Warburg effect hypothesis in autism Spectrum disorders

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disease which is characterized by a deficit in social interactions and communication with repetitive and restrictive behavior. In altered cells, metabolic enzymes are modified by the dysregulation of the canonical WNT/β-catenin pathway. In ASD, the canonical WNT/β-catenin pathway is upregulated. We focus this review on the hypothesis of Warburg effect stimulated by the overexpression of the canonical WNT/β-catenin pathway in ASD. Upregulation of WNT/β-catenin pathway induces aerobic glycolysis, named Warburg effect, through activation of glucose transporter (Glut), pyruvate kinase M2 (PKM2), pyruvate dehydrogenase kinase 1 (PDK1), monocarboxylate lactate transporter 1 (MCT-1), lactate dehydrogenase kinase-A (LDH-A) and inactivation of pyruvate dehydrogenase complex (PDH). The aerobic glycolysis consists to a supply of a large part of glucose into lactate regardless of oxygen. Aerobic glycolysis is less efficient in terms of ATP production than oxidative phosphorylation because of the shunt of the TCA cycle. Dysregulation of energetic metabolism might promote cell deregulation and progression of ASD. Warburg effect regulation could be an attractive target for developing therapeutic interventions in ASD.

Keywords: WNT/β-catenin pathway, Aerobic glycolysis, Warburg effect, Lactate, Autism spectrum disorders, LDH-a

Background

Autism spectrum disorders (ASD) is a neurodevelopmental disease which is characterized by a deficit in social interactions and communication with repetitive and restrictive behaviors [1], poor eye contact [2] and disruption of cognitive and motor development [3]. ASD is mainly diagnosed within the first three years of life. Early diagnosis is critical for better prognosis and therapeutic care [4, 5]. 10% of ASD cases are associated with a “genetic syndromic ASD” and the other cases, as “idiopathic ASD” and “primary ASD”, have no clearly known causes. Several genetic factor and environmental effects may contribute to the heterogeneity etiologic of this disease [6]. However, the etiology of ASD remains unknown.

Dysregulation of the core neurodevelopmental pathways is associated with the clinical presentation of ASD, and one of the major pathways involved in developmental cognitive disorders is the canonical WNT/β-catenin pathway [7]. Several genetic mutations observed in ASD are linked with the deregulation of the canonical WNT/β-catenin pathway by interactions between chromodomain helicase DNA binding protein 8 (CDH8) and CTNNB1 (β-catenin) [8]. Canonical WNT/β-catenin pathway has a critical role in the development of the central nervous system (CNS), and is over-expressed in ASD [7, 9, 10].

Metabolic enzymes are modified by the dysregulation of the canonical WNT/β-catenin pathway. Upregulation of WNT/β-catenin signaling leads to activation of pyruvate dehydrogenase kinase-1 (PDK-1), which decreases the activity of the pyruvate dehydrogenase complex (PDH). Upregulation of WNT/β-catenin signaling also activates monocarboxylate lactate transporter-1 (MCT-1) [11]. This do not allow the conversion of pyruvate into acetyl-coenzyme A (acetyl-CoA) in mitochondria and its entry into the tricarboxylic acid (TCA) cycle. At this stage, cytosolic pyruvate is converted into lactate for the major party. This phenomenon is called Warburg effect or aerobic glycolysis despite the availability of oxygen [12].
Mitochondrial deregulation is one of the main metabolic abnormalities observed in ASD physiopathology [13–17]. Several studies have shown a significant increase in lactate dehydrogenase kinase A (LDH-A) expression and pyruvate levels [18] with an increased lactate/pyruvate ratio [19], and elevated levels of lactate in ASD patients [20, 21].

There is some common denominator between these metabolic abnormalities, which strongly suggests the reprogramming of cellular energy metabolism with increase lactate production induced by over-expressed canonical WNT/β-catenin pathway in ASD.

We focus this review on the hypothesis of Warburg effect induced by over-expressed canonical WNT/β-catenin pathway in ASD.

### Canonical WNT/β-catenin pathway

Wingless and integration site (called WNT) pathway is a cascade of several signaling implicated in development, growth, and metabolism [22]. WNT signaling is composed by secreted lipid-modified glycoproteins [23]. WNT/β-catenin pathway is involved in numerous mechanisms such as patterning, development of synapses in the CNS [24, 25], synaptogenesis [26, 27] and the control of synaptic formation [24, 28].

