ZBTB16 and Metabolic Syndrome: a Network Perspective

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Summary
Metabolic syndrome is a prevalent, complex condition. The search for genetic determinants of the syndrome is currently undergoing a paradigm enhancement by adding systems genetics approaches to association studies. We summarize the current evidence on relations between an emergent new candidate, zinc finger and BTB domain containing 16 (ZBTB16) transcription factor and the major components constituting the metabolic syndrome. Information stemming from studies on experimental models with altered Zbtb16 expression clearly shows its effect on adipogenesis, cardiac hypertrophy and fibrosis, lipid levels and insulin sensitivity. Based on current evidence, we provide a network view of relations between ZBTB16 and hallmarks of metabolic syndrome in order to elucidate the potential functional links involving the ZBTB16 node. Many of the identified genes interconnecting ZBTB16 with all or most metabolic syndrome components are linked to immune function, inflammation or oxidative stress. In summary, ZBTB16 represents a promising pleiotropic candidate node for metabolic syndrome.

Key words
Metabolic syndrome • Systems biology • Pleiotropy • Animal models

Introduction
Metabolic syndrome is a prevalent condition with a worldwide surge of both incidence and prevalence (Aguilar et al. 2015). The syndrome is defined by presence of at least three out of five clinical criteria [elevated waist circumference, elevated triglycerides (or treatment), reduced high-density lipoprotein cholesterol (or treatment), elevated blood pressure (or treatment) and elevated fasting glucose (or treatment)] are diagnosed as having the condition (Alberti et al. 2009). Distinct cut-points are set for all criteria, except elevated waist circumference, which must rely on population and country-specific definitions. All individual constituents of metabolic syndrome are multifactorial traits with substantial heritable and environmental components. The genetic architecture of the syndrome is complex and usually involves numerous gene-gene, nutrigenetic and pharmacogenetic interactions (Seda et al. 2005c). Therefore, the identification of genetic determinants of metabolic syndrome in the general human population is complicated by numerous factors that cannot be easily controlled (Bureau et al. 2015). Despite over 1000 highly significant associations (P<5 × 10-8) of DNA polymorphisms with individual components of metabolic syndrome or the complete metabolic syndrome being currently inventoried in the NHGRI-EBI Catalog of Published Genome-Wide Association Studies (http://www.ebi.ac.uk/gwas, accessed on May 30th, 2017), we are still far from attaining a clinically utilisable algorithm for genetic risk assessment and prediction.
Systems genetic approaches are gaining ground in analysis of complex diseases, identifying not only single polymorphisms, but rather nodes within networks and pathways crucial for disease onset and pathogenesis (Civelek and Lusis 2014). One of the emergent genes with mounting evidence for its implication in metabolic syndrome is promyelocytic leukemia zinc finger.

