



De brevitatis vitae

**Nihil minus est hominis occupati quam
vivere. Nullius rei difficilior scientia est.
Vivere tota vita discendum est et, quod
magis fortasse miraberis, tota vita
discendum est mori.**

Lucius Annaeus Seneca (4BC - AD65)

Hallmarks of aging

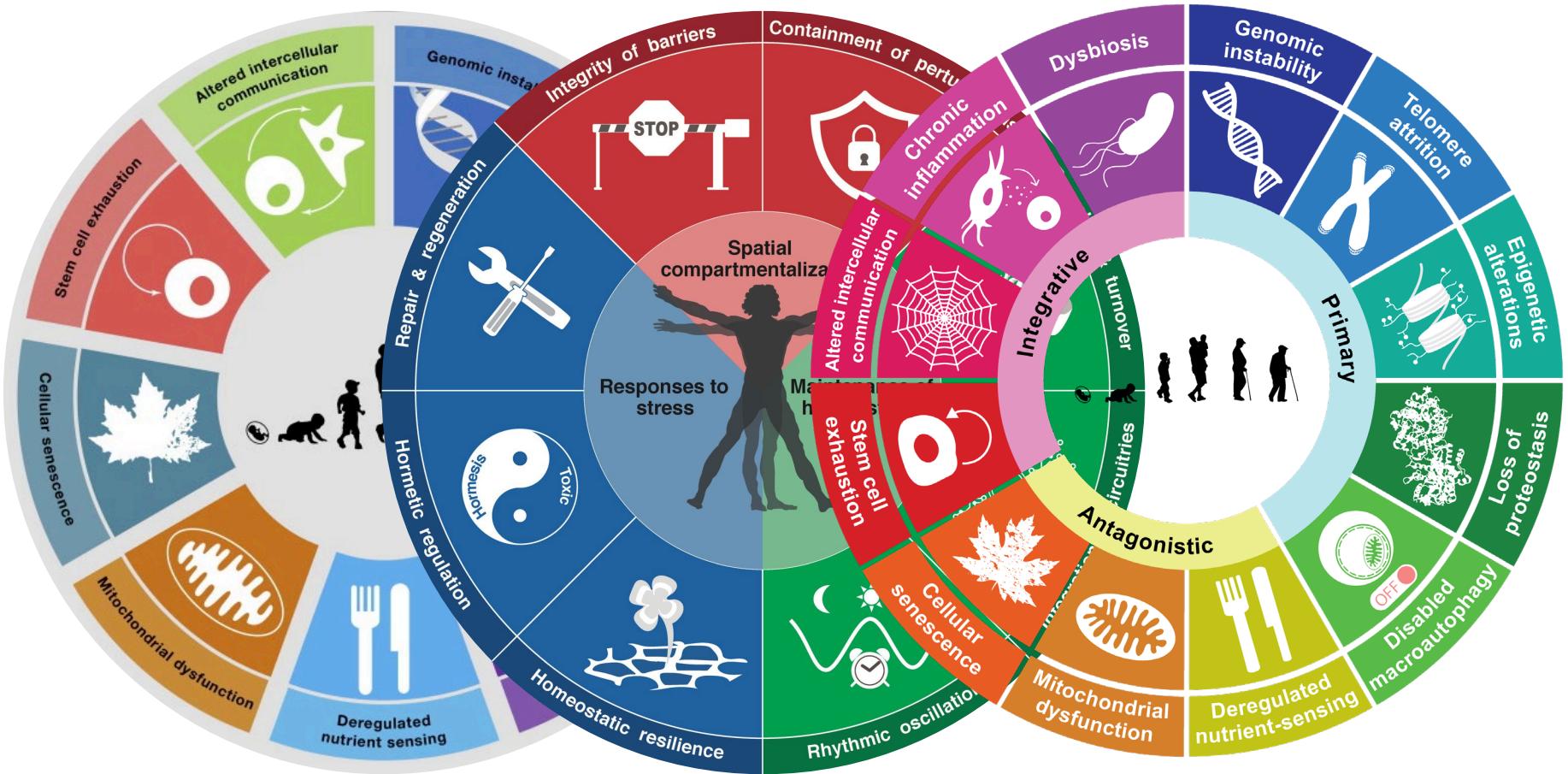
Mechanismen des Alterns

Guido Kroemer

2013

2021

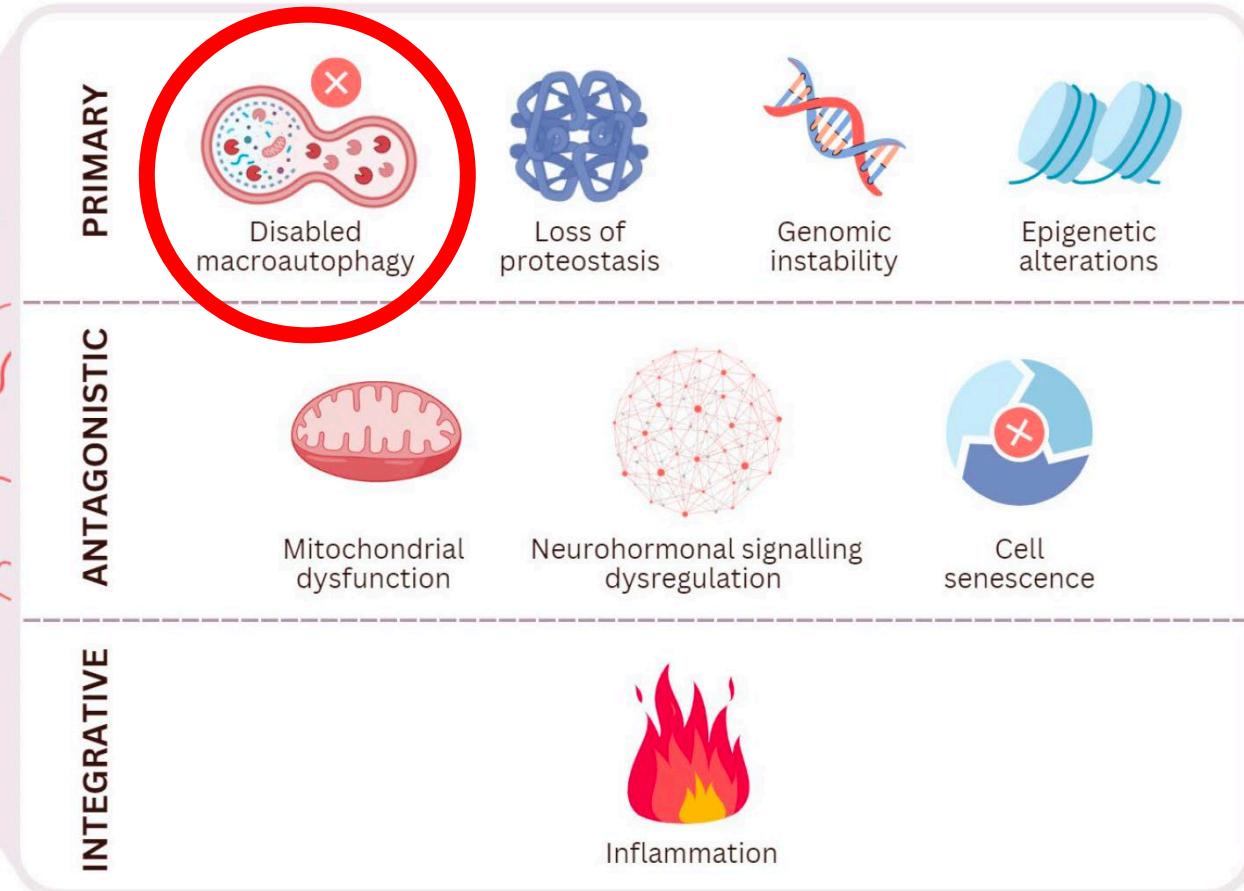
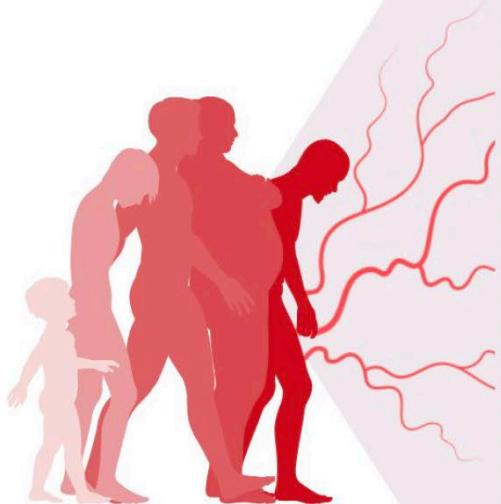
2023



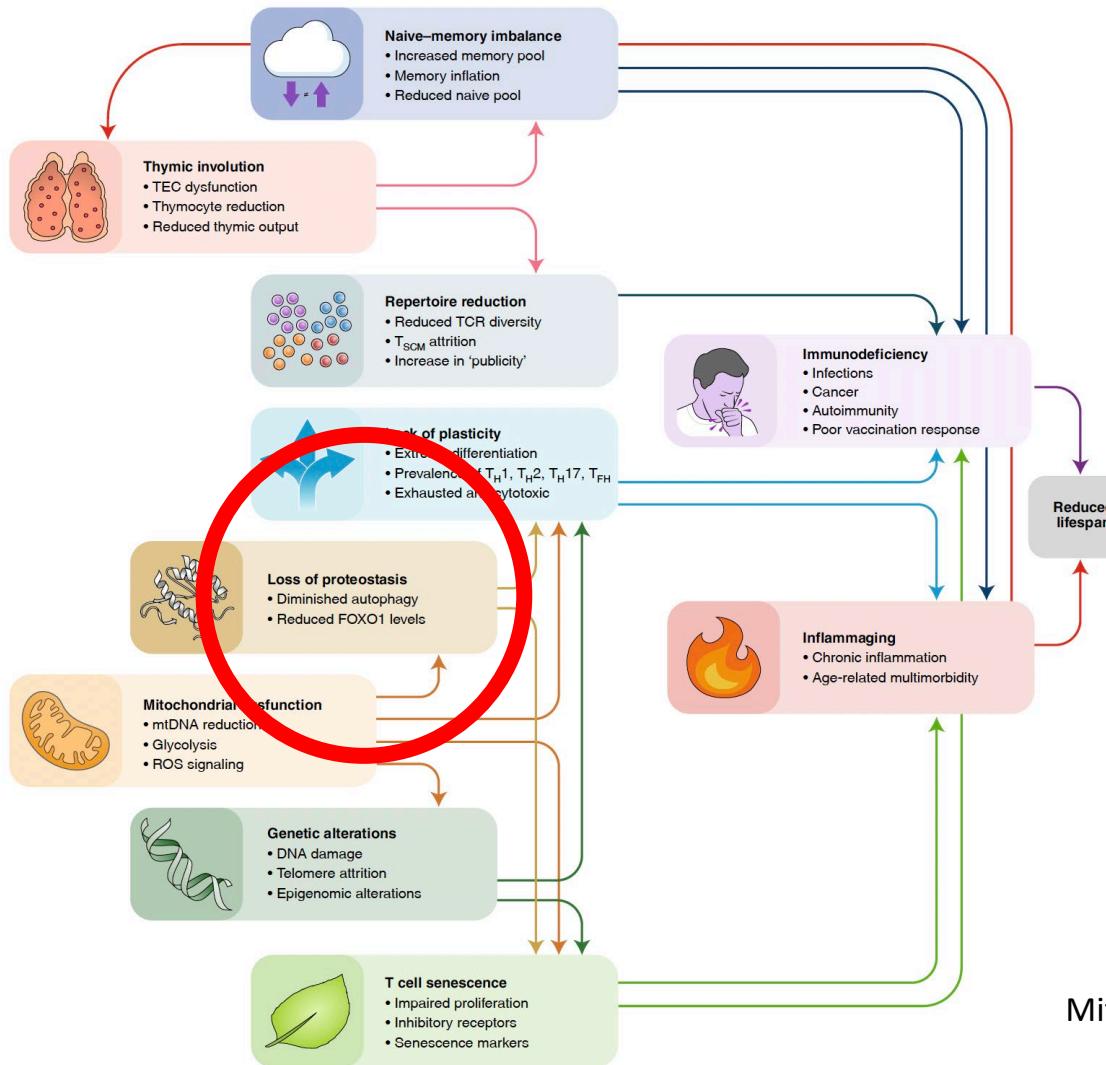
Hallmarks of Aging



Hallmarks of Cardiovascular Aging

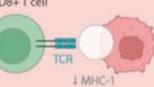


Hallmarks of T cell aging



Meta-Hallmarks of Aging and Cancer

The paradox of the ever-fitter cancer cell In the ever-unfitter aging organism

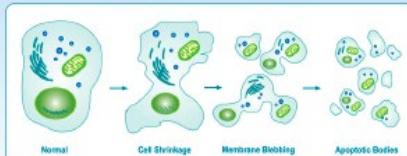
Tumor suppressive effects	Pro-carcinogenic effects
Genome Stability 	Metabolic Fitness 
Proliferative Arrest 	Proliferation 
Inflammation 	Resistance to Therapy 
Immunosurveillance (natural, therapy-induced) 	Immunosubversion 

