its deregulation is implicated in numerous inflammatory processes (Ben-Neriah and Karin, 2011; Pasparakis, 2009; Tak

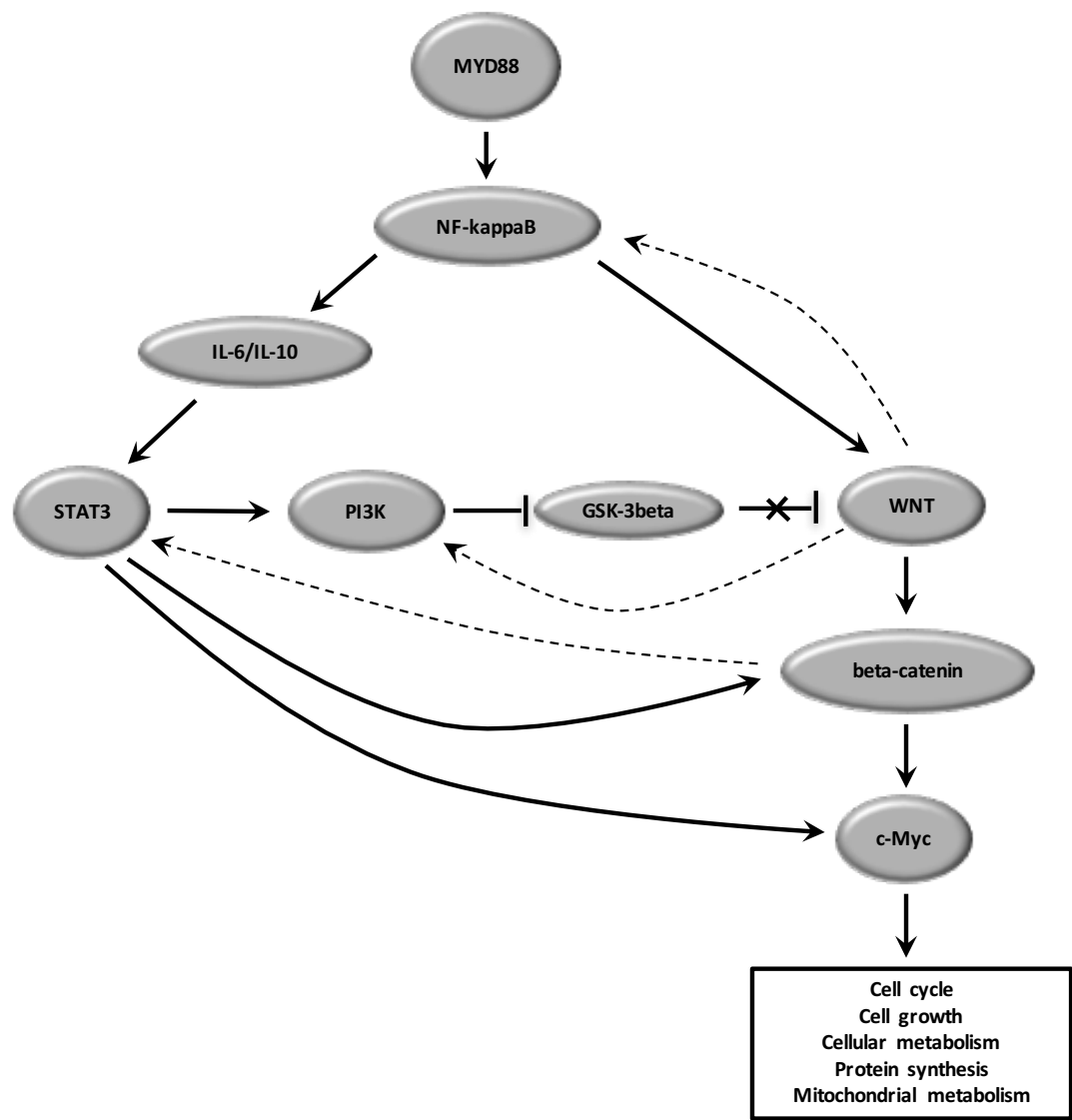


Figure 1. Oncogenic pathways involved in PCNSL. MYD88 mutations stimulate NF-kappaB activity and the neuroinflammation leading to activate IL-6 and/or IL-10. Activation of these interleukin promotes STAT3 signaling to activate PI3K/Akt pathway. PI3K inhibits GSK-3beta, the major WNT inhibitor. In PCNSL, WNT is directly activated by NF-kappaB and PI3K through the inhibition of GSK-3beta. In PCNSL, WNT ligands bind FZD receptors, LRP 5/6 and DSH, which induce beta-catenin accumulation and then beta-catenin nuclear translocation. STAT3 signaling also directly stimulates beta-catenin accumulation and c-Myc activation. In a positive feedback, WNT/beta-catenin pathway stimulates NF-kappaB, PI3K and STAT3. Nuclear beta-catenin activates c-Myc leading to stimulate cell cycle, cell growth, cellular metabolism, protein synthesis and mitochondrial metabolism.

and Firestein, 2001). NF-kappaB is a family of transcription factors which controls several genes implicated in B-cell activation, proliferation and anti-apoptotic activity (Qitang Li and Verma, 2002). NF-kappaB activity is frequently observed in DLBCL (A. L. Shaffer, Rosenwald, and Staudt, 2002). ABC-DLBCLs show high expression of NF-kappaB (Georg Lenz and Staudt, 2010) whereas GCB-DLBCL have virtually absent levels of NF-kappaB (R. E. Davis, Brown, Siebenlist, and Staudt, 2001). NF-kappaB is considered as a hallmark of ABC-DLBCL (Lam et al., 2008; Rui et al., 2016). Overexpression of NF-kappaB in ABC-DLBCLs is due to CD40 activation (Pham et al., 2002), or TNFAIP3 (A20) and MYD88 mutations (Roschewski, Staudt, and