PLZF / ZBTB16

Promyelocytic leukemia zinc finger (PLZF), also known by the HUGO Gene Nomenclature Committee approved name ZBTB16 (zinc finger and BTB domain containing 16), was initially discovered in humans as a cause of retinoic acid-resistant acute promyelocytic leukemia in the form of fusion protein PLZF-RARα associated with the t(11;17)(q23;q21) translocation (Grignani et al. 1998). ZBTB16 is expressed in numerous tissues and well conserved in mammals. Human and mouse/rat ZBTB16 proteins show 97%-96% identity over 673 aminoacid residues of the protein, respectively. Within its C-terminus, this transcription factor contains nine Cys2-His2 type zinc fingers that facilitate sequence-specific DNA binding to its target genes (Li et al. 1997, Suliman et al. 2012). There is a repressor domain RD2 which interacts with ETO co-repressor (Melnick et al. 1998) and a N-terminal BTB/POZ (bric-a-brac-tramtrack-broad complex, poxvirus and zinc-finger) multimerization/repression domain (Ahmad et al. 1998) as shown in Figure 1. As a member of the POK (POZ and Krüppel zinc finger (ZF)) family of proteins, ZBTB16 induces epigenetic changes, including histone modifications and DNA methylation, thus regulating the chromatin state (Puszyk et al. 2013). ZBTB16 also interacts, through its three N-terminal zinc-finger motifs, with nuclear receptors, in particular with retinoic acid receptor (RAR) α, blocking the RAR-RXR heterodimerization necessary for retinoic acid signaling (Martin et al. 2003). As a multifaceted signaling hub for number of cellular processes, ZBTB16 is a target of several post-translational modifications, including ubiquitination (Sobieszczuk et al. 2010), phosphorylation (Costoya et al. 2008), acetylation (Guidez et al. 2005) and sumoylation, i.e. activation of SUMO molecules (Kang et al. 2003). The regulators of PLZF activity include CBP/p300 acetyltransferase, sirtuin 1 and histone deacetylase 3 (McConnell et al. 2015, Puszyk et al. 2013). PLZF also robustly responds to glucocorticoids (Fahrenstich et al. 2003, Chen et al. 2014). Although traditionally viewed as a repressor acting through recruitment of nuclear receptor corepressors 1 and 2 and histone deacetylases, more recent findings describe a possibility of dynamic change of PLZF to an activator through interferon-triggered phosphorylation (Ozato 2009).

Fig. 1. Schematic representation of major domains of the ZBTB16 protein. BTB/POZ, bric-a-brac-tramtrack-broad complex, poxvirus and zinc-finger; RD2, repressor domain.

ZBTB16 as a pleiotropic factor

The disruption of Zbtb16 in mice by gene targeting revealed that the protein acts as a transcriptional repressor of Hox genes, via a process of chromatin remodeling, in the modulation of both embryonic limb patterning and apoptosis (Barna et al. 2000, Barna et al. 2002, Barna et al. 2005, Ivins et al. 2003). The crucial role of ZBTB16 in the limb development was further supported by data from human (Fischer et al. 2008) and rat studies (Liska et al. 2016, Liska et al. 2009). Contrasting with the loss-of function mutations in the knock-out mouse and human, the Zbtb16 mutation responsible for the morphological aberration in the polydactylous rat strain (PD/Cub) model of limb development (Kren 1975) and metabolic syndrome (Sedova et al. 2000, Seda et al. 2005a) was found to comprise 2,964-bp deletion in intron 2 of the gene, removing several deeply conserved noncoding elements (Liska et al. 2009). ZBTB16 is also involved in regulation of self-renewal and differentiation of distinct type of stem cells (Liu et al. 2016); maintenance of spermatogenesis (Costoya et al. 2004), osteo- and chondrogenesis of mesenchymal stem cells (Ikeda et al. 2005, Liu et al. 2011), regulation of hematopoietic stem cell quiescence and formation of specialized natural killer T cells. The relevance of ZBTB16 for cancer and immune system function (Suliman et al. 2012), stem cell self-
ZBTB16 and adipose tissue

ZBTB16 was identified as a potent anti-adipogenic factor in a large comparative epigenomic analysis of murine and human adipogenesis (Mikkelsen et al. 2010). The overexpression of Zbtb16 in L1 cells was sufficient to repress adipogenesis, evidenced by reduced lipid content and diminished markers of terminal differentiation. Conversely, RNAi-mediated knockdown of Zbtb16 enhanced L1 adipogenesis (Mikkelsen et al. 2010). The importance of Zbtb16 in adipogenesis and obesity was corroborated by a study showing that Zbtb16 overexpression in brown adipocytes led to the induction of components of the thermogenic program, including genes involved in fatty acid oxidation, glycolysis and mitochondrial function (Plaisier et al. 2012). Enhanced Zbtb16 expression also increased mitochondrial number, as well as the respiratory capacity and uncoupling. These effects were accompanied by decreased triglyceride content and increased carbohydrate utilization in brown adipocytes (Plaisier et al. 2012). In a study focusing on the role of diacylglycerol acyltransferase-1 (DGAT1) in synthesis of triacylglycerols and intramuscular fat deposition, Zbtb16 was substantially downregulated in Dgat1-transgenic mice favoring intramuscular fat deposition (Ying et al. 2017). Natural variation in Zbtb16 mRNA levels in multiple tissues across a panel of >100 mouse strains was inversely correlated with body weight and body fat content (Plaisier et al. 2012). In our network scan we identified 32 entities interconnecting Zbtb16 and obesity, for 18 of which there is evidence of relation to at least one more metabolic syndrome component (Fig. 2).