Autophagy

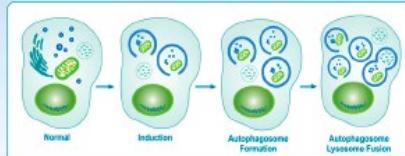
Different ways of ‘self-consumption’



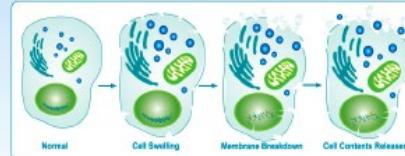
Apoptosis Regulation



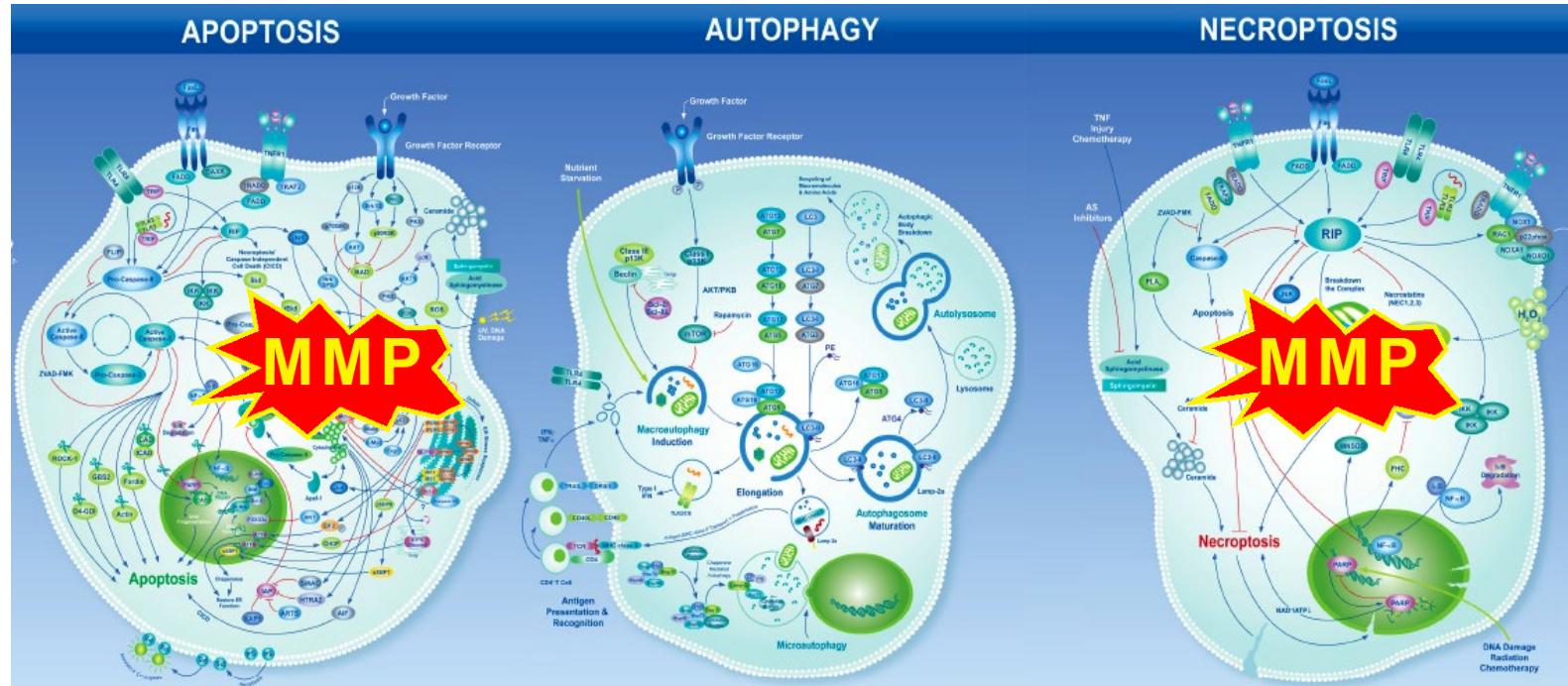
Autophagy Regulation



Necroptosis Regulation



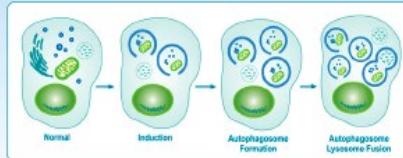
Different ways of ‘self-consumption’