Dysregulation of the canonical WNT/β-catenin pathway is observed in numerous diseases [29], such as cancers, as gliomas [30, 31] and colon cancer [32], and neurodegenerative diseases as Alzheimer’s disease [33, 34], age macular degeneration [35, 36], amyotrophic lateral sclerosis [37] and multiple sclerosis [38] (Table 1).

WNT family genes are 19 members which are classified as canonical and non-canonical WNT pathway. Canonical WNT ligands are seven, as WNT1, WNT2, WNT3, WNT8a, WNT8b, WNT10a and WNT10b). They are activators of the WNT/β-catenin pathway. Canonical WNT ligands are secreted by neurons and immune cells in the CNS [39]. The non-canonical WNT pathway is independent to β-catenin signaling and is separated into the planar cell polarity pathway and the WNT/Ca²⁺ pathway.

WNT extracellular ligands bind low density lipoprotein receptor-related protein 5 and 6 (LRP 5/6), Frizzled (FZD) receptors, and then disheveled (DSH), resulting in β-catenin accumulation and nuclear translocation. Thus, N-nuclear β-catenin bind T-cell factor/lymphoid enhancer factor (TCF/LEF) [40]. The complex formed TCF/LEF–nuclear β-catenin leads to the stimulation and the transcription of several WNT target genes (c-Myc, cyclin D1) [41].

The absence of binding between membrane receptors and WNT extracellular ligands characterizes the downregulation of WNT/β-catenin pathway. The β-catenin complex destruction is formed by adenomatous polyposis coli (APC), AXIN and glycogen synthase kinase-3β (GSK-3 β). This complex binds β-catenin to degrade it into the proteasome [42]. Activated GSK-3β downregulates β-catenin accumulation and its nuclear translocation [42, 43].

### Table 1 Canonical WNT/β-catenin pathway dysregulation

| Pathways                                      | References |
|-----------------------------------------------|------------|
| Increase Age-macular degeneration             | [35, 36]   |
| Increase Aging                                | [113]      |
| Increase Amyotrophic lateral sclerosis        | [37]       |
| Increase Atherosclerosis                      | [114]      |
| Increase Cancers                             | [97]       |
| Increase Colon cancer                         | [115]      |
| Increase Diabetes 2                          | [32]       |
| Increase Fibrosis                             | [116, 117] |
| Increase Gliomas                              | [30, 31]   |
| Increase Huntington’s disease                 | [118]      |
| Increase Multiple sclerosis                   | [34]       |
| Decrease Radiation-induced fibrosis           | [119]      |
| Decrease Alzheimer’s disease                  | [33, 34, 120] |
| Decrease Arrhythmogenic right ventricular cardiomyopathy | [121] |
| Decrease Bipolar disorder                     | [122]      |
| Decrease Osteoporosis                         | [123]      |
| Decrease Parkinson’s disease                  | [124]      |

### WNT/β-catenin pathway and PI3K/Akt pathway

Phosphatidylinositol 3-kinase/serine/threonine kinase (protein kinase B)/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway is implicated in proliferation, growth, protein synthesis and metabolism [44–47]. WNT/β-catenin pathway, through the inhibition GSK-3β activity [48], is considered as one of the main activator of PI3K/Akt/mTOR pathway [49]. GSK-3β, a major inhibitor of the WNT ligands [50], is a specific intracellular serine-threonine kinase which regulates numerous pathophysiological pathways [51–53]. PI3K/Akt pathway decreases the activity of GSK-3β in adipocyte differentiation [54, 55]. In addition, decrease of β-catenin levels downregulates the expression of PI3K/Akt/mTOR pathway [56, 57].