ZBTB16 and cardiovascular traits

ZBTB16 has been suggested as a candidate for congenital heart disease based on biallelic loss-of-expression in RNAseq analyses of surgically repaired subjects suffering from congenital heart disease (McKean et al. 2016). There are multiple lines of evidence pointing to possible contribution of ZBTB16 to the pathogenesis of hypertension, cardiac hypertrophy, and cardiac fibrosis. First, in renal epithelial cells, ZBTB16 is a part of the negative feedback regulation of mineralocorticoid action. Aldosterone induces ZBTB16 which in turn suppresses expression of beta- and gamma- epithelial sodium channel (ENaC) subunits, limiting thus sodium reabsorption (Naray-Fejes-Toth et al. 2008). Second, direct interaction of the ZBTB16 with AT2 angiotensin receptor induces expression of phosphatidylinositol-3 kinase p85α subunit (p85α PI3K). This pathway may explain missing cardiac hypertrophic response in mice deficient in AT2. Third, direct interaction of ZBTB16 with (pro)renin receptor (Ahmed et al. 2011, Shamsansurova et al. 2016) leads to increased expression of p85α PI3K, the same target as in the AT2 cascade (Funke-Kaiser et al. 2010). Moreover, renin stimulation has proliferative and antiapoptotic effects on rat cardiomyocytes that are completely dependent on ZBTB16 function. This pathway may therefore be connected to cardiac hypertrophy and/or fibrosis associated with hypertension (Scheff et al. 2006). We have previously established a SHR-Lx congenic strain that carries a mutated Zbtb16 gene of PD/Cub origin (Sedova et al. 2000) on the SHR genetic background within a 1.4 Mbp differential segment of chromosome 8 (Seda et al. 2005b). The SHR-Lx congenic subline exhibits decreased blood pressure and amelioration of left ventricular hypertrophy when compared to SHR controls (Liska et al. 2014). Sequence analysis of genes isolated within the SHR-Lx genome revealed an intronic deletion of a putative enhancer in Zbtb16 gene as the most promising candidate. Accordingly, cardiac expression of Zbtb16 in the PD5 subline (with deletion) was significantly reduced compared to SHR (without deletion) (Liska et al. 2014). In a subsequent study, we generated a null Plzf allele in the SHR using transcription activator-like effector nuclease-mediated gene targeting to assess in vivo effects of Plzf on metabolic and cardiac traits (Liska et al. 2017). The SHR-Plzf−/− (heterozygotes were used due to semilethality of the Plzf−/− knockout on SHR background) rats versus wild-type controls showed reduced cardiomyocytes hypertrophy and interstitial fibrosis and their left ventricular mass index was also significantly smaller despite no differences in blood
pressure (Liska et al. 2017). There were four chemical entities (aldosterone, glucocorticoids, prednisolone and telmisartan), single microRNA (miR-16-5p) and 27 protein-coding genes interconnecting ZBTB16 and hypertension (Fig. 2).