Wilson, 2014). High prevalence of MYD88 mutations is correlated with activation of BCR and NF-kappaB pathway in 90% of PCNSL cases (Batchelor, 2016; Braggio et al., 2015; Chapuy et al., 2016). Several genomically hard-wired aberrations in cellular signaling in ABC-DLBCL activate NF-kappaB pathway (Arthur L. Shaffer, Young, and Staudt, 2012). Nuclear translocation of NF-kappaB transactivates numerous target genes, including Bcl-2 family members (Tracey et al., 2005; Vallabhapurapu and Karin, 2009). MYD88 mutations engage NF-kappaB pathway to induce production of IL-6 and IL-10 in ABC-DLBCL (R. Eric Davis et al., 2010).

Interactions between WNT pathway and NF-kappaB pathway

Several studies have shown an interplay between canonical WNT/beta-catenin pathway and NF-kappaB signaling (Ma and Hottiger, 2016). Inflammation and immune response are modulated by this interaction between WNT/beta-catenin pathway and NF-kappaB (Ma and Hottiger, 2016; Nejak-Bowen, Kikuchi, and Monga, 2013; Oguma et al., 2008; Yuhang Zhang et al., 2009). Overexpression of WNT/beta-catenin pathway increases the NF-kappaB-mediated anti-apoptotic action (Noubissi et al., 2006; Spiegelman et al., 2000), and activates inflammatory processes through the stimulation of beta-catenin targets genes (Anson et al., 2012; Kuphal, Poser, Jobin, Hellerbrand, and Bosserhoff, 2004). WNT/beta-catenin pathway inhibits prolyl-hydroxylase and then activates NF-kappaB signaling (Cummins et al., 2006; Scholz et al., 2013). GSK3-beta upregulation also decreases NF-kappaB signaling (Buss et al., 2004; Saegusa, Hashimura, Kuwata, Hamano, and Okayasu, 2007). Beta-catenin accumulation activates NF-kappaB pathway in ABC-DLBCL cell lines (Bognar et al., 2016).

