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Molecules in focus

Metabolic aspects of cardiovascular diseases: Is FoxO1 a player or a target?

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ABSTRACT

The O subfamily of forkhead (FoxO) 1 is a crucial regulator of cell metabolism in several tissues, including the heart, where it is involved in cardiac regulation of glucose and lipid metabolic pathways, and endothelium, controlling the levels of some relevant biomarkers in atherosclerotic process.

Despite the growing understanding of FoxO1 biology, the metabolic consequences of FoxO1 modifications and its implication in CVD, atherosclerosis and T2DM are still not incompletely described.

In this review we discuss how FoxO1 affects cardiovascular pathophysiology and which of its effects should be restrained or enhanced to preserve endothelial and heart functions.

1. Metabolomics as a tool to investigate cardiovascular pathophysiology

Cardiovascular diseases (CVDs), a major cause of mortality in humans, have a complex aetiology. Multiple risk factors and pathological mechanisms contribute to this disease, including metabolic perturbations in cardiomyocytes and endothelial cells. A broad study of the pathogenetic mechanisms of the CVD onset and progression has led to focus the importance of endothelial dysfunction (ED) in these processes. Moreover, imbalance occurring in in metabolic diseases, such as diabetes, directly impact cardiovascular metabolism. In fact, CVDs, including atherosclerosis, are the primary cause of morbidity and mortality in patients with Type 2 diabetes mellitus (T2DM) and other established risk factors are of metabolic origin such hypercholesterolemia or associated with significant metabolic derangements such as hypertension (Ussher et al., 2016). In T2DM, energy metabolism is greatly re-shaped, due to a deregulation of glucose and fatty acid metabolism; furthermore, insulin resistance is recognized as an important mechanism for cardiovascular dysfunction (Arneth et al., 2019; Qi et al., 2013). Therefore, measurement of metabolic changes might have a huge impact on the discovery of clinical and pharmacological biomarkers.

Metabolomics profiling offers a potential tool for improving non-invasive diagnostics and risk stratification in patients affected by cardiovascular and metabolic disorders. In fact, metabolic changes in response to environmental factors or endogenous stimuli are the final effect of genomic, epigenetic, transcriptomic and proteomic interactions and therefore the measurement of the metabolome integrate variations in the other omics. Due to new advances in "omics" technologies, metabolomics and its application to cardiovascular diseases continue to evolve rapidly, making it possible to perform new comprehensive tests on metabolites that are crucial in the process of CVD.

2. FoxO1 effects in the cardiovascular system

The O subfamily of forkhead (FoxO) 1 is a crucial regulator of cell metabolism in several tissues, including the heart, where it is involved in cardiac regulation of glucose and lipid metabolic pathways, and endothelium, controlling the levels of some relevant biomarkers in the atherosclerotic process (Puthanveetil et al., 2013; Furuyama et al., 2004). Compartmentalization and activity of FoxO1 are regulated by numerous post-translational modifications, such as phosphorylation, methylation, glycosylation, acetylation and ubiquitination, capable of influencing several functional properties of FoxO1 (Calnan and Brunet, 2008). Despite the growing understanding of FoxO1 biology, the metabolic consequences of FoxO1 modifications and its implication in CVD, atherosclerosis and T2DM are still incompletely described. The identification of metabolic markers associated with different FoxO1 activated proteins, may extend knowledge on those processes responsible for development and progression of CVD and plaque activation such as inflammation, energy metabolism and tissue degradation. Therefore, establishing a specific metabolite signature to understand whether FoxO1 (or other transcription factors) may provide a powerful

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tool in clinical diagnosis and disease monitoring. Genetic impairment of insulin signaling cascade in endothelial cells is associated with reduced FoxO1 phosphorylation, resulting in an impaired insulin-stimulated NO release, and suggesting that FoxO1 may contribute to the genetic predisposition to develop endothelial dysfunction and cardiovascular disease (Federici et al., 2004). Moreover, hyperglycemia impairs endothelial progenitor cells (EPC) differentiation, and this process can be restored by benfotiamine administration, which affects FoxO1 activity through tight posttranslational control of phosphorylation and acetylation. This results in a better performance of the cell in physiological requests, either regulation of cell cycle or oxidative stress sensing (Marchetti et al., 2006). SIRT1, a nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylase with important roles in controlling energy metabolism (Potente et al., 2005). SIRT1 regulates FoxO1 through its deacetylase activity, promoting effects on endothelial angiogenesis, homeostasis and remodeling (Potente et al., 2005, 2007; Menghini et al., 2009).