Apoptosis Regulation



Autophagy Regulation



Necroptosis Regulation

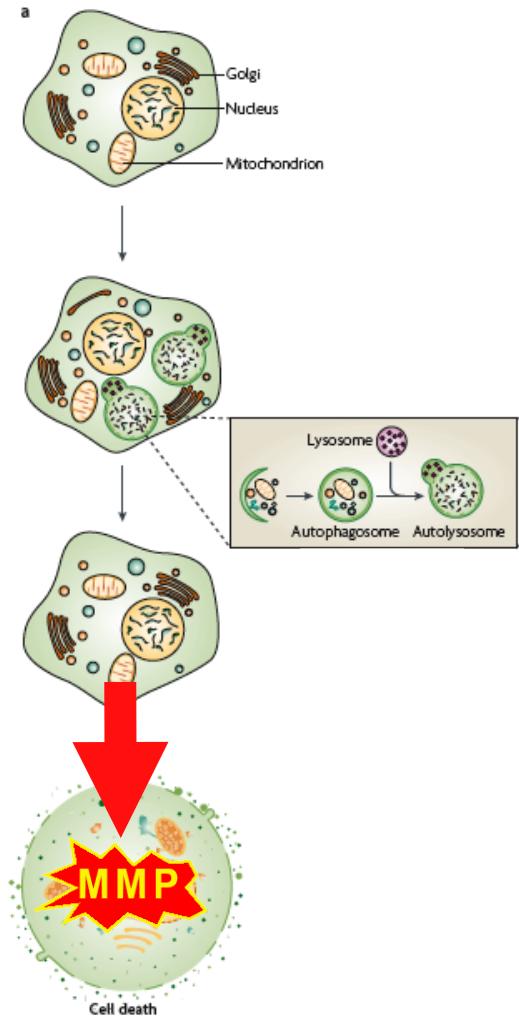


Health

Stress

Auto- phagy

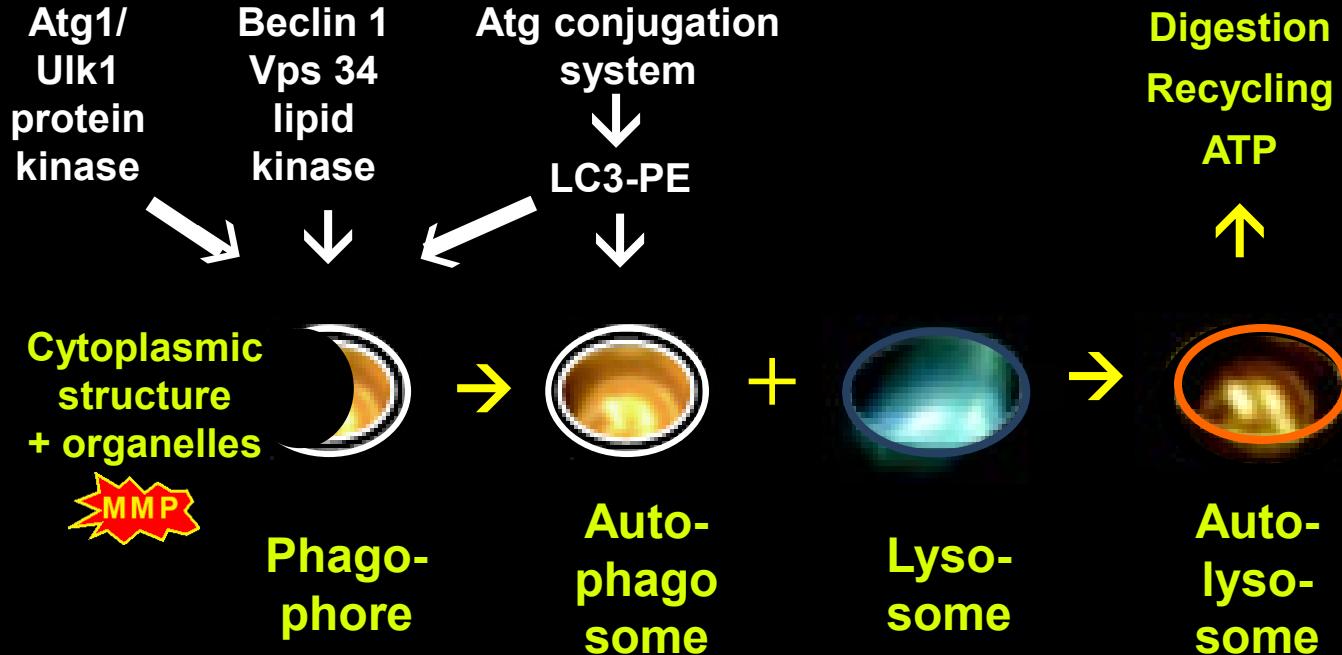
Death



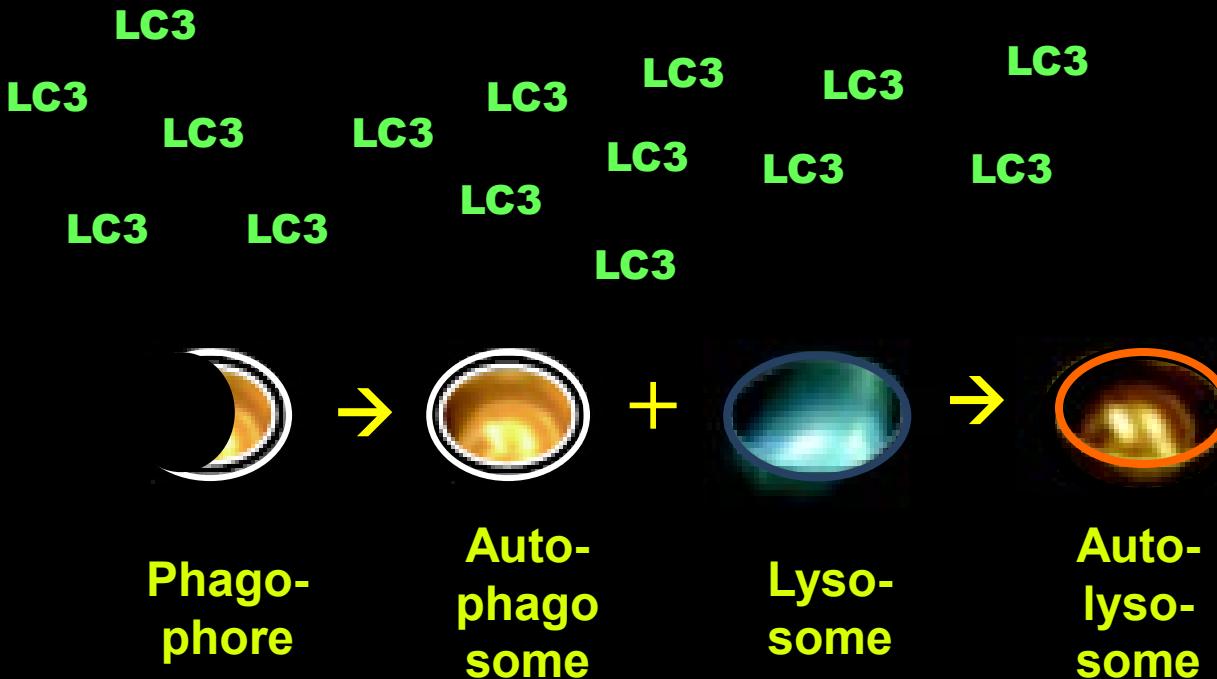
Autophagy is cyto- protective

- Boya et al. Mol Cell Biol 2005
Gonzalez-Polo et al J Cell Sci 2005
Maiuri et al. EMBO J 2007
Maiuri et al. Nature Rev MCB 2007
Tasdemir Nature Cell Biol 2008
Levine & Kroemer CELL 2008
Kroemer & Levine Nature Rev MCB 2008
Boya et al. Oncogene 2009
Green et al. Nature 2009
Eisenberg et al. Nat Cell Biol 2009
Madeo et al. Genes & Dev 2009
Morselli et al. Cell Death & Disease 2010
Criollo et al. EMBO J 2010
Maiuri et al. EMBO J 2010

