WWOX and metabolic regulation in normal and pathological conditions

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Abstract

WW domain-containing oxidoreductase (WWOX) spans the common fragile site FRA16D. There is evidence that translocations and deletions affecting WWOX accompanied by loss of expression are frequent in many cancers and often correlate with a worse prognosis. Additionally, WWOX germline mutations were also found to be the cause of pathologies of brain development. Because WWOX binds to some transcription factors, it is a modulator of many cellular processes, including metabolic processes. Recently, studies have linked WWOX to familial dyslipidemias, osteopenia, metabolic syndrome, and gestational diabetes, confirming its role as a regulator of steroid, cholesterol, glucose, and normal bone metabolism. The WW domain of WWOX is directly engaged in the control of the activity of transcription factors such as HIF1α and RUNX2; therefore, WWOX gene alterations are associated with some metabolic abnormalities. Presently, most interest is devoted to the associations between WWOX and glucose and basic energy metabolism disturbances. In particular, its involvement in the initiation of the Warburg effect in cancer or gestational diabetes and type II diabetes is of interest. This review is aimed at systematically and comprehensively presenting the current state of knowledge about the participation of WWOX in the metabolism of healthy and diseased organisms.

Keywords WW domain-containing oxidoreductase WWOX · Steroid metabolism · Lipid metabolism · Glucose metabolism · Bone metabolism

Introduction

WW domain-containing oxidoreductase (WWOX) spans the common [1] fragile site FRA16D, which is located within a region of frequent loss-of-heterozygosity (LOH) [2, 3]. It is associated with homozygous deletions [1, 2], translocations [3, 4], and other alterations in many cancers [5–7]. More recently, pathogenic variants and mutations in WWOX were also described, and these mutations cause a broad range of ultrarare neurodevelopmental and brain degenerative disorders [8], such as WWOX-related epileptic encephalopathy (WOREE syndrome) [9, 10], autosomal recessive spinocerebellar ataxia 12 (SCAR12) [9, 11], and disorder of sex differentiation (DSD) [12, 13]. WWOX alterations have also been observed in cases of disorders such as metabolic syndrome [14], gestational diabetes [15], dyslipidemia [16], and osteopenia [24].

The WWOX gene encodes a 46-kDa protein that contains two N-terminal WW domains and one short-chain dehydrogenase/reductase (SDR) domain [17]. The WW domains are responsible for protein–protein interactions and bind proteins sharing PPxY (where P is proline, Y is tyrosine, and x is any amino acid) motifs [18, 19]. Several WWOX protein partners have been recognized, including p73 [20], ErbB4 [21], Ap2α [22] and γ [23], RUNX2 [24], DVL-2 [25], and HIF1α [26]. These interactions show that WWOX is involved in many cellular processes, such as cell proliferation, differentiation, and metabolism. The central SDR domain, whose function is still unknown, is probably responsible for catalyzing the conversion of some low molecular weight ligands, most likely steroids [27].

The first report indicating the role of WWOX in metabolism was a study that used Wwox-knockout (KO) mutant
mice bred by Aqeilan et al., which suffer from severe metabolic defects that lead to growth retardation and postnatal lethality [28]. At birth, Wwox KO pups were identical to WT littermates [24]. However, at 3 days, Wwox KO pups were smaller and died by 4 weeks after birth because of severe metabolic defects, mainly hypoglycemia [24, 28]. Researchers observed that Wwox KO mice had aberrant serum levels of lipids, carbohydrates, and proteins [24]. Moreover, Wwox hypomorphic mice that display reduced levels of Wwox expression also had a shorter lifespan than WT mice. However, these mice survived, which is in contrast to the Wwox KO mice that showed postnatal lethality [29]. The authors suggested that lower Wwox levels are sufficient to overcome the postnatal lethality that was observed in Wwox KO mice [29].

The role of WWOX in steroid metabolism

The amino acid sequence analysis of the SDR (the short-chain dehydrogenase/reductase) domain in WWOX has suggested its role in steroid hormone metabolism [17, 27, 30]. WWOX is highly expressed in hormonally regulated or hormone-secreting organs, such as the prostate, mammary glands, ovaries, and the brain [31]. The high expression in this type of tissue implies that WWOX is probably involved in the modulation of steroid metabolism. In vitro experiments showed that sex steroids, such as estrogen and androgen, lead to the upregulation of WWOX expression [32, 33], and Wwox KO mice were characterized by impaired steroidogenesis [34]. Additionally, the mammary-specific KO of Wwox in mice disturbed mammary gland development, as defects in mammary branching morphogenesis and ductal outgrowth were observed [35]. Furthermore, in Wwox KO mice, defects in the mouse reproductive system were also observed [28]. They are characterized by alterations in the expression of steroidogenic enzymes, impaired levels of steroids, and gonadal dysfunction [28]. Follicle-stimulating and luteinizing hormones were attenuated, and ovaries were significantly smaller in the female Wwox KO mouse model than in the control model. Additionally, the testes of Wwox hypomorphic males had a high number of atrophic seminiferous tubules and reduced levels of testosterone and fertility disturbance in comparison to their wild-type counterparts [28]. All these data suggest that WWOX is associated with gonadal development and plays a crucial role in the normal functioning of hormonally regulated organs and in steroid metabolism.

The growth and survival of early-stage prostate cancers depend on androgens [36, 37]. It was shown that treatment to suppress or block the production or action of male hormones causes them to regress [38]. The absence or reduction of WWOX expression has been indicated to be involved in prostate carcinoma [39–41]. Some authors have suggested that the tumor suppressor function of WWOX may be important during the phase of prostate cancer progression when cancer cells shift to be androgen-independent [42]. Additionally, a Wwox-deficient mouse model showed that the loss of Wwox expression results in testosterone reduction, a condition that may affect prostate functionality. Moreover, it was reported that WWOX overexpression induced cell apoptosis and suppressed prostate cancer growth in vitro [22] and in vivo [39].

Apart from the relationship between WWOX and steroid hormone metabolism, the interrelation with estrogen receptors (ER) has also been investigated, especially in breast cancer. A reduction in estrogen receptor expression was observed in the case of WWOX KO in the MCF7 ER-positive breast cancer cell line [43], and a positive correlation between WWOX expression and ER status was observed in breast cancer patients [42]. The strong relationship between WWOX expression and ER status complements the aforementioned evidence for its involvement in sex steroid metabolism.