3. Use of metabolomics to discover the metabolic impact of FoxO1 in the endothelium

The overexpression of a constitutively nuclear form of FoxO1 (ADA-FoxO1) in human umbilical endothelial cells (HUVECs) results in a significant increase of dimethylarginine (SDMA and ADMA) levels, compared to cells overexpressing the wild type form of FoxO1 (Menghini et al., 2015). In particular, ADMA represents an endogenous inhibitor of eNOS and it has already been classified as a relevant biomarker in cardiovascular diseases. Increased serum levels of ADMA promote endothelial dysfunction, leading to the occurrence of atherosclerosis and coronary artery disease (Koleva et al., 2013; Hsu et al., 2012). Nuclear active form of FoxO1 suppresses, by direct promoter binding, the transcription of DDAH1, the main gene involved in ADMA degradation (Hu et al., 2011), thus confirming a direct molecular link between FoxO1 and ADMA metabolic pathways in endothelial cells. The relevance of this finding was confirmed by in vivo evidence, since in atherosclerotic plaques the deregulation of DDAH1/ADMA system was associated with increased FoxO1 activity, particularly highly altered in patients with features of unstable atherosclerosis (Menghini et al., 2015). Reduction of eNOS activity and NO production was also supported by the increase in cellular level of arginine, urea and ornithine in ADA-FoxO1 HUVECs. Another metabolic marker of increased FoxO1 is glutamine. Significantly reduced levels of glutamine have been shown in ADA-FoxO1 cells compared to WT; interestingly, glutamine starvation in endothelial cells is able to stimulate inflammatory signaling with an increase in ROS production (Huang et al., 2017). The lack of increase in glutathione (GSH) along with lower intracellular ascorbate levels in the ADA-FoxO1 group may suggest that ADA allele suppressed antioxidant defense in the cells. Overall, the over-expression of nuclear FoxO1 in endothelial cells was associated with decreased NO bioavailability, increased oxidative stress and inflammation, and decreased antioxidant defense implying pro-apoptotic effect (Menghini et al., 2015).

The effect of nuclear FoxO1 overexpression on vascular metabolism is controversial; in fact, expression of a constitutively nuclear form of FoxO1 in mice endothelium resulted in proliferative metabolism and increased cell size (Dharaneeswaran et al., 2014). However, another study has shown that endothelial cell-directed deletion of FoxO1 in adult mice induces excessive endothelial proliferation coupled with reduced apoptosis (Paik et al., 2007), indicating FoxO1 as a suppressor of endothelial growth and proliferation, or better as an inducer of a quiescence state. In fact, in HUVECs the overexpression of a constitutively nuclear FoxO1 form, through the repression of Myc, a driver of anabolic metabolism and growth, led to an endothelial quiescent phenotype, characterized by reduction in glucose uptake and glycolysis, proliferation, oxidative metabolism and ROS formation (Wilhelm et al., 2016). Interestingly, Myc mRNA levels are increased in high risk symptomatic and vulnerable plaques, where metabolite signature is consistent with an increased glucose utilization, a decreased fatty acid oxidation (FAO) flux and an increased amino acid anaplerosis (Tomas et al., 2018). Moreover, FoxO1 nuclear expression is increased in vulnerable plaques leading to the hypothesis that in atherosclerotic plaques, the increase of FoxO1 nuclear may worsen their phenotype through the regulation of Myc expression and metabolism (Menghini et al., 2015). Since increase in endothelial cell (EC) metabolic activity, associated with proliferation and migration, is necessary for a switch from quiescent to an angiogenic phenotype, FoxO1 is supposed to be a key regulator of angiogenic capacity through the converging actions of controlling metabolic activity and angiogenic fate of the endothelium. Endothelial FoxO1 (EC-FoxO1) deregulation coincides also with obesity-associated metabolic disturbances, given that the activity of EC-FoxO1 are correlated with adipose insulin resistance of obese subjects (Karki et al., 2015). Endothelial cell FoxO1-deficiency in obese mice is associated with vascular remodeling in the visceral adipose depot, a healthier adipose tissue expansion and improved glucose tolerance (Rudnicki et al., 2018). In contrast, EC-FoxO1 depletion induces a relatively modest expansion of skeletal muscle vasculature, suggesting that tissue-restricted pattern of FoxO1-driven vascular growth is highly dependent on the co-presence of angiogenic factors within local environment, which is in turn impacted by nutritional status. Therefore, the ability to fine-tune FoxO1 transcriptional program, that has an impact on cellular functions and is largely dependent on posttranslational modifications including serine phosphorylation and lysine acetylation, might be a target for an intervention to counteract endothelial dysfunction.