Fig. 2. Network of relations between entities (genes, chemicals) connecting Zbtb16 to single or multiple components of metabolic syndrome built using Ingenuity Pathway Analysis software. The presented relationships are based on Ingenuity Knowledge Base evidence from human, rat and mice studies; the use of capital letters in the gene name labels in the integrative scheme does not necessarily implicate the existence of human-based data. Entities interconnecting Zbtb16 with all components of metabolic syndrome are shown in red: tumor necrosis factor alpha (TNFα), interleukin 6 (IL6) and prostaglandin-endoperoxide synthase 2 (PTGS2) and thioredoxin interacting protein (TXNIP); entities interconnecting Zbtb16 with hypertension, insulin resistance and obesity are shown in orange: vitamin D receptor (VDR), angiotensinogen (AGT), androgen receptor (AR), estrogen receptor 1 (ESR1); entities interconnecting Zbtb16 with hypertension, and obesity are shown in turquoise: C-X-C motif chemokine ligand 10 (CXCL10), poly(ADP-ribose) polymerase 1 (PARP1), nuclear receptor subfamily 3 group C member 1 (NR3C1), matrix metallopeptidase 9 (MMP9), C-X-C motif chemokine receptor 4 (CXCR4), miR-16-5p; entities interconnecting Zbtb16 with insulin resistance and obesity are shown in yellow: phosphatase and tensin homolog (PTEN), C-C motif chemokine ligand 2 (CCL2), integrin subunit beta 3 (ITGB3); entities interconnecting Zbtb16 with insulin resistance and hypertension are shown in green: bone gamma-carboxyglutamate protein (BGLAP), huntingtin (HTT), microRNA 221 (miR-221). The genes with evidence of connection to single metabolic syndrome component are: angiotensin II receptor type 2 (AGTR2), bone morphogenetic protein 7 (BMP7), cyclin A2 (CCNA2), cyclin D1 molecule (CD14), CD34 molecule (CD34), cyclin D dependent kinase 1 (CDK1), cyclin dependent kinase inhibitor 1A (CDKN1A), complement factor H (CFH), cell death-inducing DFFA-like effector a (CIDEA), epidermal growth factor receptor (EGFR), eukaryotic translation initiation factor 2 alpha kinase 2 (EIF2AK2), ERG, ETS transcription factor (ERG), follicle stimulating hormone receptor (FSHFR), heparin binding EGF like growth factor (HBEGF), homeobox D10 (HOXD10), homeobox D9 (HOXD9), intercellular adhesion molecule 3 (ICAM3), interleukin 12B (IL12B), interleukin 4 (IL4), KIT proto-oncogene receptor tyrosine kinase (KIT), BCL2 family apoptosis regulator (MCL1), V-myc avian myelocytomatosis viral oncogene homolog (MYC), phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1), proline rich nuclear receptor coactivator 2 (PRNCR2), protein kinase C epsilon (PRKCE), RB transcriptional corepressor 1 (RB1), RUNX1 translation partner 1 (RUNXI1T1), secreted phosphoprotein 1 (SPP1), TIMP metalloproteinase inhibitor 1 (TIMP1), topoisomerase (DNA) II alpha (TOP2A).
ZBTB16 and lipid metabolism

The SHR-Plzf\textsuperscript{+/-} targeted model mentioned above displayed significantly reduced levels of triacylglycerols and cholesterol, both in plasma and in liver. Hepatic Plzf expression is induced in db/db and diet-induced obese mice, which exhibit severe hepatic steatosis (Chen et al. 2014). Conversely, SHR-Lx congenic strain carrying the 3kb-deletion in an intron of Zbtb16 exhibits more pronounced dyslipidemia than the SHR – higher serum LDL cholesterol after challenge by high sucrose diet and higher triacylglycerols concentration after dexamethasone administration (Seda et al. 2005b). In an experiment, during which mice were given a single oral dose of synthetic triacylglycerols composed of one single fatty acid, Zbtb16 gene was among the top genes upregulated in the heart by all of the five different treatments used in the study (Georgiadi et al. 2012). Moreover, while the majority of genes responding to fatty acid treatment were regulated in a PPAR-alpha-dependent manner, induction of Zbtb16 was completely independent of PPAR alpha (Georgiadi et al. 2012). As evident from Figure 2, dyslipidemia was connected to Zbtb16 via four genes (and a drug telmisartan) forming the "core nodes", i.e. interconnecting Zbtb16 to all metabolic syndrome components: tumor necrosis factor alpha (TNFα), interleukin 6 (IL6) and prostaglandin-endoperoxide synthase 2 (PTGS2) and thioredoxin interacting protein (TXNIP).