The WWOX gene modulates lipid metabolism

Lipid metabolism is the process of synthesis and degradation of lipids in cells [44]. It involves the processes of breakdown or storage of fats to obtain energy and the synthesis of structural and functional lipids. There are three major classes of membrane lipid molecules—phospholipids, cholesterol, and glycolipids [45]. High-density lipoproteins (HDLs) absorb cholesterol and carry it back to the liver, where it is ultimately removed from the body. Higher levels of serum HDL cholesterol (HDL-C) can lower the risk for heart disease and stroke [46, 47], and the incidence of metabolic syndrome increases as HDL levels decrease [48, 49].

Single-nucleotide variants of the WWOX gene were associated with the level of HDL-C [50, 51]. Eight genetic variants in the human WWOX gene were significantly associated with low-HDL levels [51]. Initially, an association of region-wide significance between the rs2548861 variant of WWOX and low HDL-C levels was identified in families of Mexican and European descent with dyslipidemia [16]. This association was also confirmed in the control population [16]. A population effect of this variant on HDL-C levels was demonstrated in large population-based studies [16]. Furthermore, the longitudinal effect of the rs2548861 variant was observed on HDL-C levels in a prospective cohort followed for more than 20 years [16]. Interestingly, the association between the rs2548861 variant in WWOX and HDL levels demonstrated an opposite trend in the Roma population [52]. Lee et al. proposed that the
The uptake of external lipids also plays a central role in requires high levels of fatty acid and lipid synthesis [60]. It contains an extremely high content of lipids. Myelination for the proper functioning of the nervous system [60]. It is worth mentioning that ABCA1 participates phenotypes that resemble what is observed in WOREE patients. It is worth mentioning that hippocampal neurons from Alzheimer’s disease patients are characterized by reduced WWOX protein levels compared to controls, and loss of WWOX function has an influence on tau hyperphosphorylation by modulating the activity of the GSK3β, EKR, and JNK kinases and the generation of Aβ aggregation [57, 72]. Interesting is also the mechanism by which WWOX is involved in the myelination. As it was described earlier, WWOX has a global effect on lipid metabolism pathways and maintenance of cellular lipid homeostasis, which most likely takes place also in the nervous system. Recently, it has been shown that WWOX directly interacts with proteins involved in protein trafficking, endosome, and lysosome networks, like SIMPLE, which were shown to cause the dominant demyelinating Charcot-Marie-Tooth neuropathy type 1C (CMT1C) [73].

In conclusion, WWOX gene alterations are associated with lipid metabolism. They are associated with low plasma HDL-C levels, aberrant triglyceride (TG) levels, and TG/
HDL or HDL/LDL index impairment. Thus, the WWOX gene is therefore a promising target for future research in preventing and treating cardiovascular and neurological diseases.

**Participation of WWOX in glucose metabolism**

Over the past decade, an increasing number of reports indicating the role of WWOX in the regulation of glucose metabolism have emerged [14, 15, 26, 74]. In light of the increasing incidence of sugar metabolism disorders among different human populations, gaining more knowledge about the genes and mechanisms contributing to its pathophysiology is necessary. The participation of WWOX in the control of glucose metabolism is also important in the context of its role as a tumor suppressor.

The genomic region containing the WWOX gene has been identified as a genetic risk factor for glucose metabolic diseases. A GWAS (genome-wide association study) of type 2 diabetes (T2DM) demonstrated that, among others, the rs7192960 genetic variant near the WWOX gene is associated with reduced insulin secretion [75] and that WWOX rs17797882 was associated with decreased HOMA-β (β-cell function indicator) in the Han Chinese population [76]. However, this was not confirmed in the Japanese population [77]. Other authors analyzed GWAS data from the Type 2 Diabetes Knowledge Portal and reported that several variants within WWOX are related to metabolic syndrome disorders, including T2DM [14]. Other studies have shown that the WWOX locus is also associated with other disorders linked to metabolic syndrome, such as obesity susceptibility [78], hypertension [79], and coronary artery calcification [80].

As a result of our observation in pregnancy-associated diabetes, we proposed that the WWOX gene can be an essential contributor to the pathogenesis of gestational diabetes mellitus (GDM) [15]. Decreased WWOX expression and, in particular, a reduction in the WWOX/HIF1A ratio were observed in GDM patients compared to those without GDM [15]. It is also worth mentioning that gestational diabetes patients were characterized by high HIF1α expression and its target genes. Hypoxia-inducible factors (HIFs) are transcription factors that play an essential role in controlling the cell response to hypoxia and take part in “the Warburg effect” [81, 82]. It was stated that WWOX, via its first WW domain, interacts with HIF1α and modulates its transactivation function [26]. The consequence of WWOX downregulation was the transcriptional upregulation of the glycolytic phenotype in leukocytes of patients with GDM [15]. The expression of the glucose transporter SLC2A1 and the glycolytic gene PKF, PKM2, and LDHA mRNA was significantly increased in patients with GDM compared with the control subjects. Moreover, the expression of SLC2A4, which is an insulin-dependent glucose transporter, was significantly reduced in leukocytes [15].

We did not observe differences in HK2 expression between the tested groups. However, the expression of HK2, PFK, PKM2, and SLC2A1 correlated with HIF1A, but only in the GDM patient group. More importantly, the aforementioned correlations were stronger with the WWOX/HIF1A ratio than with the expression of WWOX alone. These results indicate that WWOX can modulate HIF1α activity in normal tissues in gestational diabetes patients, regulate glucose metabolism, and participate in GDM pathogenesis. Moreover, in GDM patients, a positive correlation between HIF1A expression and glycated hemoglobin (HbA1c), an overall glycermic marker, was also observed [15].

Our further analysis of the importance of WWOX in glucose metabolism in a human fibroblast cell line revealed that in normoxic and normoglycemic conditions, WWOX deficiency leads to increased HIF1A mRNA and protein expression. Additionally, it increases the translocation of HIF1A to the nucleus and amplifies its transactivation function [74]. The expression levels of SLC2A1, ENO1, PKM2, PDK, and SLC2A4 were increased in WWOX KO cells, and insulin-dependent and insulin-independent glucose uptake, hexokinase, and lactate dehydrogenase enzymatic activities were upregulated. This clearly indicates that WWOX silencing leads to a shift toward anaerobic glycolysis under normoxic conditions. In terms of its importance in diabetes, studies in hyperglycemic conditions also found that, although fibroblasts are not typical insulin target cells and show little metabolic response to insulin, the level of insulin-dependent glucose uptake under hyperglycemic culture conditions was several times lower in WWOX KO cells than in control cells [74]. In addition, under hypoxic hyperglycemic conditions, HIF1α transactivation function was increased in WWOX KO cells, and increases in the expression of its target genes PFK, PKM2, and PDK were observed. Simultaneously, an increase in lactate concentration has been noted [74].