Another metabolite which was found to be increased by ADA-FoxO1 overexpression in HUVECs is lysophosphatidic acid (LPA) (Menghini et al., 2015), a lysophospholipid associated with atherosclerosis, which stimulates adhesion molecule expression in endothelial cells (Shimada and Rajagopalan, 2010), cytokine and chemokine secretion (Lin et al., 2006), stress-fiber and gap-junctions formation (Siess et al., 1999), endothelial-leukocyte interactions (Rizza et al., 1999), and which regulates endothelium permeability (van Nieuw Amerongen et al., 2000).

When endothelial cells are enriched in the acetylation defective mutant FoxO1-KR many metabolites involved in glucose metabolism are affected. FoxO1-KR is an isoform exhibiting both altered DNA binding and gene expression control, due to constitutive deacetylation (Qiang et al., 2010). In the extracellular environment of cells overexpressing FoxO1-KR the content of glucose levels is increased while glutamate levels significantly decreased suggesting that this FoxO1 state specifically shifts the energy source preference of cells, possibly indicating a metabolic switch from glycolysis to glutaminolysis. This speculated decrease in glycolysis is supported by a reduced release of lactate and pyruvate from the cells and a decreased intracellular glycolytic intermediate, glucose 6-phosphate. Moreover, FoxO1-KR expression is related to a lower release of TCA intermediates, suggesting a possible increase in mitochondrial biogenesis and function supporting the proposed metabolic switch from glycolysis to glutaminolysis. This evidence, combined with an increase of intracellular ATP, ADP, UTP and NAD + levels, is consistent with an increase in mitochondrial respiration (Menghini et al., 2015). The deacetylated form of FoxO1, in human atherosclerotic plaques, is associated with reduced markers of inflammation and cellular activation, and with the expression of Sirt1, a marker of plaque stability (Menghini et al., 2009). Since the metabolic signature in high risk plaque is consistent with an increased glucose utilization (Tomas et al., 2018), this data strongly suggests that deacetylated FoxO1 may promote a stable plaque phenotype, consistent with the induction of a more quiescent metabolic phenotype. In particular, deacetylated FoxO1 is significantly decreased in plaques derived from diabetic patients compared to control subjects, whereas phosphorylated form of FoxO1 acts inversely. Moreover, FoxO1 deacetylation is an important regulatory mechanism in cholesterol laden macrophages, with the potential to uncouple inflammation from apoptosis

(Tsuchiya et al., 2011). As these mechanisms underlie the progression of atherosclerotic plaques from benign to unstable lesions, it can be envisioned that the treatments promoting FoxO1 deacetylation will favorably affect cardiovascular outcomes in type 2 diabetes.

4. Impact of FoxO1 post-translational status on heart metabolism

Cardiovascular diseases involve marked changes in myocardial metabolism, and many studies have assessed the metabolic changes that take place in the heart during the progression to heart failure, both in animal models and in patients with cardiac hypertrophy and heart failure (Wang et al., 2014). Cardiac fuel substrate selection is dynamic and may differ according to prevailing physiological or pathophysiological conditions. Several recent studies have shown that metabolic therapy can be a potential and promising approach in dealing with IHD and heart failure (Gorbunova and Vilkova, 2016). Glucose oxidation is a major contributor to overall cardiac metabolism and myocardial glucose oxidation is perturbed during the progression of a variety of cardiovascular diseases, including ischemic heart disease, diabetic cardiomyopathy, and heart failure (Jaswal et al., 2011; Zlobine et al., 2016). Interventions promoting glucose oxidation have been shown to enhance pathophysiology of these cardiovascular diseases (Ussher et al., 2012).