### Canonical WNT/β-catenin and PI3K/Akt pathways in ASD

Several studies have shown the major role of activated WNT/β-catenin pathway in ASD [58–60]. Numerous genetic components are correlated with ASD development such as WNT2 ligand [61], hepatocyte growth factor receptor (MET) which is a WNT target gene
WNT3a expression and because of the shunt of the TCA cycle. PDK terms of ATP production than aerobic glycolysis oxidative phosphorylation stays more efficient in biomass, and nucleotide synthesis [94]. However, the higher production of lactate by the upregulation of both lactate dehydrogenase A (LDH-A) and MCT-1. The higher production of lactate regardless of oxygen [12]. Activated PDK1 phosphorylates the PDH in order to stop the conversion of pyruvate into acetyl-CoA in mitochondria [93]. This conversion is proportionally diminished with a consequent reduction of acetyl-CoA entering the tricarboxylic acid (TCA) cycle. Then, cytosolic pyruvate being towards the formation of lactate which is then expelled from the cell through this action favors anabolic production of biomass, and nucleotide synthesis [94]. However, the oxidative phosphorylation stays more efficient in terms of ATP production than aerobic glycolysis because of the shunt of the TCA cycle. PDK phosphorylates the PDH in order to stop the conversion of Lac regardless of oxygen [12]. Activated PDK1 phosphorylates the PDH in order to stop the conversion of pyruvate into acetyl-coA in mitochondria [93]. This conversion is proportionally diminished with a consequent reduction of acetyl-CoA entering the tricarboxylic acid (TCA) cycle. Then, cytosolic pyruvate being towards the formation of lactate which is then expelled from the cell through this action favors anabolic production of biomass, and nucleotide synthesis [94]. However, the oxidative phosphorylation stays more efficient in terms of ATP production than aerobic glycolysis because of the shunt of the TCA cycle. PDK

Warburg effect

The Warburg effect (also named aerobic glycolysis) consists to a conversion of a large part of glucose into lactate regardless of oxygen [12]. Activated PDK1 phosphorylates the PDH in order to stop the conversion of pyruvate into acetyl-coA in mitochondria [93]. This conversion is proportionally diminished with a consequent reduction of acetyl-CoA entering the tricarboxylic acid (TCA) cycle. Then, cytosolic pyruvate being towards the formation of lactate which is then expelled from the cell through this action favors anabolic production of biomass, and nucleotide synthesis [94]. However, the oxidative phosphorylation stays more efficient in terms of ATP production than aerobic glycolysis because of the shunt of the TCA cycle. PDK

Valproate and ASD

Valproate (or Valproic acid, VPA) is an anti-convulsing agent discovered in 1963 and used for treatment of bipolar disorders or migraine [86, 87]. VPA decreases GSK-3β activity and then stimulates WNT/β-catenin pathway [88–90]. In neural stem cells of the CNS, VPA can increase WNT3a expression and β-catenin accumulation [90]. In rat models, treatment with VPA activates WNT/β-catenin pathway and inhibits GSK-3β activity, which stimulates PI3K/Akt/mTOR pathway [89, 91]. VPA increases the risk of ASD in pregnant woman during prenatal development through the stimulation of WNT/β-catenin pathway [92].

Warburg effect activation through canonical WNT/β-catenin pathway stimulation (Fig. 1)

Several studies have shown that aerobic glycolysis is induced by overactivation of the WNT/β-catenin pathway through a direct activation of PDK1 and MCT-1 [31, 35, 96, 97]. β-catenin activation induces the expression of PI3K/Akt signaling [56, 57].

Increase rate of glucose metabolism is associated with the overactivation of PI3K/Akt pathway [98]. Activation of PI3K/Akt pathway stimulates HIF-1α (hypoxia-inducible factor 1-α) [99], which induces stimulation of glycolytic enzymes such as Glut, LDH-A, PDK1 and PKM2 [99, 100].

Glut-1 and Glut-3 are mainly important for the insulin-sensitive homeostasis of glucose transport [101]. Then, the conversion of phosphoenolpyruvate (PEP) and ADP into pyruvate is the final step in glycolysis after glucose entered the cell. The enzyme pyruvate kinase (PK) catalyzes this reaction. PK have four isoforms: PKM1, PKM2, PKL, and PKR. The dimeric form of PKM2 has low affinity with PEP [102]. Under high glucose concentration, PKM2 is translocated to the nucleus through the action of peptidyl-prolyl isomerase 1 (Pin1) [103], which reduces its activity and targets PKM2 toward lysosome-dependent degradation [104]. Nuclear PKM2 binds nuclear β-catenin and then induces c-Myc-mediated expression of glycolytic enzymes including Glut, LDH-A, PDK1, and PKM2 [105]. Activated c-Myc also activates glutaminolysis and tends to nucleotide synthesis [106] by activating HIF-1α which controls PDK1 [107]. A minor part of the pyruvate is converted into acetyl-CoA which enters the TCA cycle and become citrate for promoting protein and lipid synthesis.