Initially, WWOX was indicated to play a role in glucose metabolism in mouse models [14, 24, 26, 28]. As mentioned above, WWOX physically and functionally interacts with HIF1α and coordinates its transactivation function in vitro and in vivo [26]. Wwox KO mice demonstrated higher levels of serum lactate [26]. Additionally, mouse embryonic fibroblasts (MEFs) from KO embryos [26] and muscles of mice with muscle-specific ablation of Wwox [14] exhibited increases in HIF1α levels and its activity, and the expression of its target genes, which encode key glycolytic enzymes, was increased [14, 26]. This clearly indicates that the downregulation of WWOX expression and especially a low WWOX/HIF1A ratio lead to a shift toward anaerobic glycolysis. Additionally, glucose uptake is increased, which is probably due to increased GLUT1 expression [26]. Moreover, WWOX deficiency seems to be related to increases in HIF1α.
expression levels and transcription factor activity, resulting in cell metabolism modifications.

Simultaneously, pyruvate dehydrogenase kinase (PDK1) upregulation was also observed in WWOX-knockout cell lines and mouse tissues [26, 74]. PDK1 is an enzyme responsible for the inactivation of pyruvate dehydrogenase, which catalyzes the conversion of pyruvate to acetyl-CoA [83]. Acetyl-CoA is a major substrate in the citric acid cycle that carries out cellular respiration. The upregulation of PDK1 levels blocks glucose influx into the tricarboxylic acid (TCA) cycle. It was also shown that WWOX is connected with TCA cycle inhibition. It has been shown in the Drosophila melanogaster model that the WWOX ortholog plays an important role in controlling aerobic metabolism and ROS formation [84, 85]. In this model, functional WWOX interactions with isocitrate dehydrogenase (IDH) and superoxide dismutase (SOD) were identified [84]. A significant positive correlation between WWOX and the mRNA levels of the isocitrate dehydrogenase family member IDH1 was also observed in many human cancer cell lines [84]. Isocitrate dehydrogenase is an enzyme that catalyzes the oxidative decarboxylation of isocitrate in the TCA cycle [86], so the connection between WWOX and IDH1 levels confirmed the contribution of WWOX to maintaining metabolic homeostasis. Superoxide dismutase is an enzyme that catalyzes the dismutation of superoxide radicals (O$_2^−$) to molecular oxygen (O$_2$) and hydrogen peroxide (H$_2$O$_2$), assuring cellular protection against reactive oxygen species [87]. SOD1 overexpression correlates with increases in Wwox transcripts [84]. Additionally, Sod mutations in flies led to changes in endogenous Wwox transcript levels compared with flies ectopically overexpressing human SOD1. The ectopic expression of human SOD1 in the human HEK294 cell line also resulted in an increase in endogenous WWOX mRNA expression levels [84]. Ectopic WWOX expression in the D. melanogaster model led to higher ROS levels, while a decrease in WWOX led to a reduction in ROS levels [84]. These findings indicate that Wwox can play a protective role under conditions of oxidative stress. A Drosophila melanogaster model with a reduction in Wwox expression showed reduced mitochondrial respiration by decreasing the expression of all six mitochondrial respiratory chain genes (ND23, ND42, ND75, CG7580, CoVa, and CoVb) [88]. Then, a significant percentage of modified flies presented a phenotype with abnormal eye development [88]. It was previously reported that a reduction in the expression of these genes resulted in a visible disruption to eye morphology, which is indicative of cellular dysfunction. These phenotypes indicate that the decreased expression of mitochondrial respiratory complex genes leads to significant cellular dysfunction, so affecting mitochondrial function by WWOX deficiency is relevant [88]. However, the modification of other pathways underlying these developmental defects by WWOX cannot be ruled out. Mice with muscle-specific ablation of Wwox are also characterized by decreases in mitochondrial mass and TCA cycle gene expression (SDHA, OGDH, MDH2, IDH2, FH1, DDLST, and DLP1) [14]. Since active HIF1α inhibits the Krebs cycle [89], disruptions of the WWOX–HIF1α interaction are probably responsible for the occurrence of this phenotype.

The involvement of WWOX in metabolic syndrome was also proposed. Mice with a tissue-specific ablation of Wwox in skeletal muscles develop a phenotype similar to metabolic syndrome [14]. These mice exhibited hyperglycemia, obesity, and dyslipidemia. These mice also have high fasting plasma glucose and basal insulin levels, so they are deficient in their ability to take up glucose and suffer from insulin resistance [14]. Consequently, Wwox expression in skeletal muscles can be fundamental for maintaining glucose homeostasis.

Our results suggest an even more extended, systemic effect of WWOX on insulin sensitivity. It is also interesting that an analysis of the body composition of mice with muscle-specific ablation of Wwox showed a significant increase in fat mass with an accompanying decrease in the lean body mass, even though food intake was decreased, compared with control mice [14]. At the molecular level, AMP-activated protein kinase (AMPK) activity was decreased in mice with Wwox ablation in skeletal muscles [14]. The relationship between Wwox and AMPK expression was also confirmed in a mouse myoblast cell line, so Wwox is probably a direct AMPK activator. AMPK is a key metabolic regulator known for glucose uptake stimulation and is proposed as a promising target in relation to metabolic disorders [90–92].

Moreover, type II diabetes is also a major risk factor for cognitive decline and dementia in the elderly population [93]. In Goto Kakizaki rats, which are a spontaneous model of noninsulin-dependent diabetes mellitus, an increase in activated WWOX levels was detected in the brain cortex of younger rats, while a decrease was observed in older rats [94]. In the differentiated human neuroblastoma SH-SY5Y cell line, activated WWOX was observed after 24 h of culture in high glucose [94]. Generally, glucose is the main energy substrate for the mammalian brain, and because of the high energy demand of nerve cells, neurons require continuous delivery of glucose. Neurons use glucose as a supply of the precursors for neurotransmitter synthesis and ATP for fueling their activity [95]. The principal component analysis (PCA) of global transcriptome data suggested that WWOX is involved in maintaining basic glucose metabolism in undifferentiated human neural progenitor cells (hNPC) as well as in differentiated neurons [96]. Among the genes which differentiate variants with low/high WWOX expression were several important genes participating in basic metabolism, such as PDK1, LDHA, PFKP, HK2, and HIF1α [96]. Thus, disturbed expression of WWOX in nerve cells most likely leads to disordered metabolic processes.
Disruptions of glucose transport and metabolism impair neurons’ functionality, which is the case with neurodegenerative diseases, such as Alzheimer’s or Parkinson’s disease [97], with which WWOX has been associated. The changes of the glycolysis are seen early in neurodegenerative diseases [98], and some authors suggest that metabolic disturbances may be a root cause of neurodegeneration [99]. The limitation of aerobic glycolysis in brain areas of amyloid deposition and higher accumulation of tau protein was observed in the case of Alzheimer’s disease patients [98]. Glycolysis and mitochondrial function are also decreased in Parkinson’s disease patients [100]. It has been shown that increasing glycolysis may slow neurodegeneration [100]. WWOX has been also implicated in epilepsy [61, 68]. It was observed that the anaerobic glycolysis and concentration of lactate in the epileptogenic brain increased in comparison to the control [101]. What is important, lactate can act as a signal molecule in brain cells and affect neuronal excitation [101]. The role of WWOX in the control of glucose metabolism in the context of neurological diseases requires further research.