A cardiac specific deletion of FoxO1 is able to attenuate cardiomyopathy in mice, through a reduction of myocardial Pdk4 mRNA expression, the major kinase phosphorylating and subsequently inactivating PDH, the rate-limiting enzyme of glucose oxidation (Battiprolu et al., 2012). In isolated working mouse heart FoxO1 inhibition increases glucose oxidation, whereas FoxO1 overexpression reduces PDH enzymatic activity (Gopal et al., 2017). This is suggesting that reduced FoxO1 activity may induce a shift of metabolic substrate preference from fatty acids to glucose, a mechanism confirmed by the evidence that mice lacking FoxO1 in the heart are resistant to cardiac dysfunction induced by calorie excess (Qi et al., 2015). The divergent effect of FoxO1 deletion from inhibition might be interpreted that the complete loss of FoxO1 might reduce some positive actions which rely on the post-transcriptional status of the transcription factor. In fact, FoxO1 actions also display cardioprotective effects on myocardial function by dampening oxidative stress and exerting antioxidant effects, through the regulation of mitochondrial metabolism. This particular effect of FoxO1 has been found to play a protective role in ischemic heart disease (Sengupta et al., 2011).

In diabetes, alteration of lipids and glucose levels may lead to irreversible morphological and functional defects in the heart. In this context, loss of a proper regulation of FoxO1 may be associated with an increased risk of diabetic cardiomyopathy (Kandula et al., 2016). In cardiomyocytes, activation of FoxO1, induced by insulin resistance and hyperglycemia, is involved in myocardial mitochondrial biogenesis and cardiac homeostasis, and promotes cardiac contractile dysfunction at least in part by increasing expression of beta myosin heavy chain gene, a marker of heart failure (Qi et al., 2015). Accordingly, enhanced cardiac FoxO1 activation has been found in diabetic mice (Battiprolu et al., 2012), and cardiac-specific FoxO1-deficient mice are protected against diabetic cardiomyopathy which may depend from the reduction in Pdk4 expression and the consequent increase in glucose metabolism, suggesting again for FoxO1 the role of a key mediator of cardiac metabolic flexibility with a switch from fatty acid to glucose oxidation (Chistiakov et al., 2017). Moreover, FoxO1 is involved in lipids accumulation in cardiomyocytes via enhanced fatty acid flux, a condition associated with obesity, dyslipidemia and diabetes (Puthanveetil et al., 2011).

FoxO1 post-translational modifications have been shown to be involved also in cardiac remodeling and metabolic modulation, and may play a crucial role in maintaining the activity of FoxO1 in equilibrium between its cardioprotective and cardiotoxic role. In fact, FoxO1 deacetylation by Sirt1 results in the activation of specific autophagic pathway in cardiomyocytes, playing a protective role against cardiac hypertrophy, and extending longevity in the heart through activation of catalase (Hariharan et al., 2010). In mice, FoxO1 acetylation in the heart is increased by ischemia and diabetes, and the overexpression of a constitutively deacetylated variant of FoxO1 after myocardial infarction results in a significant improved cardiac phenotype (Kappel et al., 2016).

After ischemia posttranslational modification of cardiac FoxO1 differs between non-diabetic and diabetic mice, and that active post-translational modulation of FoxO1 is able to alter the cardiac outcome in a mouse model of post-ischemic heart failure. Our findings therefore suggest that posttranslational modification of FoxO1 contribute to cardiac remodeling processes after ischemia via regulation of pathways involving collagen and protein metabolism. Therefore, posttranslational modifications of FoxO1 could be an option to target remodeling processes in post-ischemic heart failure.

Overall it becomes evident that FoxO1 factor acts to integrate growth, nutrient and environmental stimuli to coordinate an appropriate metabolic response for cells and tissues, depending on which of the stimuli is dominating. Therefore, depending on the stimulus and cell type, FoxO1 is able to promote apoptosis versus proliferation or cellular activation/inflammation versus resistance to oxidative stress, or glucose production versus lipid consumption (Fig. 1).

Since selective inhibitors of FoxO1-dependent glucose production have been recently identified (Langlet et al., 2017), it is tempting to speculate that other tissue or cell specific modulators might help to

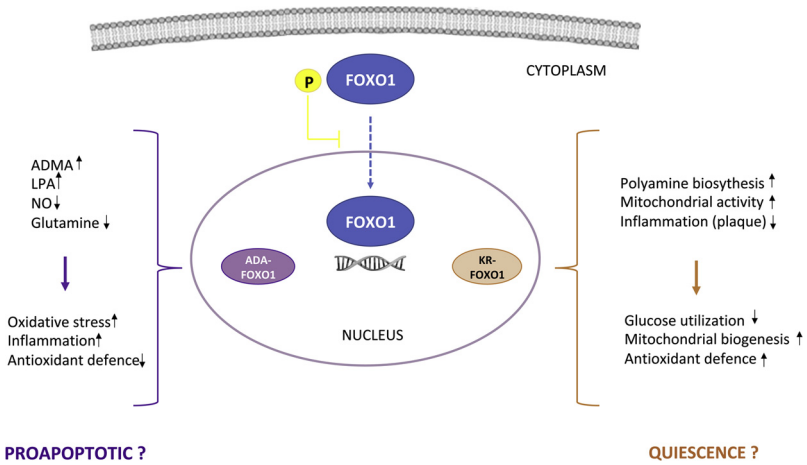

Fig. 1. FoxO1-ADA and FoxO1-FR exert different functions in the cardiovascular system.

preserve FoxO1 positive effects, and to dial out its adverse effects on cardiovascular cells.