Lactate production in ASD

Up to now, few studies have described the expression of the different glycolytic enzymes in ASD. However, several studies have shown elevated lactate levels in ASD patients [14, 18–21, 108–110]. In the same way, production of pyruvate is stimulated [20, 110] but with an increased ratio lactate-to-pyruvate [19, 20]. A recent study has observed a significant increase in LDH-A expression and pyruvate levels in ASD [18]. A recent study have shown a decrease level of pH associated with the overproduction of lactate in ASD [111]. These findings may suggest an elevation of glycolysis through the phenomenon of aerobic glycolysis in ASD since the dysregulation of this balance has been proposed as a candidate cause of ASD [112].
The canonical WNT/β-catenin pathway is upregulated in ASD, and is one of the major pathways involved in developmental cognitive disorders. In the present review, we examine accumulating evidence of the reprogramming of cellular energy metabolism induced by over-expressed canonical WNT/β-catenin pathway for a shift in energy production from mitochondrial oxidative phosphorylation to aerobic glycolysis as the alternative of ATP despite the availability of oxygen; a phenomenon called Warburg effect. Over-activation of the WNT/β-catenin pathway induces the transduction of WNT/β-catenin target genes, c-Myc and cyclin D1, and activates PI3K/Akt pathway, leading to HIF-1α stabilization. Both transcription of WNT-responsive genes and HIF-1α stabilization induce the transactivation of genes encoding aerobic glycolysis enzymes c-Myc, PDK, LDH-A, and MCT-1, which might explain the decreased glucose entry into the TCA cycle in mitochondria, and the conversion of a large part of glucose into lactate in cytosol, observed in the ASD. Dysregulation of cellular energy metabolism induced by over-expressed canonical WNT/β-catenin pathway might promote dysregulation and progression of the core neurodevelopmental pathways associated with the clinical presentation of ASD. Warburg effect regulation might be an innovative mechanism for therapeutic development in ASD, through the canonical WNT/β-catenin pathway as potential therapeutic target.
Abbreviations
Acetyl-coA: Acetyl-Coenzyme A; APC: Adenomatous polyposis coli; ASD: Autism spectrum disorders; CNS: Central nervous system; DSH: Disheveled; FZD: Frizzled; GLUT: Glucose transporter; GSK-3β: Glycogen synthase kinase-3β; HIV-1: Human Immunodeficiency Virus; LDPH: Lactate dehydrogenase; LRP5: Low-density lipoprotein receptor-related protein 5/6; MCT-1: Monocarboxylate lactate transporter-1; PDH: Pyruvate dehydrogenase complex; PDK: Pyruvate dehydrogenase kinase; PK3-Akt: Phosphatidylinositols 3-kinase-protein kinase B; PK: Pyruvate kinase; ROS: Reactive oxygen species; TCA: Tricarboxylic acid; TCF/LEF: T-cell factor/lymphoid enhancer factor; VPA: Valproic acid

Acknowledgements
Not applicable.

Funding
No funding.

Availability of data and materials
Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Authors’ contributions
Both authors listed, have made substantial, direct and intellectual contribution to the work. Both authors read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 18 October 2017 Accepted: 13 December 2017
Published online: 04 January 2018

