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

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