

TXNIP

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Contributor: Alison Domingues

Thioredoxin interacting protein (TXNIP) is a metabolism- oxidative- and inflammation-related marker induced in cardiovascular diseases and is believed to represent a possible link between metabolism and cellular redox status. TXNIP is a potential biomarker in cardiovascular and ischemic diseases but also a novel identified target for preventive and curative medicine.

TXNIP

cardiovascular diseases marker

1. Introduction

Cardiovascular diseases remain a major cause of death worldwide and are increasing due to the ageing population and poor eating habits. The pathological changes are originally characterized by metabolic disorders and endothelial dysfunction. Oxidative stress plays an important role and induces vascular-related gene expression, promoting local inflammatory response and cell life and death dysregulation. When oxidative stress occurs, vascular walls produce excessive reactive oxygen species (ROS), which causes damage to the structure and function of endothelial cells. That enhances the inflammatory response of the vascular wall and impairs vascular function or revascularization. ROS are produced continuously during cell metabolism and are used as mediators in many biological processes. Specifically, ROS reversibly activate signaling pathways that trigger adaptation systems in the cell. Previous works have associated excessive ROS with age-related pathologies [\[1\]\[2\]\[3\]\[4\]\[5\]\[6\]\[7\]](#). However, recent reviews still report that excessive ROS can lead to diseases and pathological conditions [\[8\]\[9\]\[10\]\[11\]](#). Thioredoxin interacting protein (TXNIP) is a metabolism- oxidative- and inflammation-related marker induced in cardiovascular pathologies and could represent an emergent link between physiopathology and cardiovascular events. More precisely, TXNIP has been widely described as a pro-oxidant compound [\[12\]\[13\]](#), but it is also a regulator of metabolism [\[14\]\[15\]\[16\]\[17\]](#), a modulator of the inflammatory [\[18\]\[19\]](#) or angiogenic response [\[20\]\[21\]](#), and an antiproliferative and pro-apoptotic agent [\[22\]\[23\]](#). Clinically, genetic association studies have shown that polymorphisms affecting TXNIP expression are linked to hypertension and arterial stiffness and increase the risk of coronary heart disease [\[24\]\[25\]\[26\]](#). Epigenetic modifications of TXNIP are also associated with risks of cardiovascular diseases [\[27\]\[28\]](#). Additionally, blood or mononuclear blood cells' mRNA TXNIP levels have been related to coronary and heart diseases [\[29\]\[30\]\[31\]](#).

2. TXNIP is a Multifunctional Protein

TXNIP is a 46-kDa ubiquitously expressed protein that contains 391 amino acid residues and is encoded on chromosome 1q21.1. TXNIP is an α -arrestin protein that regulates pleiotropic biological responses [\[32\]\[33\]\[34\]](#). TXNIP

appears to perform certain functions through multiple binding partners [\[35\]](#), which are summarized in [Table 1](#).

Table 1. The multiple signaling partners of TXNIP and pleiotropic effects.

Function	Signalling Partner	References
Shuttle	TRX	[36] [37]
	HIF1a	[38]
	NfkB	[39] [40]
	Itch	[41] [42] [43]
Prooxydant	TRX	[13] [21] [32] [40] [44] [45] [46] [47] [48] [49] [50] [51] [52] [53] [54] [55]
	NADPH oxidase	[13] [21] [51] [52] [56] [57] [58]
	AMPK/NrF2	[59] [60] [61] [62]
	Redd1	[63] [64]
Proinflammatory	NLRP3	[13] [18] [21] [60] [65] [66] [67] [68] [69] [70] [71] [72] [73] [74] [75] [76] [77] [78] [79] [80] [81] [82] [83] [84] [85] [86] [87] [88] [89] [90] [91] [92] [93] [94] [95] [96] [97] [98] [99] [100] [101] [102] [103] [104] [105]
	AMPK/NrF2	[60] [62] [90] [92] [102] [103] [104] [106] [107] [108]
	NF-κB	[39] [40] [72] [83] [109] [110]
	Kruppel-like factor 2	[111]
Metabolism	AMPK	[92] [112] [113]
	MondoA	[114] [115]
	IGF1	[116]
	Glut1	[33] [113] [117] [118] [119]
	Glut4	[120]
	ChREBP/FOXO1	[121]
Target of miRNA	miR-17, miR-17-5p	[122] [123] [124] [125]
	miR-20a, miR-20b	[126]