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References

Arneth, B., Arneth, R., Shams, M., 2019. Metabolomics of type 1 and type 2 diabetes. Int. J. Mol. Sci. 20 (10), 2467. https://doi.org/10.3390/ijms20102467.

Battiprolu, P.K., Hojayev, B., Jiang, N., Wang, Z.V., Luo, X., Iglewski, M., Shelton, J.M., Gerard, R.D., Rothermel, B.A., Gillette, T.G., Lavandero, S., Hil, L.J.A., 2012. Metabolic stress-induced activation of FoxO1 triggers diabetic cardiomyopathy in mice. J. Clin. Invest. 122 (3), 1109–1118. https://doi.org/10.1172/JCI60329.

Calnan, D.R., Brunet, A., 2008. The FoxO code. Oncogene 27 (16), 2276–2288. https://doi.org/10.1038/onc.2008.21.

Chistiakov, D.A., Orekhov, A.N., Bobryshev, Y.V., 2017. The impact of FOXO-1 to cardiac pathology in diabetes mellitus and diabetes-related metabolic abnormalities. Int. J. Cardiol. 245, 236–244. https://doi.org/10.1016/j.ijcard.2017.07.096.

Dharaneeswaran, H., Abid, M.R., Yuan, L., Dupuis, D., Beeler, D., Spokes, K.C., Janes, L., Sciuto, T., Kang, P.M., Jaminet, S.S., Dvorak, A., Grant, M.A., Regan, E.R., Aird, W.C., 2014. FOXO1-mediated activation of Akt plays a critical role in vascular homeostasis. Circ. Res. 115 (2), 238–251. https://doi.org/10.1161/CIRCRESAHA.115.303227.

Federici, M., Pandolfi, A., De Filippis, E.A., Pellegrini, G., Menghini, R., Lauro, D., Cardellini, M., Romano, M., Sesti, G., Lauro, R., Consoli, A., 2004. G972R IRS-1 variant impairs insulin regulation of endothelial nitric oxide synthase in cultured human endothelial cells. Circulation 109 (3), 399–405. https://doi.org/10.1161/01.CIR.0000109498.77895.6F.

Furuyama, T., Kitayama, K., Shimoda, Y., Ogawa, M., Sone, K., Yoshida-Araki, K., Hisatsune, H., Nishikawa, S., Nakayama, K., Nakayama, K., Ikeda, K., Motoyama, N., Mori, N., 2004. Abnormal angiogenesis in Foxo1 (Fkhr)-deficient mice. J. Biol. Chem. 279 (33), 34741–34749. https://doi.org/10.1074/jbc.M314214200.

Gopal, K., Saleme, B., Al Batran, R., Aburasayn, H., Eshreif, A., Ho, K.L., Ma, W.K., Almutairi, M., Eaton, F., Gandhi, M., Park, E.A., Sutendra, G., Ussher, J.R., 2017. FoxO1 regulates myocardial glucose oxidation rates via transcriptional control of pyruvate dehydrogenase kinase 4 expression. Am. J. Physiol. Heart Circ. Physiol. 313 (3), H479–H490. https://doi.org/10.1152/ajpheart.00191.2017.

Gorbunova, M.L., Vilkova, A.V., 2016. Assessment of efficacy and safety of metabolic therapy with trimetazidine MB in patients with ischemic heart disease and chronic heart failure. Kardiologiia 56 (3), 67–72.

Hariharan, N., Maejima, Y., Nakae, J., Paik, J., Depinho, R.A., Sadoshima, J., 2010. Deacetylation of FoxO by Sirt1 plays an essential role in mediating starvation-induced autophagy in cardiac myocytes. Circ. Res. 107 (12), 1470–1482. https://doi.org/10.1161/CIRCRESAHA.110.227371.