References
1. Posar A, Resca F, Visconti P. Autism according to diagnostic and statistical manual of mental disorders 5(th) edition: the need for further improvements. J Pediatr Neurosci. 2015;10:146–8.
2. Esposito G, Venuti P. Analysis of toddlers’ gait after six months of independent walking to identify autism: a preliminary study. Percept Mot Skills. 2008;106:259–69.
3. Esposito G, Venuti P, Maestro S, Muratori F. An exploration of symmetry in early autism spectrum disorders: analysis of lying. Brain and Development. 2009;31:131–8.
4. Ospina MB, Krebs Seida J, Clark B, Karkhanesh M, Hartling L, Tshipold L, et al. Behavioural and developmental interventions for autism spectrum disorder: a clinical systematic review. PLoS One. 2008;3:e3755.
5. Altermeier WA, Altermeier LE. How can early, intensive training help a genetic disorder? Pediatr Ann. 2009;38:167–70. 172.
6. Persico AM, Napolioli V. Autism genetics. Behav Brain Res. 2013;251:195–112.
7. Kwan V, Linda BK, Singh KK. Wnt signaling networks in autism spectrum disorder and intellectual disability. J Neurodev Disord. 2016;8:45.
8. Krumm N, O’Roak BJ, Shendure J, Eichler EEA. De novo convergence of autism genetics and molecular neuroscience. Trends Neurosci. 2014;37:95–105.
9. Caracci MO, Ávila ME, De Ferrari GV. Synaptic Wnt/GSK3β signaling hub in autism. Neural Plast. 2016;2016:9603751.
10. Mulligan KA, Cheyette BN. Neurodevelopmental perspectives on Wnt signaling in psychosis. Mol. Neuropsychiatry. 2017;2:219–46.
11. Rossignol DA, Frye RE. Mitochondrial dysfunction as a neurobiological subtype of autism spectrum disorder: evidence from brain imaging. JAMA Psychiatry. 2014;71:665–71.
12. Rossignol DA, Frye REA. Review of research trends in physiological abnormalities in autism spectrum disorders: immune dysregulation, inflammation, oxidative stress, mitochondrial dysfunction and environmental toxicant exposures. Mol Psychiatry. 2012;17:389–401.
13. Ghof S, Dong Z, Zhang Y, D’Mauro S, Peterson BS. Mitochondrial dysfunction as a neurobiological subtype of autism spectrum disorder: evidence from brain imaging. JAMA Psychiatry. 2014;71:665–71.
14. Rossignol DA, Frye RE. Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. Mol Psychiatry. 2012;17:290–314.
15. Rossignol DA, Frye RE. Review of research trends in physiological abnormalities in autism spectrum disorders: immune dysregulation, inflammation, oxidative stress, mitochondrial dysfunction and environmental toxicant exposures. Mol Psychiatry. 2012;17:389–401.
16. Rossignol DA, Frye RE. Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. Mol Psychiatry. 2012;17:290–314.
17. Rossignol DA, Frye RE. Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. Mol Psychiatry. 2012;17:290–314.
18. Rossignol DA, Frye RE. Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. Mol Psychiatry. 2012;17:290–314.
19. Rossignol DA, Frye RE. Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. Mol Psychiatry. 2012;17:290–314.
20. László A, Horváth E, Eck E, Fekete M. Serum serotonin, lactate and pyruvate levels in infantile autistic children. Clin. Chim. Acta Int. J Clin Chem. 1994;229:265–272.
21. Weissman JR, Kelley RI, Bauman ML, Cohen BH, Murray KF, Mitchell RL, et al. Mitochondrial disease in autism spectrum disorder patients: a cohort analysis. PLoS One. 2008;3:e3815.
22. van Amerongen R, Nusse R. No funding.
23. AH-Nahli. L. Wnt/B-catenin and its diverse physiological cell signaling pathways in neurodegenerative and neuropsychiatric disorders. J Neurolinguine Pharmacol. 2012:72:50–30.
24. Ahmad-Ahman A, Cian I, Simeonidis I, Herrera J, Fredy NB, Rosso SB, et al. Signaling across the synapse: a role for Wnt and Dishevelled in synapspent complex and modulation by PPAR alpha/gamma profiles in diseases with primary mitochondrial dysfunction. J Cell Biol. 2006;174:127–39.
25. Inestrosa NC, Ares J. Emerging roles of Wnts in the adult nervous system. Nat Rev Neurosci. 2010;11:77–86.
26. Itasaki N, Jones CM, Mercurio S, Rowe A, Domingos PM, Smith JC, et al. Wise, a context-dependent activator and inhibitor of Wnt signaling. Dev Comp Immunol. 2003;130:495–505.
27. Caricasole A, Ferraro T, Iacovelli L, Barletta E, Caruso A, Melchiorri D, et al. Functional characterization of WNT7A signaling in PC12 cells: interaction with a FZD5 x LRP6 receptor complex and modulation by Dickkopf proteins. J Biol Chem. 2003;278:7024–31.
28. Sharma K, Choi S-Y, Zhang Y, Nieland TJF, Long S, Li M, et al. High-throughput genetic screen for synthetogenic factors: identification of LRP6 as critical for excitatory synapse development. Cell Rep. 2013;5:130–84.
29. Caricasole A, Ferraro T, Iacovelli L, Barletta E, Caruso A, Melchiorri D, et al. Functional characterization of WNT7A signaling in PC12 cells: interaction with a FZD5 x LRP6 receptor complex and modulation by Dickkopf proteins. J Biol Chem. 2003;278:7024–31.
30. Sharma K, Choi S-Y, Zhang Y, Nieland TJF, Long S, Li M, et al. High-throughput genetic screen for synthetogenic factors: identification of LRP6 as critical for excitatory synapse development. Cell Rep. 2013;5:130–84.
31. Lecarpentier Y, Claes V, Vallée A, Guillevin R, Vallée J-N. Thermodynamics in gliomas: interactions between the canonical WNT/Beta-catenin pathway and PPAR gamma. Front Physiol. 2017;8:352.
32. Lecarpentier Y, Claes V, Duthoit G, Hébert J-L. Circadian rhythms, Wnt/beta-catenin pathway and PPAR alpha/gamma profiles in diseases with primary mitochondrial dysfunction. Front Psychiatry. 2017;45:429.
33. Lecarpentier Y, Cronin A, Guillemin R, Vallée J-N. Thermodynamics in gliomas: interactions between the canonical WNT/Beta-catenin pathway and PPAR gamma. Front Physiol. 2017;8:352.
34. Lecarpentier Y, Vallée A, Guillemin R, Vallée J-N. Thermodynamics in gliomas: interactions between the canonical WNT/Beta-catenin pathway and PPAR gamma. Front Physiol. 2017;8:352.
35. Lecarpentier Y, Vallée A, Guillemin R, Vallée J-N. Thermodynamics in gliomas: interactions between the canonical WNT/Beta-catenin pathway and PPAR gamma. Front Physiol. 2017;8:352.
36. Lecarpentier Y, Vallée A, Guillemin R, Vallée J-N. Thermodynamics in gliomas: interactions between the canonical WNT/Beta-catenin pathway and PPAR gamma. Front Physiol. 2017;8:352.
34. Vallée A, Lecarpentier Y, Guillevin R, Vallée J-N. Effects of Cannabidiol interactions with Wnt/β-catenin pathway and PPARγ on oxidative stress and neuroinflammation in Alzheimer’s disease. Acta Biochim Biophys Sin. 2017;1–4.