Function	Signalling Partner	References
	miR-25-5p	[127]
	miR-30c-5p	[128]
	miR-33	[129]
	miR-146a	[130]
	miR-370	[131]
	miR-497	[132]

3. TXNIP is a Novel Marker in Cardiovascular Diseases

TXNIP is a genetic, blood, peripheral blood cells, and tissue ischemia marker associated with cardiovascular diseases, as summarized in [Figure 1](#) and in [Table 2](#), thus making TXNIP an interesting target for prognostic and treatment.

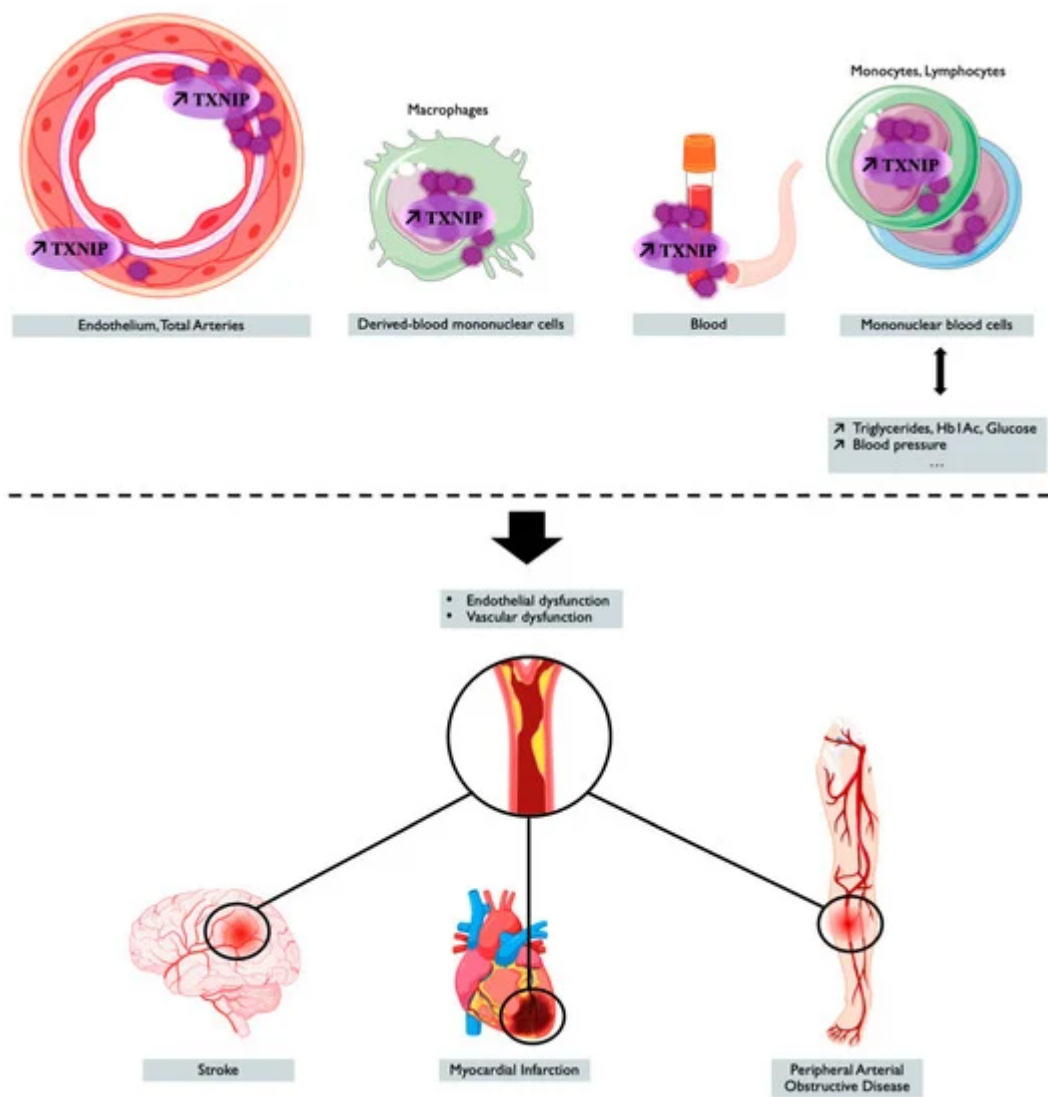


Figure 1. TXNIP overexpression is associated with cardiovascular outcomes and diseases. Tissue, blood levels of TXNIP, and the genetic regulation of TXNIP make it a potential marker associated with cardiovascular risk factors or cardiovascular event or diseases. Created with [BioRender.com](https://www.biorender.com).

Table 2. TXNIP as a marker of cardiovascular risk and disease.

	Location	Parameter or Disease	References
Genetic Marker	TXNIP rs7211 variant	Arterial stiffness, obesity	[24][133]
	TXNIP rs7211-rs7212 variants	Glucose, blood pressure, coronary atherosclerosis	[24][26]
	Various epigenetic changes	T2D	[134][135]

	Location	Parameter or Disease	References
	DNA methylation cg19693031	Blood pressure, T2D, coronary artery disease	[26] [27] [28] [136] [137] [138] [139] [140] [141] [142] [143]
		Triglycerides and/or HbA1C levels	[27] [136] [137] [138] [139] [144]
		Carotid Intima Media Thickness	[30]
		Stroke or heart attack	[55] [145]
Blood Marker	Plasma or serum levels of TXNIP	Diabetes associated macrovascular endothelial dysfunction	[17]