Hsu, C.P., Lin, S.J., Chung, M.Y., Lu, T.M., 2012. Asymmetric dimethylarginine predicts clinical outcomes in ischemic chronic heart failure. Atherosclerosis 225 (2), 504–510. https://doi.org/10.1016/j.atherosclerosis.2012.09.040.

Hu, X., Atzler, D., Xu, X., Zhang, P., Guo, H., Lu, Z., Fassett, J., Schwedhelm, E., Böger, R.H., Bache, R.J., Chen, Y., 2011. Dimethylarginine dimethylaminohydrolase-1 is the critical enzyme for degrading the cardiovascular risk factor asymmetrical dimethylarginine. Arterioscler. Thromb. Vasc. Biol. 31 (7), 1540–1546. https://doi.org/10.1161/ATVBAHA.110.222638.

Huang, H., Vandekeere, S., Kalucka, J., Bierhansl, L., Zecchin, A., Brüning, U., Visnagri, A., Yuldasheva, N., Goveia, J., Cruys, B., Brepoels, K., Wyns, S., Rayport, S., Ghesquière, B., Vinckier, S., Schoonjans, L., Cubbon, R., Dewerchin, M., Eelen, G., Carmeliet, P., 2017. Role of glutamine and interlinked asparagine metabolism in vessel formation. EMBO J. 36 (16), 2334–2352. https://doi.org/10.15252/embj.201695518.

Jaswal, J.S., Keung, W., Wang, W., Ussher, J.R., Lopaschuk, G.D., 2011. Targeting fatty acid and carbohydrate oxidation–a novel therapeutic intervention in the ischemic and failing heart. Biochim. Biophys. Acta 1813 (7), 1333–1350. https://doi.org/10.1016/j.bbamcr.2011.01.015.

Kandula, V., Kosuru, R., Li, H., Yan, D., Zhu, Q., Lian, Q., Ge, R.S., Xia, Z., Irwin, M.G., 2016. Forkhead box transcription factor 1: role in the pathogenesis of diabetic cardiomyopathy. Cardiovasc. Diabetol. 15, 44. https://doi.org/10.1186/s12933-016-0361-1.

Kappel, B.A., Stöhr, R., De Angelis, L., Mavilio, M., Menghini, R., Federici, M., 2016. Posttranslational modulation of FoxO1 contributes to cardiac remodeling in post-ischemic heart failure. Atherosclerosis 249, 148–156. https://doi.org/10.1016/j.atherosclerosis.2016.04.001.

Karki, S., Farb, M.G., Ngo, D.T., Myers, S., Puri, V., Hamburg, N.M., Carmine, B., Hess, D.T., Gokce, N., 2015. Forkhead box O-1 modulation improves endothelial insulin resistance in human obesity. Arterioscler. Thromb. Vasc. Biol. 35 (6), 1498–1506. https://doi.org/10.1161/ATVBAHA.114.305139.

Koleva, D., Orbetzova, M., Deneva, T., 2013. Asymmetric dimethylarginine as a mediator of endothelial dysfunction and its association with insulin resistance syndromes. Endokrinologya 18, 33–40.

Langlet, F., Haeusler, R.A., Lindén, D., Ericson, E., Norris, T., Johansson, A., Cook, J.R., Aizawa, K., Wang, L., Buettner, C., Accili, D., 2017. Selective inhibition of FOXO1 Activator/Repressor balance modulates hepatic glucose handling. Cell 171 (4), 824–835. https://doi.org/10.1016/j.cell.2017.09.045. e18.

Lin, C.I., Chen, C.N., Chen, J.H., Lee, H., 2006. Lysophospholipids increase IL-8 and MCP-1 expressions in human umbilical cord vein endothelial cells through an IL-1-dependent mechanism. J. Cell. Biochem. 99 (4), 1216–1232. https://doi.org/10.1002/jcb.20963.

Marchetti, V., Menghini, R., Rizza, S., Vivanti, A., Feccia, T., Lauro, D., Fukamizu, A., Lauro, R., Federici, M., 2006. Benfotiamine counteracts glucose toxicity effects on endothelial progenitor cell differentiation via Akt/FoxO signaling. Diabetes 55 (8), 2231–2237. https://doi.org/10.2337/db06-0369.

Menghini, R., Casagrande, V., Cardellini, M., Martelli, E., Terrinoni, A., Amati, F., Vasa-Nicotera, M., Ippoliti, A., Novelli, G., Melino, G., Lauro, R., Federici, M., 2009. MicroRNA 217 modulates endothelial cell senescence via silent information regulator 1. Circulation 120 (15), 1524–1532. https://doi.org/10.1161/CIRCULATIONAHA.109.864629.

