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Review article

The role of lysosomes in metabolic and autoimmune diseases

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Supplementary table 1 | Pharmacological modulators of lysosome functions in pre-clinical and clinical evaluation in autoimmune and metabolic diseases*

Pharmacological agent	Mechanism	Stage of development	Comments	Refs
Lysosomal acidification inhibitors				
HCQ and derivatives (e.g. dimeric CQ derivatives Ly05 and DQ661)	Inhibits lysosomal acidification and autolysosomal hydrolysis; blocks autophagosome-lysosome fusion and autophagic flux	Tool compound/phase IV	• HCQ blocks autoreactive T cell responses in SLE, RA, SS, autoimmune hepatitis and other autoimmune diseases via its effect on antigen presentation to T cells • CQ inhibits the differentiation of osteoclast precursors into mature osteoclasts *in vitro* and *in vivo* • Ongoing clinical trials alone or in combination in diseases including SLE (NCT00413361), SS (NCT01601028), RA (NCT03085940) and autoimmune hepatitis (NCT01980745)	2,3
• **Cathepsin inhibitors**				
CA030, CA-074, and their analogues	Cathepsin B inhibitor	Preclinical	• High amounts of cathepsin B in patients with compared to patients with OA	4
α1-Antichymotrypsin and phenylmethylsulfonyl fluoride	Cathepsin G inhibitor	Preclinical	• Increased cathepsin G in RA patients compared to patients with OA • Monocyte chemotactic activity in the synovial fluid of RA patients was directly proportional to cathepsin G expression	5
CLIK-148, CLIK-181, and CLIK-195	Cathepsin L inhibitor	Preclinical	• Inhibitors obtained as leads from *in vitro* and *in vivo* studies. • High expression of cathepsin L in RA compared to patients with OA • siRNA-mediated inhibition protected mice from autoimmune diabetes	6,7
LHVS and CLIK-60	Cathepsin S inhibitor	Preclinical	• Cathepsin S inhibitors (CLIK-60) inhibited autoantigen presentation in mouse model of SS • Cathepsin S-deficient mice are less susceptible to CIA	8-10
RO5461111/Roche		Preclinical	• Inhibition of cathepsin S has beneficial effects in SLE and SS *via* inhibiting autoantigen presentation • Cathepsin S, from tears of SS patients, enhanced the degradation of tear proteins	11-13
• **v-ATPase inhibitors**				
Bafilomycin A1	Blocks the transport of protons for lysosomal acidification; inhibits LAP			14
• **Ion channel modulators**				
SF-22	TRPML1/3 agonist	Preclinical	• May have therapeutic uses autoimmune diseases (WO2015118167A1)	15
• **PIK kinase modulators**‡				
YM-201636	Class III PI kinase: PIKfyve kinase inhibitor	Preclinical	• Inhibits glucose influx in adipocytes	17
Apilimod (LAM-002A (apilimoddimesylate)/STA-5326)/AI Therapeutics	Class III PI kinase: PIKfyve kinase inhibitor	Preclinical	• An inhibitor of Th1 and Th17 cell responses in RA and CD	18-20
SAR088	PI5P4K	Preclinical	• Obese SDF mice	21
• **Lysosome biogenesis**				
Trehalose	TFEB activator	Clinical	• Clinical trial for SS	22
Chaperone modulators				
P140 peptide (Lupuzor)/ImmuPharma	CMA inhibitor	Clinical/phase III (lupus)	• Binds HSPA8 and blocks dysregulated CMA activity in murine models of SLE, SS, IBD, CIDP and other autoimmune diseases.	23-27

*Modified with permission from Bonam et al.[1] The efficacy of other molecules is currently evaluated in preclinical proof-of-concept studies in animal models (see text).

‡See ref. 16 for other molecules in the clinic or currently evaluated at the pre-clinical stage.

Abbreviations: CD, Crohn's Disease; CIA, collagen-induced arthritis; CIDP, chronic inflammatory demyelinating polyneuropathy CLIK, cathepsin L inhibitor Katunuma; HCQ/CQ, hydroxychloroquine/chloroquine; IBD, intestinal bowel disease; LHVS, morpholinurea-leucine-homophenylalanin-

vinyl phenyl-sulfone; N/A not available; ClinicalTrials.gov Identifier: NCT number; OA, osteoarthritis; PIKfyve, FYVE finger-containing phosphoinositide kinase; PI kinase, Phosphoinositide kinase; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; TFEB, transcription factor EB.

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