Moreover, the NF-kappaB signaling activates canonical WNT/beta-catenin pathway (Lamberti et al., 2001). NF-kappaB activation stimulates the expression of the TCF/LEF complex and provides an indirect positive control of WNT/beta-catenin pathway (Yun, Choi, Nam, Park, and Im, 2007). Stimulation of IKKB kinase (IKK) alpha, an activator of NF-kappaB, leads to cytosolic accumulation of beta-catenin and then activates WNT/beta-catenin pathway targets genes (Albanese et al., 2003; Lamberti et al., 2001).

Interactions between c-Myc and NF-kappaB pathway

The proliferative index of B-cell lymphomas is largely due to the activation of NF-kappaB pathway but also due to the dysregulation of c-Myc activity (Ott, Rosenwald, and Campo, 2013). c-Myc participates to the proliferation of NF-kappaB activated B cells (David et al., 2017). The interplay between NF-kappaB and STAT pathway upregulates c-Myc expression in ABC-BLCLs (Ding et al., 2008).

4. STAT pathway in ABC-DLBCLs

IL-6, epidermal growth factor (EGFR), or interferons stimulate Janus kinase (JAK) to activate signal transducer and activator of transcription 3 (STAT3) (Akira et al., 1994; Hirano, Ishihara, and Hibi, 2000; Levy and Lee, 2002). JAKs phosphorylate STAT3 at tyrosine -705 (Tyr-705) to dimerize and translocate it to the nucleus where it activates several target genes (O'Shea, 1997). Phosphorylation at Serine-727 (Ser-727) activates STAT3 in response to cytokine stimulation (Decker and Kovarik, 2000; Schuringa, Schepers, Vellenga, and Kruijer, 2001; Wen, Zhong, and Darnell, 1995). STAT pathway is aberrantly activated in ABC-DLBCL (Ding et al., 2008) and regulates genes expression to promote survival of malignant cells (Hardee et al., 2013; Scuto et al., 2011). STAT pathway induces several genes expression, including c-Myc (Rui et al., 2010, 2016). MYD88 activates NF-kappaB pathway which induces IL-6 and IL-10 expression to stimulate JAK/STAT pathway (E. Chen, Staudt, and Green, 2012; Stark and Darnell, 2012). STAT3 forms a complex with several NF-kappaB transcription factors to regulate several genes such as NFKBIA, NFKBIZ, CXCR5, CD44, and PIM2 (Hardee et al., 2013; J. Yang et al., 2007). IL-4, IL-10 and STAT pathway overexpression are correlated with aberrant activation of MYD88 pathway (Paydas, 2017).

Interactions between STAT3 signaling and WNT/beta-catenin pathway

Activation of WNT/beta-catenin pathway is related to PI3K/Akt pathway through its inhibition of GSK-3beta (Voskas, Ling, and Woodgett, 2010), and directly by STAT3 (Michaud-Levesque, Bousquet-Gagnon, and Béliveau, 2012) which is also connected with PI3K/Akt pathway (Vogt and Hart, 2011; Yokogami, Wakisaka, Avruch, and Reeves, 2000). In hepatocellular carcinoma, STAT3 signaling regulates beta-catenin and GSK-3beta protein expression (Wang et al., 2011). Beta-catenin/TCF complex directly binds to the STAT3 gene promoter to activate it (Yan et al., 2008). In breast cancer, STAT3 signaling stimulates the expression and transcriptional activity of beta-catenin (Armanious, Gelebart, Mackey, Ma, and Lai, 2010). Inhibition of STAT3 blocks glioma cell growth, invasion, migration, differentiation and cell cycle progression (Kang et al., 2010; G.-H. Li, Wei, Lv, Ji, and Wang, 2010; Sherry, Reeves, Wu, and Cochran, 2009).