In cancer cells, glucose metabolism is converted to fuel cell growth and division in adaptation to excessive and uncontrolled cancer cell proliferation [102]. Alterations cause changes within glucose transporters (GLUTs), enzymes of the glycolytic pathway, hypoxia-inducible factor (HIF), monocarboxylate transporters (MCTs), and lactate dehydrogenase [102]. Metabolic rearrangements lead to a preference for aerobic glycolysis by most cancer cells [102]. Aberrant glycolysis, instead of oxidative phosphorylation, in the presence of oxygen is a phenomenon called the Warburg effect [103]. WWOX knockdown in the MCF7 breast cancer cell line led to the upregulation of HIF1α glycolytic genes. Additionally, in breast cancer samples, WWOX expression negatively correlated with GLUT1 levels, which supports the hypothesis that WWOX modulates cancer glucose metabolism [26]. Furthermore, in a rescue experiment in MCF7 breast cancer cells, the upregulation of WWOX suppressed HIF1α target gene expression [26].

**Influence of WWOX on bone metabolism**

Apart from the aforementioned defects, the homozygous deletion of Wwox in mice caused disturbances in bone metabolism, such as osteopenia [24]. The decrease in trabecular bone density along with the thinning of the inner cortex led to the development of disproportionately smaller limbs in Wwox-deficient mice [24]. Osteoblasts isolated from Wwox-deficient mice exhibited disturbances in differentiation, beginning at the mineralization stage [24]. Additionally, an increase in osteoclast activity was observed [24]. In Wwox KO mouse osteoblasts, it was shown that the expression of markers of the early stage (Runx2, Alp), matrix production (Bsp, ColII), and mineralization stage (Oc) significantly declined, so they could not produce sufficient bone matrix to compensate for bone loss [24]. Microcomputed tomography analyses showed significantly decreased parameters of bone formation, such as changes in bone growth, density, formation, and resorption characteristics in Wwox−/− mice [24]. Moreover, measurements showed a 50% reduction in serum calcium and a 20% increase in serum phosphate concentration in Wwox-deficient mice [24]. Calcium and phosphate metabolism and the maintenance of their homeostasis are key for physiology and skeletal mineralization [104]. Interestingly, in Wwox KO mice, the upregulation of thyroid hormone was identified, which is known to contribute to metabolic bone disease [24].

The principal transcriptional regulator involved in osteoblast differentiation is RUNX2 [105–107]. It was shown that WWOX physically interacts with RUNX2 [24]. This inhibits the transcription factor function of RUNX2, leading to the repression of many RUNX2 targets involved in bone matrix formation [24]. In Wwox KO mice, Runx2 expression was increased in calvarial and femoral bones [24]. Therefore, WWOX is able to regulate RUNX2 at two levels: as an indirect inhibitor of RUNX2 expression and as a suppressor of RUNX2 transcriptional activity. Nearly one-third of Wwox KO mice develop osteosarcomas [28]. In human osteosarcomas, WWOX expression is reduced, and a positive correlation between WWOX expression and patient response to chemotherapy was found [108]. In a human osteosarcoma cell line model, the ectopic expression of WWOX inhibited proliferation and attenuated invasion in vitro and suppressed tumorigenicity in mice [109]. Most likely, the disruption of the WWOX–RUNX2 interaction is crucial for osteosarcoma development. RUNX2 mRNA and protein levels increase in bony tissues of Wwox−/− deficient mice [109]. It was also found that high WWOX expression was associated with reduced RUNX2 expression in osteosarcoma cell lines [109]. An inverse WWOX and RUNX2 interaction was not as clear in human osteosarcomas as in cell lines. Thus, this relationship may be more complicated in in vivo tumors due to the complexity of various further aberrations [110]. The suppression of the transactivation function of RUNX2 by WWOX probably contributes to the tumor suppressor role of WWOX. It is also meaningful that RUNX2 is overexpressed in breast and prostate cancer metastases to bone [111, 112].

**Conclusions**

In this review, we have attempted to emphasize what we consider to be important knowledge about the role of the WWOX gene in metabolism. There is growing evidence of the tumor suppressor activity of WWOX in a number of different
cancers. Moreover, WWOX germline mutations were recognized as the cause of severe developmental pathologies of the brain, such as autosomal recessive spinocerebellar ataxia 12 (SCAR12) and WWOX-related epileptic encephalopathy (WOREE syndrome). In addition to typical tumor suppressor functionalities related to proliferation or invasion, WWOX-related metabolic changes have been observed in many different cancers. Several reports have indicated the role of WWOX in the regulation of steroid, cholesterol, glucose, and bone metabolism, which is summarized in Fig. 1.

WWOX binding is capable of binding to hundreds of different proteins, including many transcription factors (TF), thereby modulating the transcription of a wide variety of genes. One of the most important known partners of WWOX is TFs, such as HIF1α and RUNX2. WWOX is involved in the control of the transcriptomic activity of these factors; therefore, WWOX gene alterations are associated with multiple metabolic abnormalities. One of particular interest is the involvement of WWOX in the pathology of glucose and basic energy metabolism. WWOX participates in the induction of the Warburg effect in cancer or the pathology of gestational diabetes and diabetes type II. Conceivably, the partnership between WWOX and HIF1α is crucial in the regulation of tumor metabolism and diabetes pathology. WWOX can play a protective role by controlling HIF1α activity, and it makes the influx of glucose into mitochondria possible. Therefore, it is able to correct the operation of the Krebs cycle and thus prevents the Warburg effect. Moreover, WWOX is associated with pathologies related to mineral metabolism, including bone formation and calcification. Proper WWOX protein structure and concentration are crucial requirements in postnatal survival, growth, and metabolism and probably play an essential role in the regulation of bone tissue formation. According to the current knowledge, all these functions and disorders are realized through the WW domain through which WWOX binds to a number of proteins to modify their action. Furthermore, mouse models and human genetic studies have established a significant physiological role for WWOX in lipid and lipoprotein metabolism. WWOX is probably involved in the complicated interactions that maintain cholesterol homeostasis and is an important regulator of HDL and TG levels, in both humans and mice.