35. Vallée A, Lecarpentier Y, Guillevin R, Vallée J-N. Aerobic glycolysis hypothesis through WNT/β-catenin pathway in exudative age-related macular degeneration. J Mol Neurosci. MN. 2017;62:368–79.

36. Vallée A, Lecarpentier Y, Guillevin R, Vallée J-N. PPARγ agonists: potential treatments for exudative age-related macular degeneration. Life Sci. 2017; 188:123–30.

37. Lecarpentier Y, Vallée A. Opposite interplay between PPAR gamma and canonical Wnt/β-catenin pathway in amyotrophic lateral sclerosis. Front Neuro. 2016;100.

38. Vallée A, Vallée J-N, Guillevin R, Lecarpentier Y. Interactions between the canonical WNT/β-catenin pathway and PPAR gamma on Neuroinflammation, demyelination, and Remyelination in multiple sclerosis. Cell Mol Neurobiol. 2017. https://doi.org/10.1007/s10571-017-0550-9.

39. Marchetti B, Fluchino S. Wnt your brain be inflamed? Yes, it Wnt. Trends Mol Med. 2013;19:144–66.

40. Logan CY, Nusse R. The Wnt signaling pathway in development and disease. Annu Rev Cell Dev Biol. 2004;20:781–810.

41. Angers S, Moon RT. Proximal events in Wnt signal transduction. Nat Rev Mol Cell Biol. 2009;10(7):468–77.

42. Clevers H, Nusse R. Wnt/β-catenin signaling and disease. Cell. 2012;149:1192–205.

43. Aberle H, Bauer A, Stappert J, Kispert A, Kemler R. β-catenin is a target for the ubiquitin–proteasome pathway. EMBO J. 1997;16:3797–804.