Interactions between NF-kappaB, STAT3 and PI3K pathways

ABC-DLBCLs show stimulation of cytokines IL-6 and IL-10 which activate STAT3 pathway (Ding et al., 2008; Lam et al., 2008; Scuto et al., 2011). Cytokines production results from high levels of NF-kappaB activity (Staudt, 2010). Activation of NF-kappaB, STAT3 signaling and PI3K/Akt pathway are concomitant in B cell lymphomas (Dutton, Reynolds, Dawson, Young, and Murray, 2005; Fillmore et al., 2005; Rudelius et al., 2006). These three pathways play a major role in growth control, survival and chemotherapy resistance of B-cell lymphomas (Bhardwaj et al., 2007; Ghosh, Kay, Secreto, and Shanafelt, 2009; Shair et al., 2007). NF-kappaB and STAT3 stimulate c-Myc (Ding et al., 2008; Duyao, Buckler, and Sonenshein, 1990; Kiuchi et al., 1999; Murphy et al., 2008; M. Wu et al., 1996).

5. PPAR gamma

Peroxisome proliferator receptor gamma (PPAR gamma) is a ligand activated transcriptional factor which forms a heterodimer with retinoid X receptor (RXR) to activate specific peroxisome response elements (PPRE) (Ahmadian et al., 2013). PPAR gamma expression is involved in several mechanisms such as glucose and lipid metabolism, immune response, and inflammation (Elbrecht et al., 1996; Fajas et al., 1997). PPAR gamma decreases NF-kappaB activity and then represses inflammation (Ricote and Glass, 2007). PPAR gamma is expressed in several cells, such as adipocytes,

muscle cells, brain cells, immune cells (Lakatos et al., 2007). 15d-prostaglandin J2 (15d-PGJ2), lysophosphatidic acid, and nitrolinoleic acid are natural activators of PPAR gamma (E. J. Park, Park, Joe, and Jou, 2003), whereas thiazolidinediones (TZDs) and oleanic acid derivatives such as triterpenoids (2-cyano-3,12-dioxoolean-1,9-dien-28-oic-acid (CDDO)) are synthetic activators of PPAR gamma. PPAR gamma expression mediates the functions of many signaling such as connective tissue regulation, mesenchymal cell activation, differentiation and cell survival creating a link between metabolism and fibrogenesis (Wei, Bhattacharyya, Tourtellotte, and Varga, 2011).

Numerous inflammatory cytokines, chemokines, or intracellular signaling decrease PPAR gamma expression such as canonical WNT/beta-catenin pathway, TNF-alpha, interleukin (IL)-1, IL-13, Connective Tissue Growth Factor (CTGF), leptin, and lysophosphatidic acid (LPA) (Simon et al., 2005; Tan et al., 2008; Yamasaki et al., 2004). The transcription factor COUP II is a canonical WNT target and represses PPAR gamma expression (Okamura et al., 2009). In adipocytes, adiponectin increases PPAR gamma expression and decreases LPS-induced NF-kappaB expression and IL-6 production (Ajuwon and Spurlock, 2005).

PPAR gamma in ABC-DLBCLs (Figure 2)

Exposure of DLBCL cells to PPAR gamma ligands results in cell death and induction of apoptosis (J. Padilla, Kaur, Cao, Smith, and Phipps, 2000; Josué Padilla, Leung, and Phipps, 2002; Ray, Bernstein, and Phipps, 2004). TZDs and 15d-PGJ2 decrease NF-kappaB activation (Ray, Akbiyik, Bernstein, and Phipps, 2005). Telmisartan decreases NF-kappaB activity and MYD88 activation and then blocks neuroinflammation through the stimulation of PPAR gamma (Prathab Balaji, Vijay Chand, Justin, and Ramanathan, 2015). Rosiglitazone increases levels of Bcl-2 and decreases levels of Bcl-2 associated X protein (Bax) in spinal cord tissue (X. Li et al., 2013; Lv et al., 2016). The synthetic triterpenoid CDDO activates PPAR gamma to induce apoptosis in DLBCL cells (Ray et al., 2006). In DLBCL, PPAR gamma ligands regulate the expression of both mRNA and protein of GSK-3beta to promote apoptosis and beta-catenin degradation (J.-J. Liu et al., 2012). PPAR gamma ligands directly decrease WNT/beta-catenin pathway to downregulate expression of c-Myc and cyclin D1 and then inhibit tumor cell growth (Fujisawa et al., 2008; Lu and Carson, 2010).