WWOX is a hub protein that globally regulates gene expression by modifying TF activity in particular, and it is one of the crucial molecular elements of cell functioning. Specific pathologies associated with mutations, genetic variants, and differential WWOX transcription are dependent on the type of cell and tissue, the stage of differentiation, and the development or physiological state. Thorough understanding of the complex mechanisms of action of the WWOX protein will surely provide an understanding of many pathologies and hopefully pave the way for new therapies. Thus, accumulating reports demonstrating the potential

![Fig. 1 Schematic model of information about the WWOX role in metabolism](image-url)
role of WWOX in many types of metabolic disorders and metabolic rearrangements in cancer opens the possibility for its therapeutic implementation while also contributing to our understanding on a basic science level.

**Author contribution** All authors contributed to the conception and design of the review article. Izabela Baryła performed the literature search and wrote the first draft of the manuscript. Katarzyna Kosla and Andrzej K. Bednarek critically revised the work. All authors read and approved the final manuscript.

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**Declarations**

**Ethics approval and consent to participate** Not applicable.

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**References**

1. Paige AJ, Taylor KJ, Stewart A, Sgouros JG, Gabra H, Sellari GC, Smyth JF, Porteous DJ, Watson JE (2000) A 700-kb physical map of a region of 16q23.2 homozygously deleted in multiple cancers and spanning the common fragile site FRA16D. Cancer Res 60:1690–1697

2. Mangelsdorf M, Ried K, Woollatt E, Dayan S, Eyre H, Finnis M, Hobson L, Nancarrow J, Venter D, Baker E et al (2000) Chromosomal fragile site FRA16D and DNA instability in cancer. Cancer Res 60:1683–1689

3. Ried K, Finnis M, Hobson L, Mangelsdorf M, Dayan S, Nancarrow J, Woollatt E, Kremmendidios G, Gardner A, Venter D et al (2000) Common chromosomal fragile site FRA16D sequence: identification of the FOR gene spanning FRA16D and homologous deletions and translocation breakpoints in cancer cells. Hum Mol Genet 9:1651–1663. https://doi.org/10.1093/hmg/9.11.1651

4. Tchurikov NA, Uroshiev LA, Klushevskaya ES, Alembekov IR, Lagarkova MA, Kravatskaya GI, Makeyev YY, Kravatsky YV (2021) Chromosomal translocations in NK-cell lymphomas originate from inter-chromosomal contacts of active RDNA clusters possessing hot spots of DSBs. Cancer 13:3889. https://doi.org/10.3390/cancers13153889

5. Eki ziglu S, Bulut P, Karaman E, Kilic E, Buyru N (2015) Epigenetic and genetic alterations affect the WWOX gene in head and neck squamous cell carcinoma. PLoS ONE 10:e0115353. https://doi.org/10.1371/journal.pone.0115353

6. Abdeen SK, Ben-David U, Shweiki A, Maly B, Ageilan RI (2018) Somatic loss of WWOX is associated with TP53 perturbation in basal-like breast cancer. Cell Death Dis 9:832. https://doi.org/10.1038/s41419-018-0896-z

7. Kosla K, Pluciennik E, Kurzak A, Jesienek-Kupniczka D, Kordek R, Potemski P, Bednarek AK (2011) Molecular analysis of WWOX expression correlation with proliferation and apoptosis in glioblastoma multiforme. J Neurooncol 101:207–213. https://doi.org/10.1007/s10937-010-0254-1

8. Iacomin M, Baldassari S, Tochigi Y, Kosla K, Buffelli F, Torella A, Severino M, Paladini D, Mandarà L, Riva A et al (2020) Loss of Wwox perturbs neuronal migration and impairs early cortical development. Front Neurosci 14:644. https://doi.org/10.3389/fnins.2020.00644

9. Gribaa M, Salih M, Anheim M, Lagier-Tourenne C, H’mida D, Drouot N, Mohamed A, Elmalik S, Kabiraj M, Al-Rayess M et al (2007) A new form of childhood onset, autosomal recessive spinocerebellar ataxia and epilepsy is localized at 16q21-Q23. Brain 130:1921–1928. https://doi.org/10.1093/brain/awm078

10. Su T, Yan Y, Xu S, Zhang K, Xu S (2020) Early onset epileptic encephalopathy caused by novel compound heterozygous mutation of WWOX gene. Int J Dev Neurosci 80:157–161. https://doi.org/10.1002/jidn.10013

11. Mallaret M, Synofzik M, Lee J, Sagun MA, Mahajnah M, Sharkia R, Drouot N, Renaud M, Klein FAC, Anheim M et al (2014) The tumour suppressor gene WWOX is mutated in autosomal recessive spinocerebellar ataxia with epilepsy and mental retardation. Brain 137:411–419. https://doi.org/10.1093/brain/awt338

12. White S, Hewitt J, Turbitt E, van der Zwan Y, Hersmus R, Drop S, Koopman P, Harley V, Cools M, Looijenga L et al (2012) A multi-exon deletion within WWOX is associated with a 46, XY disorder of sex development. Eur J Hum Genet 20:348–351. https://doi.org/10.1038/ejhg.2011.204

13. Piard J, Hawkes L, Milh M, Villard L, Borgatti R, Romaniello R, Fradin M, Capri Y, Hérion D, Nougues M-C et al (2019) The phenotypic spectrum of WWOX-related disorders: 20 additional cases of WOREE syndrome and review of the literature. Genet Med 21:1308–1318. https://doi.org/10.1038/s41436-018-0339-3

14. Abu-Rmeileh M, Abu-Rmeileh M, Akkawi R, Knani I, Udi S, Pacold ME, Tam J, Ageilan RI (2019) WWOX somatic ablation in skeletal muscles alters glucose metabolism. Mol Metab 22:132–140. https://doi.org/10.1016/j.molmet.2019.01.010

15. Baryla I, Pluciennik E, Kosla K, Wojcik M, Zieniuk A, Zarawsk-Klis M, Cypryk K, Wozniak LA, Bednarek AK (2021) Identification of a novel association for the WWOX/HIF1A axis with gestational diabetes mellitus (GDM). PeerJ 9:e10604. https://doi.org/10.7717/peerj.10604

16. Lee JC, Weissvelg-Volkov D, Kytälä M, Dastani Z, Cantor RM, Sobel EM, Plaisier CL, Engert JC, van Greevenbroek MJM, Kane JP et al (2008) WW-domain-containing oxidoreductase is associated with low plasma HDL-C levels. The American Journal of Human Genetics 83:180–192. https://doi.org/10.1016/j.ajhg.2008.07.002

17. Bednarek AK, Laflin KJ, Daniel RL, Liao Q, Hawkins KA, Aldaz CM (2000) WWOX, a novel WW domain-containing protein mapping to human chromosome 16q23.3–24.1, is a Region Frequently Affected in Breast Cancer. Cancer Res 60:2140–2145.