		Diabetes associated vascular complications	[19]
		At-risk Takayasu arteritis, atherosclerosis, coronary artery disease, leukostasis	[80] [94] [110] [146] [147] [148] [149]
	TXNIP in peripheral blood cells	Unstable angina pectoris, acute myocardial infarction	[29] [150]
mRNA Marker		Diabetes associated macrovascular endothelial dysfunction	[17]
		Diabetes associated vascular complications	[19] [151]
	TXNIP in cardiac tissue	Heart attack	[55]
		At-risk Takayasu arteritis, atherosclerosis, arterial aging	[51] [146] [148] [152]
	TXNIP in aortic tissue	Diabetes associated macrovascular endothelial dysfunction	[17]
		Diabetes associated vascular complications	[19]
Tissue Marker	TXNIP in bone marrow	Mobilization of cells	[148]
	TXNIP in Myocardial ischemia	I/R damage (infarct size or ventricular remodeling or heart failure or atrial fibrillation)	[153] [154]

Location	Parameter or Disease	References
TXNIP in Hind limb ischemia	I/R damage in diabetic hearts or survival	[64][100][109][155][156][157] [158][159][160]
	Reperfusion of ischemic limb, tissue-recovery, capillary density in diabetic mouse	[161][162][163]
	Reperfusion of ischemic limb, tissue-recovery, capillary density in mouse with fat diet	[164][165]
	Ischemic stroke	[58][60][61][102][103][108][127] [166][167][168][169][170][171] [172][173][174]
	Subarachnoid haemorrhage	[62][175][176][177]
	Neonatal hypoxic-ischemia	[124][125][178]
	Vascular dementia	[179]

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