6. Opposite interplay between WNT/beta-catenin pathway and PPAR gamma

In several diseases, WNT/beta-catenin pathway and PPAR gamma act in an opposite manner such as cancers (Lecarpentier, Claes, Vallée, and Hébert, 2017a, 2017b; Vallée, Lecarpentier, Guillevin, and Vallée, 2017b) and neurodegenerative diseases (Lecarpentier and Vallée, 2016; Vallée and Lecarpentier, 2016; Vallée, Lecarpentier, Guillevin,

and Vallée, 2017a). WNT/beta-catenin pathway and PPAR gamma interact through a TCF/LEF beta-catenin domain and a catenin-binding domain within PPAR gamma (J. Liu et al., 2006; Lu and Carson, 2010; Sharma et al., 2004; Takada, Kouzmenko, and Kato, 2009). The stimulation of PPAR gamma can be involved by the downregulation of the WNT/ β -catenin pathway (Garcia-Gras et al., 2006) whereas PPAR gamma agonists can downregulate

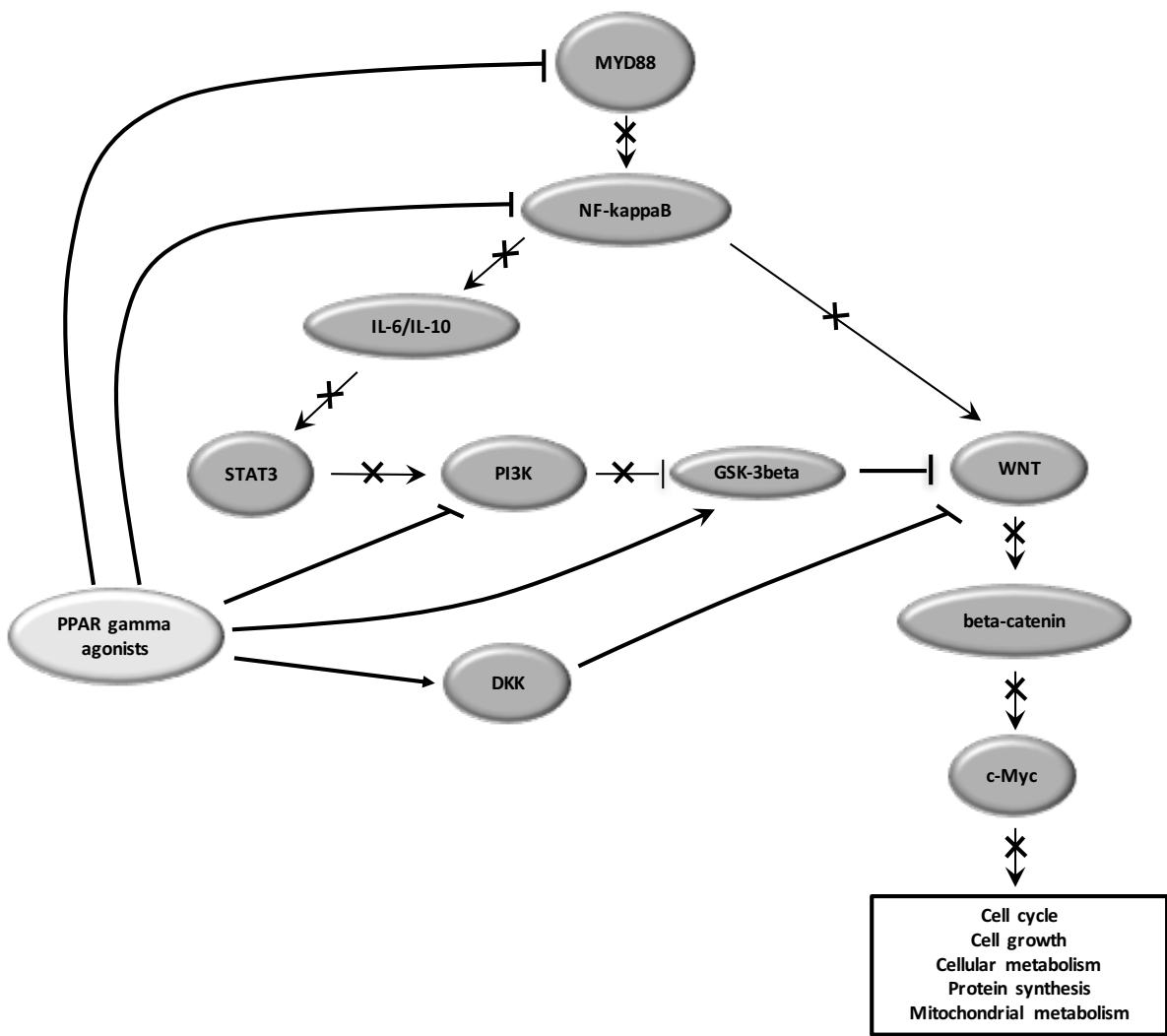


Figure 2. Actions of PPAR gamma in PCNSL. PPAR gamma agonists directly inhibit MYD88 expression and NF-kappaB activity, leading to reduce neuroinflammation. PPAR gamma agonists also decrease PI3K/Akt pathway whereas they activate GSK-3beta activity to inhibit WNT pathway. PPAR gamma agonists stimulate DKK, which downregulates WNT/beta-catenin pathway. Absence of WNT ligands prevents binding with FZD/LRP 5/6. The beta-catenin destruction complex is formed and composed by APC, AXIN and GSK-3beta, which mediates proteasomal degradation of beta-catenin. Thus, c-Myc is not activated.

expression levels of beta-catenin in many cellular systems (Elbrecht et al., 1996; Fajas et al., 1997; Moldes et al., 2003). PPAR gamma agonists can be considered as neuroprotective agents and can promote synaptic plasticity through a WNT/beta-catenin/PI3K/Akt pathway interaction (Farshbaf, Ghaedi, Shirani, and Nasr-Esfahani, 2014). The regulation of mesenchymal stem cell differentiation can also show the existence of this crosstalk (Xu et al., 2016).