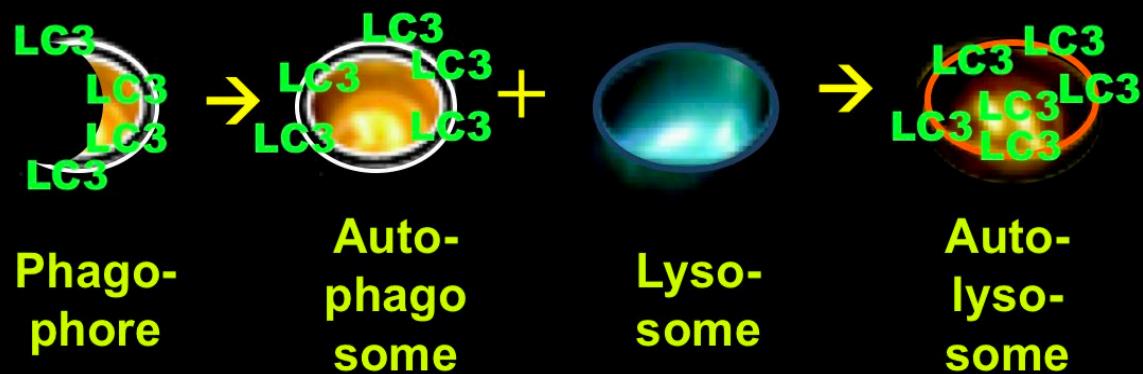
Autophagy



Autophagy



Autophagy



Starvation
Caloric restriction



AcCoA /CoA
ratio reduced



Protein
deacetylation

Cytoplasmic
structures
+ organelles



Phago-
phore



Auto-
phago-
some



Lyo-
some

Digestion
Recycling

ATP

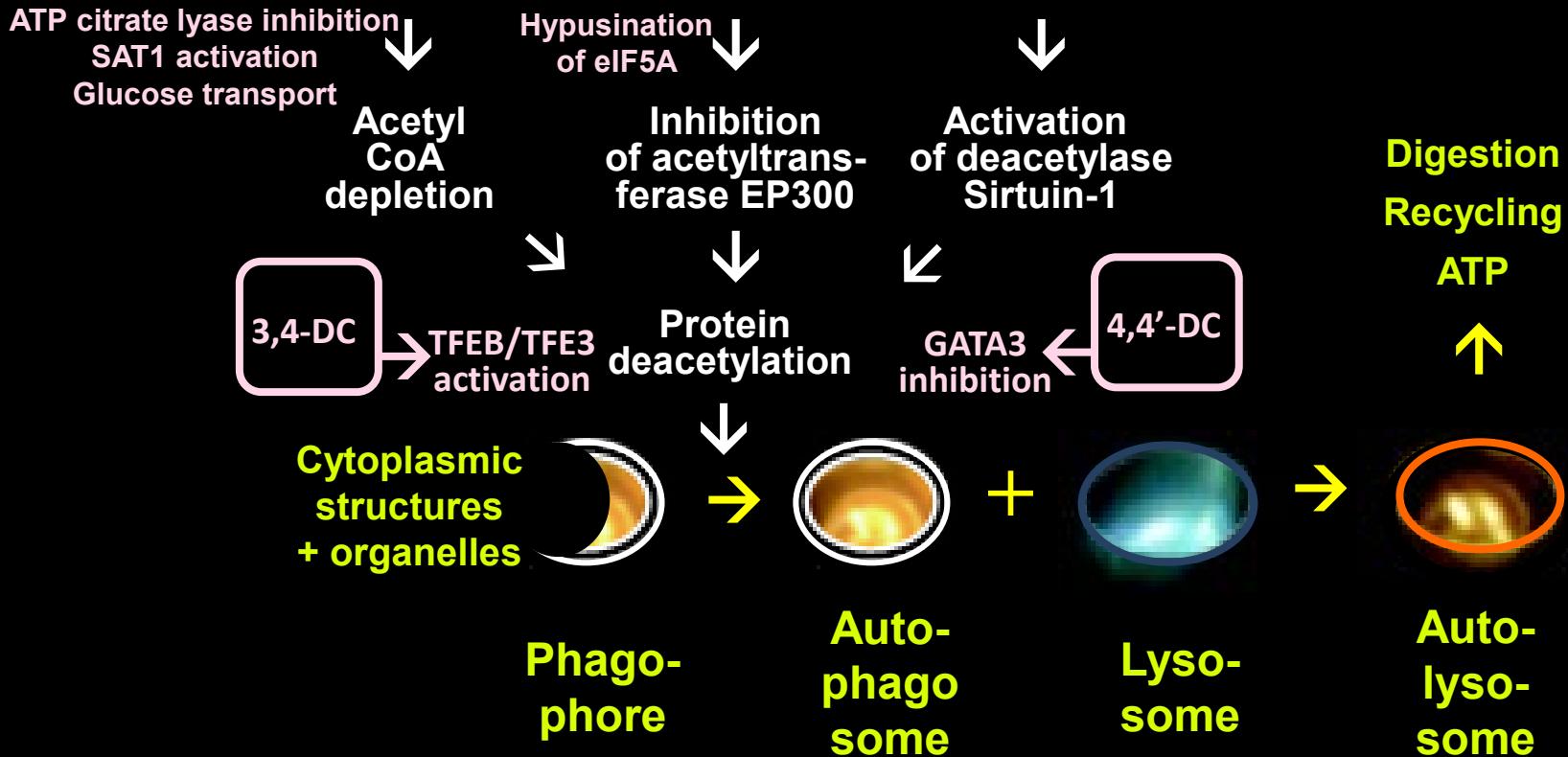


Auto-
lyso-
some



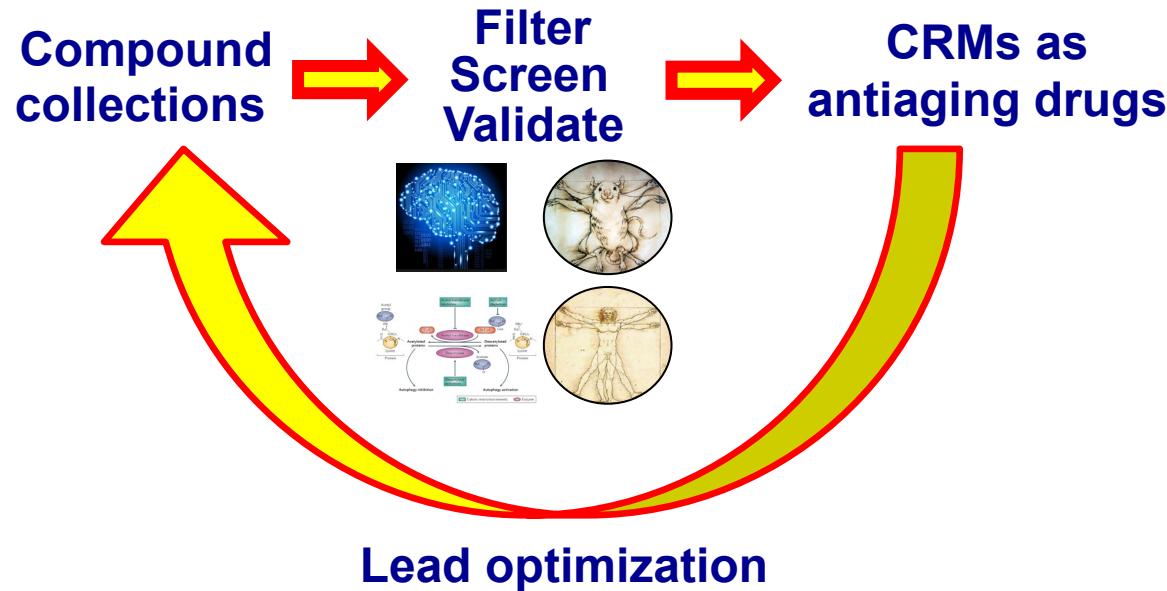
**CALORIC
RESTRICTION
MIMETICS
(CRMs)**

Hydroxycitrate Spermidine, C464 Resveratrol
TETA, IGF1Ri EGCG, salicylate Nicotinamide





Screen for autophagy inducers or « caloric restriction mimetics » (CRMs)



Caloric restriction mimetics (CRMs)

Conditions	CRMs	References
Aging of yeast, nematodes, flies, mice & humans	Resveratrol (nematodes) Spermidine (all species) 4,4' DMC (yeast+flies)	Eisenberg et al. 2009 <i>NCB</i> Eisenberg et al. 2016 <i>Nat Med</i> Pietrocola et al. 2018 <i>Cell Rep</i> Madeo et al. 2018 <i>Science</i> Carmona et al. 2019 <i>Nat Commun</i> Motiño et al. 2022 <i>PNAS</i> Hofet et al. 2022 <i>Nat Aging</i> Montégut et al. 2023 <i>Aging Cell</i>
Obesity/diabetes in mice	Resveratrol, spermidine, aspirin Triethylentetramine (TETA)	