Menghini, R., Casagrande, V., Cardellini, M., Ballanti, M., Davato, F., Cardolini, I., Stoehr, R., Fabrizi, M., Morelli, M., Anemona, L., Bernges, I., Schwedhelm, E., Ippoliti, A., Mauriello, A., Böger, R.H., Federici, M., 2015. FoxO1 regulates asymmetric dimethylarginine via downregulation of dimethylaminohydrolase 1 in human endothelial cells and subjects with atherosclerosis. Atherosclerosis 242 (1), 230–235. https://doi.org/10.1016/j.atherosclerosis.2015.07.026.

Paik, J.H., Kollipara, R., Chu, G., Ji, H., Xiao, Y., Ding, Z., Miao, L., Tothova, Z., Horner, J.W., Carrasco, D.R., Jiang, S., Gilliland, D.G., Chin, L., Wong, W.H., Castrillon, D.H., DePinho, R.A., 2007. FoxOs are lineage-restricted redundant tumor suppressors and regulate endothelial cell homeostasis. Cell 128 (2), 309–323. https://doi.org/10.1016/j.cell.2006.12.029.

Potente, M., Urbich, C., Sasaki, K., Hofmann, W.K., Heeschen, C., Aicher, A., Kollipara, R., DePinho, R.A., Zeiher, A.M., Dimmeler, S., 2005. Involvement of Foxo transcription factors in angiogenesis and postnatal neovascularization. J. Clin. Invest. 115 (9), 2382–2392. https://doi.org/10.1172/JCI23126.

Potente, M., Ghaeni, L., Baldessari, D., Mostoslavsky, R., Rossig, L., Dequiedt, F., Haendeler, J., Mione, M., Dejana, E., Alt, F.W., Zeiher, A.M., Dimmeler, S., 2007. SIRT1 controls endothelial angiogenic functions during vascular growth. Genes Dev. 21 (20), 2644–2658. https://doi.org/10.1101/gad.435107.

Puthanveetil, P., Wang, Y., Zhang, D., Wang, F., Kim, M.S., Innis, S., Pulinilkunnil, T., Abrahani, A., Rodrigues, B., 2011. Cardiac triglyceride accumulation following acute lipid excess occurs through activation of a FoxO1-iNOS-CD36 pathway. Free Radic. Biol. Med. 51 (2), 352–363. https://doi.org/10.1016/j.freeradbiomed.2011.04.009.

Puthanveetil, P., Wan, A., Rodrigues, B., 2013. FoxO1 is crucial for sustaining cardiomyocyte metabolism and cell survival. Cardiovasc. Res. 97 (3), 393–403. https://doi.org/10.1093/cvr/cvs426.

Qi, Y., Xu, Z., Zhu, Q., Thomas, C., Kumar, R., Feng, H., Dostal, D.E., White, M.F., Baker, K.M., Guo, S., 2013. Myocardial loss of IRS1 and IRS2 causes heart failure and is controlled by p38α MAPK during insulin resistance. Diabetes 62 (11), 3887–3900. https://doi.org/10.2337/db13-0095.

Qi, Y., Zhu, Q., Zhang, K., Thomas, C., Wu, Y., Kumar, R., Baker, K.M., Xu, Z., Chen, S., Guo, S., 2015. Activation of Foxo1 by insulin resistance promotes cardiac dysfunction and β-myosin heavy chain gene expression. Circ. Heart Fail. 8 (1), 198–208. https://doi.org/10.1161/CIRCHEARTFAILURE.114.001457.

Qiang, L., Banks, A.S., Accili, D., 2010. Uncoupling of acetylation from phosphorylation regulates FoxO1 function independent of its subcellular localization. J. Biol. Chem. 285 (35), 27396–27401. https://doi.org/10.1074/jbc.M110.140228.

Rizza, C., Leitinger, N., Yue, J., Fischer, D.J., Wang, D.A., Shih, P.T., Lee, H., Tigyi, G., Berliner, J.A., 1999. Lysophosphatidic acid as a regulator of endothelial/leukocyte interaction. Lab. Invest. 79 (10), 1227–1235.