18. Luís-Meyers JH, Kil H, Bednarek AK, Drake J, Bedford MT, Aldaz CM (2004) WWOX binds the specific proline-rich ligand PPXY: identification of candidate interacting proteins. Oncogene 22:132–140. https://doi.org/10.1038/sj.onc.1207680

19. Rotem-Bamberger S, Fahoum J, Keinan-Adamsky K, Tsaban T, Avraham O, Shaley DE, Chill JH, Schueler-Furman O (2021) Tandem WW/PPXY motif interactions in WWOX: the multifaceted role of the second WW domain. Biophysics. https://doi.org/10.1101/2021.12.01.470705
Abdeen SK, Salah Z, Khawaled S, Aqeilan RI (2013) Characterization of WWOX inactivation in murine mammary gland development. J Cell Physiol 228:1391–1396. https://doi.org/10.1002/jcp.24310

Dehm SM, Tindall DJ (2006) Molecular regulation of androgen action in prostate cancer. J Cell Biochem 99:333–344. https://doi.org/10.1002/jcb.20794

Basu S, Tindall DJ (2010) Androgen action in prostate cancer. HORM CANC 1:223–228. https://doi.org/10.1007/s12672-010-0044-4

Gomella LG (2009) Effective testosterone suppression for prostate cancer: is there a best castration therapy? Rev Urol 11:52–60

Qin HR, Iliopoulos D, Semb S, Fabbri M, Druck T, Volinia S, Croce CM, Morrison CD, Klein RD, Huebner K (2006) A role for the WWOX gene in prostate cancer. Cancer Res 66:6477–6481. https://doi.org/10.1158/0008-5472.CAN-06-0956

Lin J-T, Li H-Y, Chang N-S, Lin C-H, Chen Y-C, Lu P-J (2015) WWOX suppresses prostate cancer cell progression through cyclin D1-mediated cell cycle arrest in the G1 phase. Cell Cycle 14:408–416. https://doi.org/10.4161/15384101.2014.977103

Qin HR, Iliopoulos D, Nakamura T, Costinean S, Volinia S, Druck T, Sun, Okumura H, Huebner K (2007) Wwox suppresses prostate cancer cell growth through modulation of ErbB2-mediated androgen receptor signaling. Mol Cancer Res 5:957–965. https://doi.org/10.1158/1541-7786.MCR-07-0211

Abdeen RI, Sultan Z, Al Shibli D, Sarea E, Abu-Odeh M, Zanesi N, Croce CM, Nawaz Z, Aqeilan RI (2011) WWOX inactivation enhances mammary tumorigenesis. Oncogene 30:3900–3906. https://doi.org/10.1038/onc.2011.115

Gyamfi D, Ofori Awuah E, Owusu S (2019) Lipid metabolism. Mol Nutr Fats. Elsevier pp. 17–32 ISBN 978-0–12–811297–7

Albert B, Johnson A, Lewis J, et al. (2002) Molecular Biology of the Cell, 4th edn. Garland Science: New York. ISBN 978–0–8153–3218–3

Wannamethee SG, Shaper AG, Ebrahim S (2005) HDL-cholesterol, total cholesterol, and the risk of stroke in middle-aged British men. Stroke 31:1882–1888. https://doi.org/10.1161/11.1888

Bots ML, Elwood PC, Nikitin Y, Salonen JT, de Convalles AF, Inzitari D, Sivenius J, Benetou V, Tuomaine L, Koudstaal PJ et al (2002) Total and HDL cholesterol and risk of stroke. EUROSTROKE: a collaborative study among research centres in Europe. J Epidemiol Commun Health 56:119–124. https://doi.org/10.1136/jech.56.suppl_1.i19

Liu X, Tao L, Cao K, Wang Z, Chen D, Guo J, Zhu H, Yang X, Wang Y, Wang J et al (2015) Association of high-density lipoprotein with development of metabolic syndrome components: a five-year follow-up in adults. BMC Public Health 15:412. https://doi.org/10.1186/s12889-015-1747-9

Mani P, Ren H-Y, Neeland U, McGuire DK, Ayers CR, Khera A, Rohatgi A (2017) The association between HDL particle concentration and incident metabolic syndrome in the multi-ethnic Dallas heart study. Diabetes Metab Syndr 11:S175–S179. https://doi.org/10.1016/j.dsx.2016.12.028

Sánchez ME, González-Pérez A, Martínez-Larrad MT, Gayán J, Real LM, Serrano-Ríos M, Ruiz A (2010) WWOX gene is associated with hdl cholesterol and triglyceride levels. BMC Med Genet 11:148. https://doi.org/10.1186/1471-2350-11-148