ZBTB16 and carbohydrate metabolism/insulin sensitivity

PLZF is a downstream effector for PGC-1-controlled gluconeogenesis and at the same time PLZF negatively regulates the insulin signaling pathway by decreasing the phosphorylation of IRS1, Akt, and FoxO1 in normal mice (Chen et al. 2014). Liver-specific knockdown of PLZF relieved hyperglycemia in db/db mice and led to decreased insulin levels, improved glucose and pyruvate tolerance and insulin sensitivity (Chen et al. 2014). We showed earlier that SHR-Lx congenic strain carrying the 3kb-deletion in an intron of Zbtb16 displays higher sensitivity to dexamethasone-induced insulin resistance of the skeletal muscle when compared to SHR controls (Seda et al. 2005b). Furthermore, there is a significant deterioration of glucose tolerance and increase of triacylglycerols concentration after administration of all-trans retinoic acid in SHR-Lx, but not in SHR (Krupkova et al. 2009, Krupkova et al. 2014). The SHR-Plzf\textsuperscript{+/-} targeted model exhibited lower levels of serum insulin and significantly increased sensitivity of adipose and muscle tissue to insulin action when compared with wild-type controls and were more tolerant to glucose during oral glucose tolerance test (Liska et al. 2017).

ZBTB16 and GWAS

Despite the evidence gathered in the above-mentioned studies, ZBTB16 has not been so far associated with any metabolic syndrome-related traits in human genome-wide association studies (GWAS). However, polymorphisms within and near ZBTB16 showed significant associations to other complex traits, including diisocyanate-induced occupational asthma (Yucesoy et al. 2015), susceptibility to non-glioblastoma glioma (Kinnersley et al. 2015), gestational age at birth in premature rupture of membrane-initiated deliveries (Bacelis et al. 2016) and behavioral traits (Sonuga-Barke et al. 2008), documenting the wide-range of action of the gene over several major biological systems. There are several possible reasons for the current lack of GWAS-based evidence for the role of ZBTB16 in metabolic syndrome. The effects of ZBTB16 polymorphisms might be too subtle to be detected using the statistical models with strict multiple comparison correction; even more likely is the possibility that the effect is contextual in nature as documented previously for distinct genomic backgrounds or environmental (diet, medication) conditions in the experimental models (Seda et al. 2002, Seda et al. 2008).

ZBTB16 and metabolic syndrome – a network perspective

The data summarized in this review provide ample evidence of involvement of ZBTB16 in processes underlying pathogenesis of practically all major constituents of metabolic syndrome. While the information from experimental models with altered Zbtb16 expression clearly shows its effect on adipogenesis, cardiac hypertrophy and fibrosis, lipid levels and insulin sensitivity, the underlying mechanisms remain mostly elusive. Among the identified nodes interconnecting ZBTB16 with all or most metabolic syndrome components there are many genes linked to
immune function, inflammation or oxidative stress, i.e. processes frequently associated with the onset and pathogenesis of the metabolic syndrome itself (Rani et al. 2016). Other putative nodes include e.g. osteocalcin (bone gamma-carboxyglutamate protein, BGLAP), implicated in both cardiovascular risk and type 2 diabetes (Magni et al. 2016), androgen and estrogen receptors, but also huntingtin (Hult et al. 2011) and microRNAs mir-16 and mir-222. The presented network view of ZBTB16 interactions within the frame of metabolic syndrome thus provides a compendium of testable hypotheses for future functional studies.

**Conflict of Interest**
There is no conflict of interest.

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