Indeed, in many diseases beta-catenin signaling inhibits PPAR gamma expression (Drygiannakis et al., 2013; Farmer, 2005; Jeon et al., 2014; Kumar, Munda, and Mahato, 2014; Lee et al., 2013; Qinghua Li et al., 2012; J. Liu and Farmer, 2004; Qian, Niu, Zhai, Zhou, and Zhou, 2012; Segel et al., 2003; Shim et al., 2014). PPAR gamma agonists are considered as interesting treatments through this crosstalk (Sabatino et al., 2014). Troglitazone, a PPAR gamma agonist, can diminish c-Myc levels, a WNT target gene (Akinyeke and Stewart, 2011). In intestinal fibrosis, the activation of WNT/beta-catenin has been shown, and the use of PPAR gamma agonist can downregulate WNT/beta-catenin pathway activation and then inhibit fibrosis formation (Di Gregorio et al., 2017). PPAR gamma agonists activate Dickkopf-1 (DKK1) activity, which downregulate the canonical WNT/beta-catenin pathway and then repress the differentiation of fibroblasts (Gustafson, Eliasson, and Smith, 2010). During adipogenesis in 3T3-L1 cells, PI3K/Akt pathway activation downregulates PPAR gamma expression (Prusty, Park, Davis, and Farmer, 2002). PI3K/Akt signaling inhibits PPAR gamma expression in adipocyte differentiation (S. Kim et al., 2010; X.-D. Peng et al., 2003; H. H. Zhang et al., 2009). PI3K/Akt pathway phosphorylates GSK-3beta and then downregulates it, which negatively regulates PPAR gamma expression (Grimes and Jope, 2001; Ross et al., 1999). In adipocytes and 2T2-L1 preadipocytes, beta-catenin signaling, through the activation of Akt signaling, downregulates PPAR gamma expression (Huelsen and Behrens, 2002; Moldes et al., 2003). Moreover, inhibition of Akt pathway in 3T3-L1 cells activates PPAR gamma expression (H. J. Park et al., 2014). PPAR gamma agonists can decrease the activity of PI3K/Akt signaling pathway (Aljada, O'Connor, Fu, and Mousa, 2008; Goetze et al., 2002). Numerous inflammatory cytokines, chemokines, or intracellular signaling downregulates PPAR gamma expression, such as canonical WNT/beta-catenin pathway, TNF-alpha, interleukin (IL)-1, and IL-13 (Simon et al., 2005; Tan et al., 2008; Yamasaki et al., 2004). The