44. Brazil DP, Yang Z-Z, Hemmings BA. Advances in protein kinase B signalling: AKTion on multiple fronts. Trends Biochem Sci. 2004;29:233–42.

45. Cuffreda L, Di Sanza C, Incani UC, Milella M. The mTOR pathway: a new target in cancer therapy. Curr Cancer Drug Targets. 2010;10:484–95.

46. Heras-Sandoval D, Pérez-Rojas JM, Hernández-Damián J, Pedraza-Chaverri J. The role of PI3K/AKT/mTOR pathway in the modulation of autophagy and the clearance of protein aggregates in neurodegeneration. Cell Signal. 2014;26:2694–701.

47. Vallée A, Lecarpentier Y, Guillevin R, Vallée J-N. PPAR γ hypothesis in neuroinflammation. Front Neurol. 2016;5:210.

48. Vallée A, Lecarpentier Y, Guillevin R, Vallée J-N. Aerobic glycolysis hypothesis through WNT/β-catenin pathway in exudative age-related macular degeneration. Life Sci. 2017; 188:123–30.

49. Chen J, Alberts I, Li X. Dysregulation of the IGF-I/PI3K/AKT/mTOR signaling pathway in neurodegeneration. Cell Death Dis. 2014;5:e1379.

50. Zhou B, Buckley ST, Patel V, Liu Y, Luo J, Krishnaveni MS, et al. Troglitazone attenuates TGF-β-induced EMT in alveolar epithelial cells via a PPARγ-independent mechanism. PLoS One. 2012;7:e38827.

51. Ambarchi KH, Pitzul KB, Karajgikar M, Hamilton A, Ferguson SS, Cregan SP. Sequence phosphorylation of CCAAT enhancer-binding protein beta by MAPK and glycogen synthase kinase 3beta is required for adipogenesis. Proc Natl Acad Sci U S A. 2005;102:9766–71.

52. Ross SE, Erickson RL, Hemati N, MacDougald OA. Glycogen synthase kinase 3 is an insulin-regulated C/EBPalpha kinase. Mol Cell Biol. 1995;15:8433–41.

53. Ross SE, Erickson RL, Hemati N, MacDougald OA. Glycogen synthase kinase 3 is an insulin-regulated C/EBPalpha kinase. Mol Cell Biol. 1995;15:8433–41.

54. Ross SE, Erickson RL, Hemati N, MacDougald OA. Glycogen synthase kinase 3 is an insulin-regulated C/EBPalpha kinase. Mol Cell Biol. 1995;15:8433–41.

55. Ross SE, Erickson RL, Hemati N, MacDougald OA. Glycogen synthase kinase 3 is an insulin-regulated C/EBPalpha kinase. Mol Cell Biol. 1995;15:8433–41.

56. Ross SE, Erickson RL, Hemati N, MacDougald OA. Glycogen synthase kinase 3 is an insulin-regulated C/EBPalpha kinase. Mol Cell Biol. 1995;15:8433–41.

57. Ross SE, Erickson RL, Hemati N, MacDougald OA. Glycogen synthase kinase 3 is an insulin-regulated C/EBPalpha kinase. Mol Cell Biol. 1995;15:8433–41.

58. Ross SE, Erickson RL, Hemati N, MacDougald OA. Glycogen synthase kinase 3 is an insulin-regulated C/EBPalpha kinase. Mol Cell Biol. 1995;15:8433–41.
82. Mao H, Lebrun DG, Yang J, Zhu VF, Li M. Deregulated signaling pathways in glioblastoma multiforme: molecular mechanisms and therapeutic targets. Cancer Investig. 2012;30:48–56.

83. Kwon C-H, Luikart BW, Powell OM, Zhou J, Matheny SA, Zhang W, et al. Pten regulates neuronal arborization and social interaction in mice. Neuron. 2006;50:177–88.

84. Lugo JN, Smith GD, Arbuckle EP, White J, Holley AJ, Floruta CM, et al. Deletion of Pten produces autism-like behavioral deficits and alterations in synaptic proteins. Front Mol Neurosci. 2014;7:27.

85. Chen Y, Huang W-C, Séjourné J, Clippeon-Allen AE, Page DT. Pten mutations Alter brain growth trajectory and allocation of cell types through elevated β-catenin signaling. J Neurosci. 2015;35:10252–67.