Oncoprevention of <i>Kras</i> -induced lung cancer (NSCLC) <i>Apc</i> ^{Min} -induced colon cancer (CRC) Luminal B breast cancer (LumB) Carcinogen-induced liver cancer (HCC)	Hydroxycitrate (NSCLC) Aspirin, resveratrol Nicotinamide	Rao et al. 2014 <i>Nat Comm</i> Lissa et al. 2014 <i>PNAS</i> Pietrocola et al. 2016 <i>Cancer Cell</i> Buqué et al. 2020 <i>Nat Commun</i> Li et al. unpublished
Improvement of chemoimmuno- therapy with ICD inducers + PD1 blockade	Aspirin, 3,4' DMC Hydroxycitrate/SB204990 Spermidine/C646, thiostreptone Picropodophyllin/linsitinib (IGF1R inh.) Isobavachalcone (AKT inhibitor)	Pietrocola et al. 2016 <i>Cancer Cell</i> Wang et al. 2020 <i>J ImmunoTher Cancer</i> Wu et al. 2020 <i>Cell Death & Disease</i> Buqué et al. 2020 <i>Nat Commun</i> Wu et al. 2021 <i>J ImmunoTher Cancer</i> Montégut et al. unpublished
Cystic fibrosis in mice and patients carrying the CFTR-Del506 mutation (phase II)	Epigallocatechin gallate (EGCG) plus cysteamine Thymosin- α	Stefano et al. 2014 <i>Autophagy</i> Tosco et al. 2016 <i>CDD</i> Izzo et al. 2017 <i>Cell Cycle</i> Romani et al. 2017 <i>Nat Med</i> Galluzzi et al. 2017 <i>Nat Rev Drug Discov</i>
Cardioprotection (C) Hepatoprotection (H) Pneumoprotection (P)	Aspirin (C, H) 3,4' DMC (C, H) Nicotinamide (C, H) IGFR1 inhibition (C)	Eisenberg et al. 2016 <i>Nat Med</i> Abdellatif et al. 2020 <i>Sci Transl Me</i> Abdellatif et al. 2021 <i>Circulation</i> Motiño et al. 2022 <i>PNAS</i> Montégut et al. 2023 <i>Aging Cell</i>

Caloric restriction mimetics (CRMs)