transcription factor COUP II is a canonical WNT target and downregulates PPAR gamma expression (Okamura et al., 2009). In adipocytes, adiponectin increases PPAR gamma expression and then downregulates LPS-induced NF-kappaB expression and IL-6 production (Ajuwon and Spurlock, 2005). Mesenchymal stem cell differentiation shows also a crosstalk between WNT pathway and PPAR gamma (Xu et al., 2016). Hepatic fatty acid metabolism, fatty acid oxidation, hepatic mitochondrial function and energy balance are regulated by the interaction between WNT/beta-catenin pathway and PPAR gamma (Gebhardt and Hovhannisyan, 2010; Lehwald et al., 2012; J. Liu et al., 2006). PPAR gamma is considered as a negative beta-catenin target gene (Ajmone-Cat et al., 2016; Jansson et al., 2005).

Conclusion

PCNSLs are angiocentric neoplasia which are infiltrative and extend beyond the primary lesion. ABC-DLBCL subtype represents more than 90% of PCNSLs and is the most aggressive subtype with a cure rate of only 40%. Therefore, it is essential to investigate the mechanisms underlying the development and progression of PCNSLs and to explore more effective therapeutic strategies.

In PCNSLs, the canonical WNT/beta-catenin pathway is upregulated while PPAR gamma is downregulated. These two systems act in an opposite manner. Activation of WNT/beta-catenin pathway leads to the transcription of genes involved in cell proliferation, mitochondrial metabolism, protein synthesis, and tumor growth, such as c-Myc (cf. Figure 1). c-Myc is considered as a key prognostic and predictive biomarker for survival in DLBCL, its expression is associated with worst survival rates.

In addition, STAT3 signaling pathway upregulates the expression and transcriptional activity of beta-catenin. STAT3 is a tumor aggressiveness factor. MYD88 stimulates inflammation in ABC-DLBCL through the activation of NF-kappaB pathway. NF-kappaB increases STAT3 pathway through the stimulation of IL-6 and/or IL-10 and directly increases WNT/beta-catenin pathway. STAT3 increases PI3K/Akt pathway, which inhibits GSK-3beta to activate WNT/beta-catenin pathway and thus allow beta-catenin accumulation, stabilization and nuclear translocation. Nuclear beta-catenin translocation activates WNT target genes, such as c-Myc.

Canonical WNT/beta-catenin pathway activation induces inactivation of PPAR gamma leading to a decreased in insulin sensitivity and an increased in neuro-inflammation. PPAR gamma agonists induce the inhibition of several signaling pathways such as the NF-kappaB, STAT, WNT/beta-catenin and PI3K/Akt pathways through the activation of GSK-3beta. PPAR gamma agonists may have a major negative key role in the regulation of progression of PCNSLs. The opposite interplay between WNT/beta-catenin signaling and PPAR gamma in PCNSLs provides a better understanding of the mechanisms underlying PCNSLs progression.

Author contributions

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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