86. Meunier H, Garaz G, Neunier Y, Fymard P, Aimard M. Pharmacodynamic properties of N-dipropylacetic acid. Therapie. 1963;18:435–8.

87. Peterson GM, Naunton M. Valproate: a simple chemical with so much to offer. J Clin Pharm Ther. 2005;30:417–21.

88. Phiel CJ, Zhang F, Huang EY, Guenther MG, Lazar MA, Klein PS. Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. J Biol Chem. 2001;276:36734–41.

89. Go HS, Kim KC, Choi CS, Jeon SJ, Kwon XL, Han S-H, et al. Pten expression to valproic acid increases the neural progenitor cell pool and induces macrocephaly in rat brain via a mechanism involving the GS3-38/β-catenin pathway. Neuropathology. 2012;63:1028–41.

90. Wang L, Liu Y, Li S, Long Z-Y, Wnt WY-M. Signaling pathway participates in valproic acid-induced neural differentiation of neural stem cells. Int J Clin Exp Pathol. 2015;8:8578–85.

91. Qin L, Dai X, Yin Y. Valproic acid exposure sequentially activates Wnt and mTOR pathways in rats. Mol Cell Neurosci. 2016;75:27–35.

92. Christensen J, Gränborg TK, Sørensen MJ, Schendel D, Parmer ET, Pedersen LH, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA. 2013;309:1696–703.

93. Roche TE, Baker JC, Yari X, Hiromasa Y, Gong X, Peng T, et al. Distinct regulatory properties of pyruvate dehydrogenase kinase and phosphatase isoforms. Proc Natl Acad Sci U S A. 2001;70:33–75.

94. Zhang S, Huver MW, McMillan RP, Cline MA, Gilbert ER. The pivotal role of pyruvate dehydrogenase kinase in metabolic flexibility. Nutr Metab. 2014;11:10.

95. Lee HK. The role of pyruvate dehydrogenase kinase in diabetes and obesity. Diabetes Metab J. 2014;38:181–6.

96. Thompson CB. Wnt meets Warburg: another piece in the puzzle? EMBO J. 2014;33:1420–2.

97. Lecarpentier Y, Claes V, Vallée A, Hebert J-L. Thermodynamics in cancers: opposing interactions between PPAR gamma and the canonical WNT/β-catenin pathway. Clin Transl Med. 2017;6:14.

98. Reuter S, Gupta SC, Chatunvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? Free Radic Biol Med. 2010;49:1603–16.

99. Sun Q, Chen X, Ma J, Peng H, Wang F, Zha X, et al. Mammalian target of rapamycin up-regulation of pyruvate kinase isoenzyme type M2 is critical for aerobic glycolysis and tumor growth. Proc Natl Acad Sci U S A. 2011;108:4129–34.

100. Serrano GL, HIF-1: upstream and downstream of cancer metabolism. Curr Opin Genet Dev. 2010;20:51–9.

101. McEwen BS, Reagan LP. Glucose transporter expression in the nervous system: relationship to synaptic function. Eur J Pharmacol. 2004;490: 13–24.

102. Christofk HR, Vander Heiden MG, Harris MH, Ramanathan A, Gersztken RE, Wei R, et al. The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. Nature. 2008;452:230–3.

103. Harris RA, Tindle L, Cumming RC. Age-dependent metabolic dysregulation in cancer and Alzheimer's disease. Biogerontology. 2014;15:559–77.

104. Lu L, Li D, Zhao D, Lin R, Chu Y, Zhang H, et al. Acetylation targets the M2 isoform of pyruvate kinase for degradation through chaperone-mediated autophagy and promotes tumor growth. Mol Cell. 2011;42:719–30.

105. Yang W, Xia Y, Hawke D, Li X, Liang J, Xing D, et al. PRK2 phosphorylates histone H3 and promotes gene transcription and tumorigenesis. Cell. 2012;150:685–96.

106. Wise DR, DeBerardinis RJ, Mancuso A, Sayed N, Zhang X-Y, Pfeiffer HK, et al. Myc regulates a transcriptional program that stimulates mitochondrial glutaminolysis and leads to glutamine addiction. Proc Natl Acad Sci U S A. 2008;105:18782–7.