Iatan I, Choi HY, Ruel I, Reddy MVPL, Kil H, Lee J, Odeh MA, Salah Z, Abu-Remaileh M, Weissgass-Volkov D et al (2014) The WWOX gene modulates high-density lipoprotein and lipid
metabolism. Circ Cardiovasc Genet 7:491–504. https://doi.org/10.1161/CIRCGENETICS.113.000248
52. Piko P, Fiatal S, Kós Z, Sándor J, Ádány R (2019) Generalizability and applicability of results obtained from populations of European descent regarding the effect direction and size of hdl-c level-associated genetic variants to the Hungarian general and Roma populations. Gene 686:187–193. https://doi.org/10.1016/j.gene.2018.11.067
53. Leduc MS, Lyons M, Darvishi K, Walsh K, Sheehan S, Amend S, Cox A, Orho-Melander M, Kathiresan S, Paigen B et al (2011) The mouse QTL map helps interpret human genome-wide association studies for HDL cholesterol. J Lipid Res 52:1139–1149. https://doi.org/10.1194/jlr.M009175
54. Babashamsi MM, Koutkiaho SO, Halalkhor S, Salimi A, Babashamsi M (2019) ABCA1 and metabolic syndrome; a review of the ABCA1 role in HDL-VLDL production, insulin-glucose homeostasis, inflammation and obesity. Diabetes Metab Syndr 13:1529–1534. https://doi.org/10.1016/j.dsx.2019.03.004
55. Peregó C, Da Dalt L, Pirillo A, Galli A, Catapano AL, Norata GD (2019) Cholesterol metabolism, pancreatic ß-cell function and diabetes. Biochimica et Biophysica Acta (BBA) - Mol Basis Dis 1865:2149–2156. https://doi.org/10.1016/j.bbadis.2019.04.012
56. Sánchez-Aguilera P, Diaz-Vegas A, Campos C, Quinteros-Waltemath O, Cerda-Kohler H, Barrientos G, Contreras-Ferrat A, Llanos P (2018) Role of ABCA1 on membrane cholesterol content, insulin-dependent Akt phosphorylation and glucose uptake in adult skeletal muscle fibers from mice. Biochimica et Biophysica Acta (BBA) - Mol Cell Biol Lipids 1863:1469–1477. https://doi.org/10.1016/j.bbalip.2018.09.005
57. Aldaz CM, Hussain T (2020) WWOX loss of function in neurodevelopmental and neurodegenerative disorders. Int J Mol Sci 21:E8922. https://doi.org/10.3390/ijms21238922
58. Estes RE, Lin B, Khera A, Davis MY (2021) Lipid metabolism influence on neurodevelopmental disease progression: is the vehicle as important as the cargo? Front Mol Neurosci 9:203–208. https://doi.org/10.3389/fnins.2021.78663
59. Chrast R, Saher G, Nave K-A, Verheijen MHG (2011) Lipid metabolism in myelinating glial cells: lessons from human inherited disorders and mouse models. J Lipid Res 52:419–434. https://doi.org/10.1194/jlr.R009761
60. Poitelon Y, Kopec AM, Belin S (2020) Myelin fat facts: an overview of lipids and fatty acid metabolism. Cells 9:E812. https://doi.org/10.3390/cells9040812
61. Repudi S, Steinberg DJ, Elazar N, Breton VL, Aquilino MS, Saleem R, Saher G, Nave K-A, Verheijen MHG (2011) Replication of genome-wide association signals of type 2 diabetes in Han Chinese in a prospective cohort: replication of Chinese diabetes GWAS. Clin Endocrinol 76:365–372. https://doi.org/10.1111/j.1365-2265.2010.04175.x
62. Baryla I, Styczerski-Binkowska E, Plucienik E, Kosla K, Bednarek AK (2022) The WWOX/HIF1A axis downregulation alters glucose metabolism and predispose to metabolic disorders. J Mol Biol 23:3326. https://doi.org/10.3390/jmbs23063326
63. Chang Y-C, Chiu Y-F, Liu P-H, Shih K-C, Lin M-W, Sheu WH-H, Quertermous T, Curb JD, Hsiung CA, Lee W-J et al (2012) Replication of genome-wide association signals of type 2 diabetes in Han Chinese in a prospective cohort: replication of Chinese diabetes GWAS. Clin Endocrinol 76:365–372. https://doi.org/10.1111/j.1365-2265.2011.04175.x
64. Permana S, Lukman H, Norahmawati E, Eka Puspita O (2019) Faisal Moh Al Zein, D.; Kawamoto, Y.; Tri Endharti, A. East Asian genome-wide association study derived loci in relation to type 2 diabetes in the Han Chinese population. Acta Biochim Pol 66:679–686. https://doi.org/10.18388/abp.2020_5563
65. Sakakai K, Imamura M, Tanaka Y, Iwata M, Hirose H, Kaku K, Maegawa H, Watada H, Toke K, Kashiwagi A et al (2013) Replication study for the association of 9 East Asian GWAS-derived loci with susceptibility to type 2 diabetes in a Japanese population. PLoS ONE 8:e76317. https://doi.org/10.1371/journal.pone.0076317
66. Wang K, Li W-D, Zhang CK, Wang Z, Glessner JT, Grant SF, Zhao H, Hakonarson H, Price RA (2011) A genome-wide association study on obesity and obesity-related traits. PLoS ONE 6:e18939. https://doi.org/10.1371/journal.pone.0018939
67. Yang H-C, Liang Y-J, Chen J-W, Chuang C-M, Ho H-Y, Ting C-T, Lin T-H, Sheu S-H, Tsai W-C et al (2012) Identification of IGF1, SLC4A4, WWOX, and SFMBT1 as hypertension susceptibility genes in Han Chinese with a genome-wide
gene-based association study. PLoS ONE 7:e32907. https://doi.org/10.1371/journal.pone.0032907

80. Polfus LM, Smith JA, Shimmin LC, Bielak LF, Morrison AC, Kardia SLR, Peyser PA, Hixson JE (2013) Genome-wide association study of gene by smoking interactions in coronary artery calcification. PLoS ONE 8:e74642. https://doi.org/10.1371/journal.pone.0074642

81. Courtnay R, Ngo DC, Malik N, Ververis K, Tortorella SM, Karagiannis TC (2015) Cancer metabolism and the Warburg effect: the role of HIF-1 and PI3K. Mol Biol Rep 42:841–851. https://doi.org/10.1007/s11033-015-3858-x

82. Kietzmann T, Mennerich D, Dimova EY (2016) Hypoxia-inducible factors (HIFs) and phosphorylation: impact on stability, localization, and transactivity. Front Cell Dev Biol 4. https://doi.org/10.3389/fcell.2016.00011

83. Milne JLS (2013) Structure and regulation of pyruvate dehydrogenases. In Encyclopaedia of biological chemistry. Elsevier. pp. 321–328 ISBN 978-0-12-378631-9.

84. O’Keefe LV, Colella A, Dayan S, Chen Q, Choo A, Jacob R, Price G, Venter D, Richards RI (2011) Drosophila orthologue of WWOX, the chromosomal fragile site FRA16D tumour suppressor gene, functions in aerobic metabolism and regulates reactive oxygen species. Hum Mol Genet 20:497–509. https://doi.org/10.1093/hmg/ddq495

85. O’Keefe LV, Lee CS, Choo A, Richards RI (2015) Tumor suppressor WWOX contributes to the elimination of tumorigenic cells in Drosophila melanogaster. PLoS ONE 10:e0136356. https://doi.org/10.1371/journal.pone.0136356

86. Al-Khallal H (2017) Isocitrate dehydrogenases in physiology and cancer: biochemical and molecular insight. Cell Biosci 7(37). https://doi.org/10.1186/s13578-017-0165-3

87. Wang Y, Branicky R, Noë A, Hekimi S (2018) Superoxide dismutases: dual roles in controlling ROS damage and regulating ROS signaling. J Cell Biol 217:1915–1928. https://doi.org/10.1083/jcb.201708007

88. Choo A, O’Keefe LV, Lee CS, Gregory SL, Shaukat Z, Colella A, Lee K, Denton D, Richards RI (2015) Tumor suppressor WWOX moderates the mitochondrial respiratory complex: WWOX’S dehydrogenase/reductase enzyme function. Genes Chromosomes Cancer 54:745–761. https://doi.org/10.1002/gcc.22286

