

Sphingomyelinases: their regulation and roles in cardiovascular pathophysiology.

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Table. Sphingomyelinases in cardiovascular physiology and pathophysiology

Group	Acid sphingomyelinases		Neutral sphingomyelinases		
Gene	<i>Smpd1</i> ^{24,25}		<i>Smpd2</i> ²⁹	<i>Smpd3</i> ³⁰	<i>Smpd4</i> ¹²
Protein	L-ASMase ⁵²	S-ASMase ⁵²	NSMase1 ²⁹	NSMase2 ³⁰	NSMase3 ¹²
Biochemical properties	Zn ²⁺ , pH 5 optimum ^{4,9,11,22}		Mg ²⁺ , pH 7.4 optimum ^{4,9,29}	Mg ²⁺ , pH 7.4 optimum ^{4,9,29}	Mg ²⁺ , pH 7.4 optimum ^{4,9,29}
Subcellular compartment	Lysosomes/ endosomes ^{9,53} , Outer plasma membrane ⁵⁶	Secreted ^{9,11,26,52,54}	ER ²⁹	Golgi ^{30,33} Plasma membrane ²	ER, golgi ¹² Plasma membrane ^{13,14}
Cellular expression	Ubiquitous ^{23,28,34} with high expression in EC ^{54,55}		Ubiquitous ²⁷	Ubiquitous ³³	Ubiquitous with high expression in heart ¹²
Biological activator	I/R insult (CM) ⁴⁶⁻⁴⁸ Ischemic preconditioning (CM) ^{47,49} Fas/ FasL (EC) ⁵⁹⁻⁶⁰ MR1 agonist (VSMC) ⁶¹ Oxidized phospholipids (VSMC) ⁶⁷ ROS ⁷⁶⁻⁷⁸	IFN gamma (EC) ⁵⁵ IL1-beta (EC) ⁵⁵		TNF, ROS, oxLDL (VSMC) ⁹⁵⁻⁹⁷	TNF (CM, VSMC) ^{83-84,95} IL1-beta (CM) ⁹⁵ ApoC1HDL, oxLDL (VSMC) ⁹³⁻⁹⁴ Hypoxia/ reoxygenation (CM) ¹⁰⁴
Biological effect	Lysosomal sphingolipid storage (all cell types) ²³ Post-IR cell death, contractile dysfunction (CM) ⁴⁶⁻⁴⁹ Vascular tone constriction (EC, VSMC) ⁵⁹⁻⁶¹ Oxidized phospholipids -induced apoptosis (VSMC) ⁶⁷			Growth ³³ TNF-, ROS-, oxLDL-induced proliferation (VSMC) ⁹⁵⁻⁹⁷	TNF-, IL-1, hypoxia/reoxygenation-induced apoptosis (CM) ^{83-85, 104,109} TNF-, IL1-beta-induced negative inotropic effect (CM) ^{84,112,85} ApoC1HDL-induced apoptosis (VSMC) ⁹³ OxLDL-, TNF-induced proliferation (VSMC) ⁹⁴⁻⁹⁵ Vasorelaxation (EC) ^{14,100-101}
Pathophysiology	Niemann-Pick disease (<i>smpd1</i> null mutation) ^{23,35} Atherosclerosis ^{59-61,68}	Atherosclerosis ^{62-66,68} Heart failure ^{79,81}			Heart failure ⁹¹⁻⁹² Atherosclerosis ^{93,95-97}
Biological inhibitor		Oxidized glutathione ⁹	Oxidized/ reduced glutathione ^{29,88}		Oxidized/ reduced glutathione ^{29,88-92}
Pharmacological inhibitor	D609 ⁴⁶ , Desipramine ^{48-49,81} , NB6 ¹¹⁹ , L-carnitine ¹²⁰			Scyphostatin ^{14,122} , GW4869 ^{101,123}	NAC ^{89,92} , Lipoic acid ¹⁰²
Pharmacological activator	Doxorubicine ¹²⁰				
Therapeutical target	Atherosclerosis ⁵⁹⁻⁶⁸ Pre/post conditioning ^{46,48}			Atherosclerosis ⁹³⁻⁹⁷	Heart failure ⁹¹⁻⁹²
Diagnostic tool		Heart failure ^{79,81}			

VSMC, vascular smooth muscle cells; EC, endothelial cells; CM, cardiomyocytes; ER, endoplasmic reticulum; I/R, ischemia/ reperfusion; ROS, reactive oxygen species.