Conditions	CRMs	References
Aging of yeast, nematodes, flies, mice & humans	Resveratrol (nematodes) Spermidine (all species) 4,4' DMC (yeast+flies) ACBP/DBI KO (yeast)	Eisenberg et al. 2009 <i>NCB</i> Eisenberg et al. 2016 <i>Nat Med</i> Pietrocola et al. 2018 <i>Cell Rep</i> Madeo et al. 2018 <i>Science</i> Carmona et al. 2019 <i>Nat Commun</i> Motiño et al. 2022 <i>PNAS</i> Hofet et al. 2022 <i>Nat Aging</i> Montégut et al. 2023 <i>Aging Cell</i>
Obesity/diabetes in mice	Effects depend on autophagy induction Resveratrol, spermidine, aspirin Triethylentetramine (TETA) ACBP/DBI KO or neutralization (mice)	Rao et al. 2014 <i>Nat Comm</i> Lissa et al. 2014 <i>PNAS</i> Pietrocola et al. 2016 <i>Cancer Cell</i> Buqué et al. 2020 <i>Nat Commun</i> Li et al. unpublished
Oncoprevention of Kras-induced lung cancer (NSCLC) <i>Apc</i> ^{Min} -induced colon cancer (CRC) Luminal B breast cancer (LumB) Carcinogen-induced liver cancer (HCC)	Effects depend on autophagy induction Hydroxycitrate (NSCLC) Aspirin, resveratrol Nicotinamide ACBP/DBI neutralization	Pietrocola et al. 2016 <i>Cancer Cell</i> Wang et al. 2020 <i>J ImmunoTher Cancer</i> Wu et al. 2020 <i>Cell Death & Disease</i> Buqué et al. 2020 <i>Nat Commun</i> Wu et al. 2021 <i>J ImmunoTher Cancer</i> Montégut et al. unpublished
Improvement of chemoimmuno-therapy with ICD inducers + PD1 blockade	Effects depend on autophagy induction in cancer cells Aspirin, 3,4' DMC Hydroxycitrate/SB204990 Spermidine/C646, thiostreptone Picropodophyllin/linsitinib (IGF1R inh.) Isobavachalcone (AKT inhibitor) ACBP/DBI neutralization	Stefano et al. 2014 <i>Autophagy</i> Tosco et al. 2016 <i>CDD</i> Izzo et al. 2017 <i>Cell Cycle</i> Romani et al. 2017 <i>Nat Med</i> Galluzzi et al. 2017 <i>Nat Rev Drug Discov</i>
Cystic fibrosis in mice and patients carrying the CFTR-Del506 mutation (phase II)	Effects depend on autophagy induction Epigallocatechin gallate (EGCG) plus cysteamine Thymosin- α	Eisenberg et al. 2016 <i>Nat Med</i> Abdellatif et al. 2020 <i>Sci Transl Me</i> Abdellatif et al. 2021 <i>Circulation</i> Motiño et al. 2022 <i>PNAS</i> Montégut et al. 2023 <i>Aging Cell</i>
Cardioprotection (C) Hepatoprotection (H) Pneumoprotection (P)	Effects depend on autophagy induction Aspirin (C, H) 3,4' DMC (C, H) Nicotinamide (C, H) IGFR1 inhibition (C) ACBP/DBI neutralization (C, H, P)	

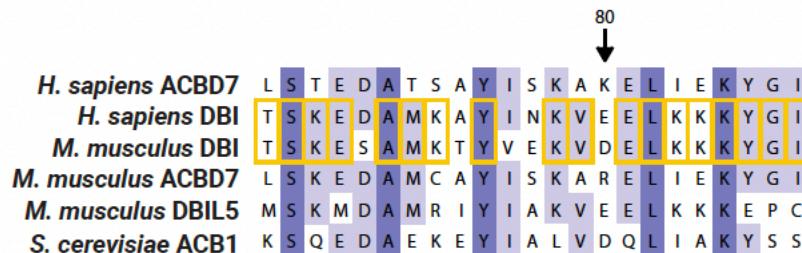
ACBP/DBI: the first peptide hormone

A

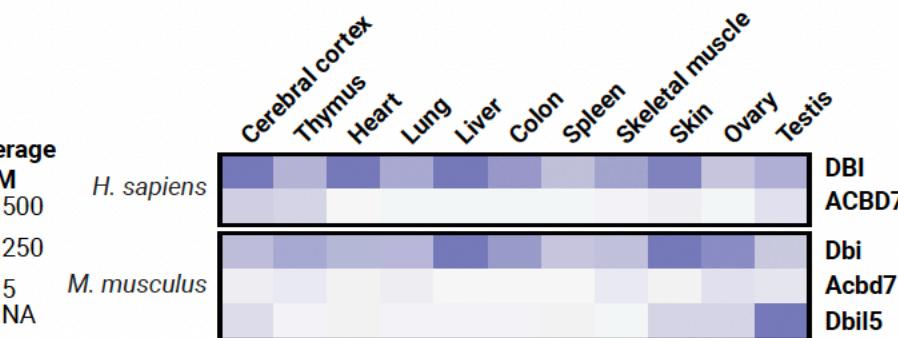


Sequence conservation

- Conserved in all sequences
- Conserved in 4/6 or 5/6 sequences
- Conserved in *M. musculus* and *H. sapiens* DBI



