Table 1. Preclinical Investigations of Targeted Therapeutic Strategies in Sepsis

Targets	Mechanism	Results	Animal models and cell lines	Diseases	References
2-DG	HK2 inhibitor	Lung tissue pathological injury, accumulation of neutrophil, oxidative stress, expression of proinflammatory factors.	Mouse model, Primary murine peritoneal macrophages	ALI	[1]
2-DG	HK2 inhibitor	Protective effects against sepsis-induced AKI through the promotion of autophagy via the lactate/SIRT3/AMPK signaling pathway.	Mouse model, HK-2 cells	Sepsis-induced AKI	[2]
Lonidamine	HK2 inhibitor	Mitigates inflammatory damage; lonidamine directly interacts with the inflammasome ligand ASC, thereby preventing its oligomerization.	Mouse model, BMDMs	Autoimmune disease-multiple sclerosis (MS), ischemic stroke and sepsis	[3]
Sodium oxamate	LDHA inhibitor	Reduces circulating exosomal HMGB1	YAP^{flox}/TAZ^{flox}, Lyz2-Cre , and wild-	Sepsis	[4]

		levels and enhances survival outcomes in polymicrobial sepsis.	type mice; Murine RAW 264.7 macrophages		
Celastrol	PKM2 inhibitor	Binds Cys424 of PKM2 to inhibit aerobic glycolysis, Cys106 of HMGB1 to reduce IL-1β secretion, and Cys residues in LDHA.	Mouse; RAW264.7 cells	Sepsis	[5]
4-OI	GAPDH inhibitor	Downregulates aerobic glycolysis in activated macrophages, leading to anti-inflammatory effects.	Mouse; RAW 264.7 cells	Endotoxaemia	[6]
Sodium oxamate, 2-DG, STM2457,	LDHA inhibitor, HK2 inhibitor, METTL3 inhibitor,	Inhibits septic hyper-lactate-induced ferroptosis in alveolar epithelial cells and alleviates lung injury.	Mouse;MLE12 cells	Sepsis-associated lung injury	[7]
Sodium oxamate	LDH inhibitor	Alleviated glycocalyx degradation and ALI, improving survival outcomes in mice with polymicrobial sepsis.	Mouse; primary murine pulmonary microvascular endothelial cells	Sepsis-induced ALI	[8]
Glycyrrhizin;	HMGB1	Reversed the	Mouse	Lactate-	[9]

oxamate	inhibitors; LDH inhibitor	lactate- and low-dose LPS-induced upregulation of NETs in both blood and PMN cell supernatants, thereby alleviating AKI associated with lactate accumulation. .	model, HK-2 cells	induced AKI	
GSK2837808A	LDH inhibitor	Reduced lactate production, attenuated the 3-TYP-mediated increase in Fis1 K20la, and mitigated AKI.	Mouse model, HK-2 cells	Sepsis-induced AKI	[10]
BAY-876	GLUT1 inhibitor	Alleviated inflammation and apoptosis	Mouse model; HK-2, TCMK-1 and HEK293T cell	Sepsis-associated AKI	[11]

Abbreviation: 2-DG: 2-deoxyglucose; HK2: Hexokinase 2; ASC: Apoptosis-associated speck-like protein containing a CARD; AKI:Acute kidney injury; ALI:Acute lung injury; BMDMs: Bone marrow-derived macrophages; GLUT1: Glucose Transporter 1; LDHA: Lactate dehydrogenase A; LDH: Lactate dehydrogenase; TCMK-1: Tubular Cell line derived from Mouse Kidney – 1; HEK293T: Human Embryonic Kidney 293 Transformed.

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