89. Kim J, Tchernyshyov I, Semenza GL, Dang CV (2006) HIF-1-mediated expression of pyruvate dehydrogenase kinase: a metabolic switch required for cellular adaptation to hypoxia. Cell Metab 3:177–185. https://doi.org/10.1016/j.cmet.2006.02.002

90. Entezari M, Hashemi D, Taherizam A, Zabolian A, Mohammadi S, Fahki F, Hashemi M, Hushmandi K, Ashrafzadeh M, Zarrabi A et al (2022) AMPK signaling in diabetes mellitus, insulin resistance and diabetic complications: a pre-clinical and clinical investigation. Biomed Pharmacother 146:112563. https://doi.org/10.1016/j.biopha.2021.112563

91. Long YC, Zierath JR (2006) AMP-activated protein kinase signaling in metabolic regulation. J Clin Invest 116:1776–1783. https://doi.org/10.1172/JCI29044

92. Srivastava RAK, Finkosky SL, Filippov S, Hanselman JC, Cramer CT, Newton RS (2012) AMP-activated protein kinase: an emerging drug target to regulate imbalances in lipid and carbohydrate metabolism to treat cardio-metabolic diseases. J Lipid Res 53:2490–2514. https://doi.org/10.1194/jlr.R025882

93. Umegaki H (2014) Type 2 diabetes as a risk factor for cognitive impairment: current insights. CIA 1011. https://doi.org/10.2147/CIA.S48926

94. Carvalho C, Moreira PI (2021) WWOX: a new therapeutic target in type 2 diabetes-associated neurodegeneration. Metabolism 116:154616. https://doi.org/10.1016/j.metabol.2020.154616

95. Mengenthaler P, Lindauer U, Dineel GA, Meisel A (2013) Sugar for the brain: the role of glucose in physiological and pathological brain function. Trends Neurosci 36:587–597. https://doi.org/10.1016/j.tins.2013.07.001

96. Kosla K, Plucienick E, Styczek-Binkowska E, Nowakowska M, Orzechowska M, Bednarek AK (2019) The WWOX gene influences cellular pathways in the neuronal differentiation of human neural progenitor cells. Front Cell Neurosci 13:391. https://doi.org/10.3389/fncel.2019.00391

97. Han R, Liang J, Zhou B (2021) Glucose metabolic dysfunction in neurodegenerative diseases-new mechanistic insights and the potential of hypoxia as a prospective therapy targeting metabolic reprogramming. Int J Mol Sci 22:5887. https://doi.org/10.3390/ijms22115887

98. Bell SM, Burgess T, Lee J, Blackburn DJ, Allen SP, Moritibos H (2020) Peripheral glycolysis in neurodegenerative diseases. Int J Mol Sci 21:E8924. https://doi.org/10.3390/ijms21238924

99. Muddapa VR, Dharsini SAP, Chakravarty VS, Gromiha MM (2020) Neurodegenerative diseases - is metabolic deficiency the root cause? Front Neurosci 14:213. https://doi.org/10.3389/fnins.2020.00213

100. Cai R, Zhang Y, Simmering JE, Schultz JL, Li Y, Fernandez-Carasa I, Consiglio A, Raya A, Polgreen PM, Narayanan NS et al (2019) Enhancing glycolysis attenuates Parkinson’s disease progression in models and clinical databases. J Clin Invest 129:4539–4549. https://doi.org/10.1172/JCI129987

101. Fei Y, Shi R, Song Z, Wu J (2020) Metabolic control of epilepsy: a promising therapeutic target for epilepsy. Front Neurol 11:592514. https://doi.org/10.3389/fneur.2020.592514

102. Fadaka A, Ajiboye B, Ojo O, Adewale O, Olayide I, Emuwohocore R (2017) Biology of glucose metabolism in cancer cells. Journal of Oncological Sciences 3:45–51. https://doi.org/10.1016/j.jons.2017.06.002

103. Warburg O (1925) The metabolism of carcinoma cells. The Journal of Cancer Research 9:148–163. https://doi.org/10.1158/jcr.1925.148

104. Shaker JL, Deftos L (2018). Calcium and Phosphate Homeostasis. In Feingold K. R. (Eds.) Endotext, MDText.com, Inc. 286. https://doi.org/10.3389/fnins.2018.00011

105. Wang Y, Zeng Y, Fan W, Wang Y, Lu M, Li J (2017) Hypoxia induced inactivation of WWOX nuclear isoform WWOX-O by DNA methylation: implications for WWOX tumor suppressor gene. J Biol Chem 292:12960–12969. https://doi.org/10.1074/jbc.M117.741811

106. Komori T (2006) Regulation of osteoblast differentiation by transcription factors. J Cell Biochem 99:1233–1239. https://doi.org/10.1002/jcb.20958

107. Bruderer M, Richards RG, Alini M, Stoddart MJ (2014). Role and regulation of RUNX2 in osteogenesis. eCM 28:269–286. https://doi.org/10.22203/ECM.v028a19

108. Wen J, Xu Z, Li J, Zhang Y, Fan W, Wang Y, Lu M, Li J (2017) Decreased WWOX expression promotes angiogenesis in osteosarcoma. Oncotarget 8:60917–60932. https://doi.org/10.18632/oncotarget.17126

109. Kurek KC, Del Mare S, Salah Z, Abdeen S, Sadiq H, Lee S, Gaudio E, Zanesi N, Jones KB, DeYoung B et al (2010) Frequent attenuation of the WWOX tumor suppressor in osteosarcoma is associated with increased tumorigenicity and aberrant RUNX2 expression. Cancer Res 70:5577–5586. https://doi.org/10.1158/0008-5472-CAN-09-4602

110. Del Mare S, Kurek KC, Stein GS, Lian JB, Aqeilian RI (2011) Role of the WWOX tumor suppressor gene in bone
homeostasis and the pathogenesis of osteosarcoma. Am J Cancer Res 1:585–594
11. Akech J, Wixted JJ, Bedard K, van der Deen M, Hussain S, Guise TA, van Wijnen AJ, Stein JL, Languino LR, Altieri DC et al (2010) Runx2 association with progression of prostate cancer in patients: mechanisms mediating bone osteolysis and osteoblastic metastatic lesions. Oncogene 29:811–821. https://doi.org/10.1038/onc.2009.389

112. Mendoza-Villanueva D, Zeef L, Shore P (2011) Metastatic breast cancer cells inhibit osteoblast differentiation through the Runx2/CFBβ-dependent expression of the Wnt antagonist, sclerostin. Breast Cancer Res 13:R106. https://doi.org/10.1186/bcr3048

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