Rudnicki, M., Abdifarkosh, G., Nwadozi, E., Ramos, S.V., Makki, A., Sepa-Kishi, D.M., Ceddia, R.B., Perry, C.G., Roudier, E., Haas, T.L., 2018. Endothelial-specific FoxO1 depletion prevents obesity-related disorders by increasing vascular metabolism and growth. Elife 7https://doi.org/10.7554/eLife.39780.001. pii, e39780.

Sengupta, A., Molkentin, J.D., Paik, J.H., DePinho, R.A., Yutzey, K.E., 2011. FoxO transcription factors promote cardiomyocyte survival upon induction of oxidative stress. J. Biol. Chem. 286 (9), 7468–7478. https://doi.org/10.1074/jbc.M110.179242.

Shimada, H., Rajagopalan, L.E., 2010. Rho kinase-2 activation in human endothelial cells drives lysophosphatidic acid-mediated expression of cell adhesion molecules via NF-kappaB p65. J. Biol. Chem. 285 (17), 12536–12542. https://doi.org/10.1074/jbc.M109.099630.

Siess, W., Zangl, K.J., Essler, M., Bauer, M., Brandl, R., Corrinth, C., Bittman, R., Tigyi, G., Aepfelbacher, M., 1999. Lysophosphatidic acid mediates the rapid activation of platelets and endothelial cells by mildly oxidized low density lipoprotein and accumulates in human atherosclerotic lesions. Proc. Natl. Acad. Sci. U.S.A. 96 (12), 6931–6936. https://doi.org/10.1073/pnas.96.12.6931.

Tomas, L., Edsfeldt, A., Mollet, I.G., Perisic Matic, L., Prehn, C., Adamski, J., Paulsson-Berne, G., Hedin, U., Nilsson, J., Bengtsson, E., Gonçalves, I., Björkbacka, H., 2018. Altered metabolism distinguishes high-risk from stable carotid atherosclerotic plaques. Eur. Heart J. 39 (24), 2301–2310. https://doi.org/10.1093/eurheartj/ehy124.

Tsuchiya, K., Banks, A.S., Liang, C.P., Tabas, I., Tall, A.R., Accili, D., 2011. Homozygosity for an allele encoding deacetylated FoxO1 protects macrophages from cholesterol-induced inflammation without increasing apoptosis. Arterioscler. Thromb. Vasc. Biol. 31 (12), 2920–2928. https://doi.org/10.1161/ATVBAHA.110.219477.

Ussher, J.R., Wang, W., Gandhi, M., Keung, W., Samokhvalov, V., Oka, T., Wagg, C.S., Jaswal, J.S., Harris, R.A., Clanachan, A.S., Dyck, J.R., Lopaschuk, G.D., 2012. Stimulation of glucose oxidation protects against acute myocardial infarction and reperfusion injury. Cardiovasc. Res. 94 (2), 359–369. https://doi.org/10.1093/cvr/cvs129.

Ussher, J.R., Elmariah, S., Gerszten, R.E., Dyck, J.R., 2016. The emerging role of metabolomics in the diagnosis and prognosis of cardiovascular disease. J. Am. Coll.

Cardiol. 68 (25), 2850–2870. https://doi.org/10.1016/j.jacc.2016.09.972.
van Nieuw Amerongen, G.P., Vermeer, M.A., van Hinsbergh, V.W., 2000. Role of RhoA and Rho kinase in lysophosphatidic acid-induced endothelial barrier dysfunction. Arterioscler. Thromb. Vasc. Biol. 20 (12), E127–E133. https://doi.org/10.1161/01.ATV.20.12.e127.
Wang, Z.V., Li, D.L., Hill, J.A., 2014. Heart failure and loss of metabolic control. J. Cardiovasc. Pharmacol. 63 (4), 302–313. https://doi.org/10.1097/FJC.0000000000000054.
Wilhelm, K., Happel, K., Eelen, G., Schoors, S., Oellerich, M.F., Lim, R., Zimmermann, B., Aspalter, I.M., Franco, C.A., Boettger, T., Braun, T., Fruttiger, M., Rajewsky, K., Keller, C., Brüning, J.C., Gerhardt, H., Carmeliet, P., Potente, M., 2016. FOXO1 couples metabolic activity and growth state in the vascular endothelium. Nature 529 (7585), 216–220. https://doi.org/10.1038/nature16498.
Zlobine, I., Gopal, K., Ussher, J.R., 2016. Lipotoxicity in obesity and diabetes-related cardiac dysfunction. Biochim. Biophys. Acta 1861 (10), 1555–1568. https://doi.org/10.1016/j.bbalip.2016.02.011.