B



Conserved secretion pathway

Intracellular ACBP/DBI



Autophagy-dependent unconventional secretion

Extracellular ACBP/DBI

Fungi
Amoebozoa
Animals

Divergent ACBP/DBI receptors

Saccharomyces cerevisiae



ACB1

Ste3
GPCR receptor

MAPK cascade

Dictyostelium discoideum



ACBA

SDF-2

DhkA
Histidine kinase

cAMP accumulation
PKA activation

Mammalian cells



ACBP/DBI

GABA_A receptor
Subunit γ2
GABRG2

Positive allosteric modulation
ODN-GPCR ?
CNS-specific putative receptor

TTN, ODN

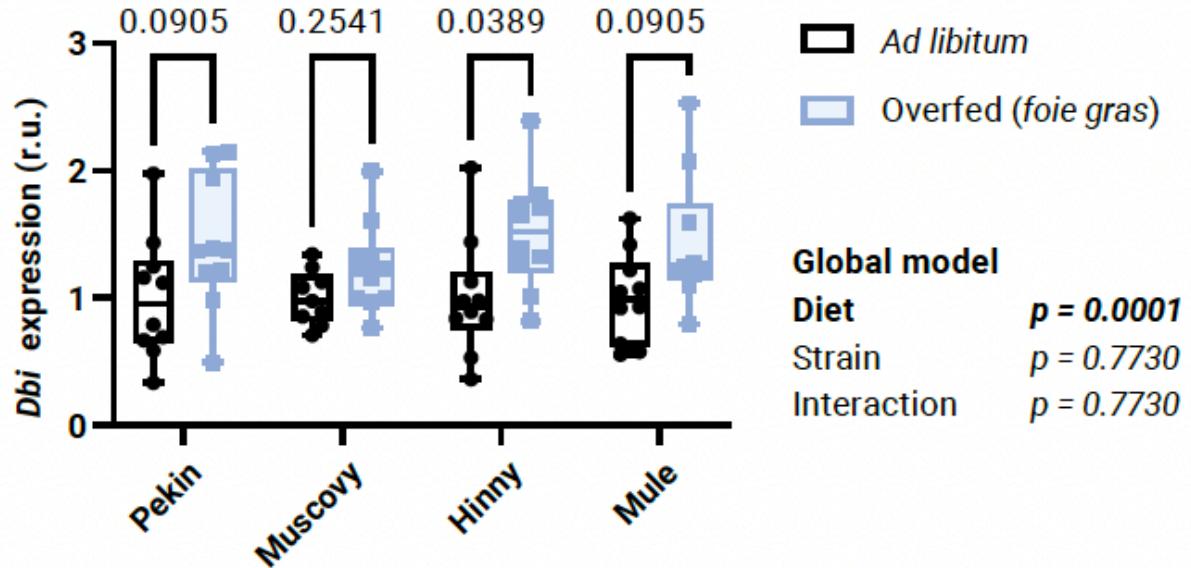
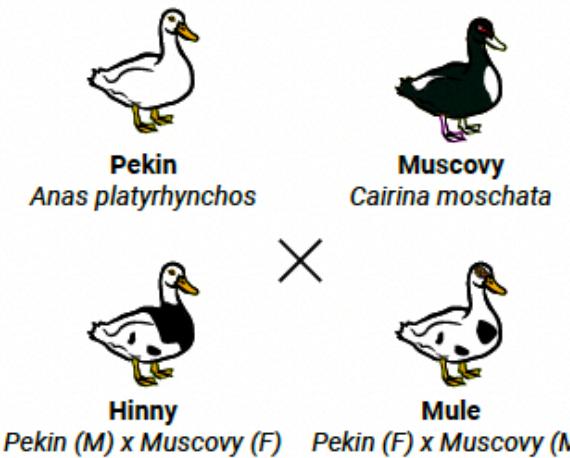
TSPO
Mitochondrial receptor



A

	Non-mammalian species	DBI ortholog	Consequences of knockout
Protista	 <i>Neospora caninum</i>	<i>ACBP</i>	<ul style="list-style-type: none">Enhances fitness and pathogenicity in mice
	 <i>Dictyostelium discoideum</i>	<i>AcbA</i>	<ul style="list-style-type: none">Inhibits terminal differentiation and sporulation
Fungi	 <i>Saccharomyces cerevisiae</i>	<i>ACB1</i>	<ul style="list-style-type: none">Extends lifespan (autophagy-dependent)Inhibits sporulation
	 <i>Pichia pastoris</i>	<i>ACB1</i>	<ul style="list-style-type: none">Inhibits sporulation
Plantae	 <i>Cryptococcus neoformans</i>	<i>ACB1</i>	<ul style="list-style-type: none">Inhibits yeast-to-hypha transition
	 <i>Arabidopsis thaliana</i>	<i>ACBP3</i>	<ul style="list-style-type: none">Protects from darkness-induced senescence
Animalia	 <i>Caenorhabditis elegans</i>	<i>acbp-1</i> <i>acbp-3</i>	<ul style="list-style-type: none">Increases autophagyDecreases pharyngeal pumpingExtends the longevity of females exposed to males
	 <i>Drosophila melanogaster</i>	<i>Anox</i>	<ul style="list-style-type: none">Decreases food intake in larvae and adultsShortens lifespan in adults
	 <i>Bombyx mori</i>	<i>BmACBP</i>	<ul style="list-style-type: none">Decreases triglyceride storage and pheromone production

ACBP/DBI is involved in the (patho)genesis of foie gras



Beneficial effects of ACBP/DBI neutralization in mice

Neuroprotection

- Middle cerebral artery occlusion

Reduced infarction volume

Cardioprotection

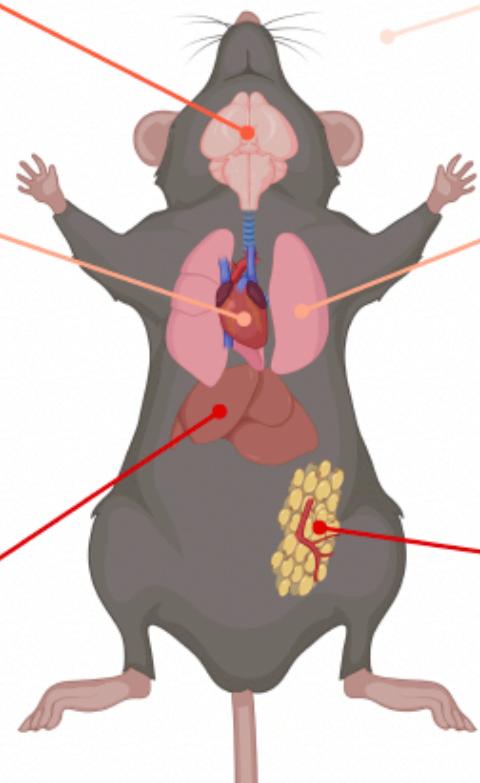
- Infarction
- Chronic doxorubicin challenge

Preserved function, ↓ p16/CDKN2A

Hepatoprotection

- Acetaminophen
- Bile duct ligation
- Carbon tetrachloride
- Concanavalin A
- High-fat diet
- Ischemia-reperfusion
- Methionine-choline deficient diet

*Reduced micro- and macrosteatosis
Reduced inflammation and fibrosis*



Anti-aging effects ?

*Increased mRNA levels in the liver of aged mice
Liver transcriptome of DBI^{KO} mice resembles that of long-lived strains*

Pneumoprotection

- Bleomycin

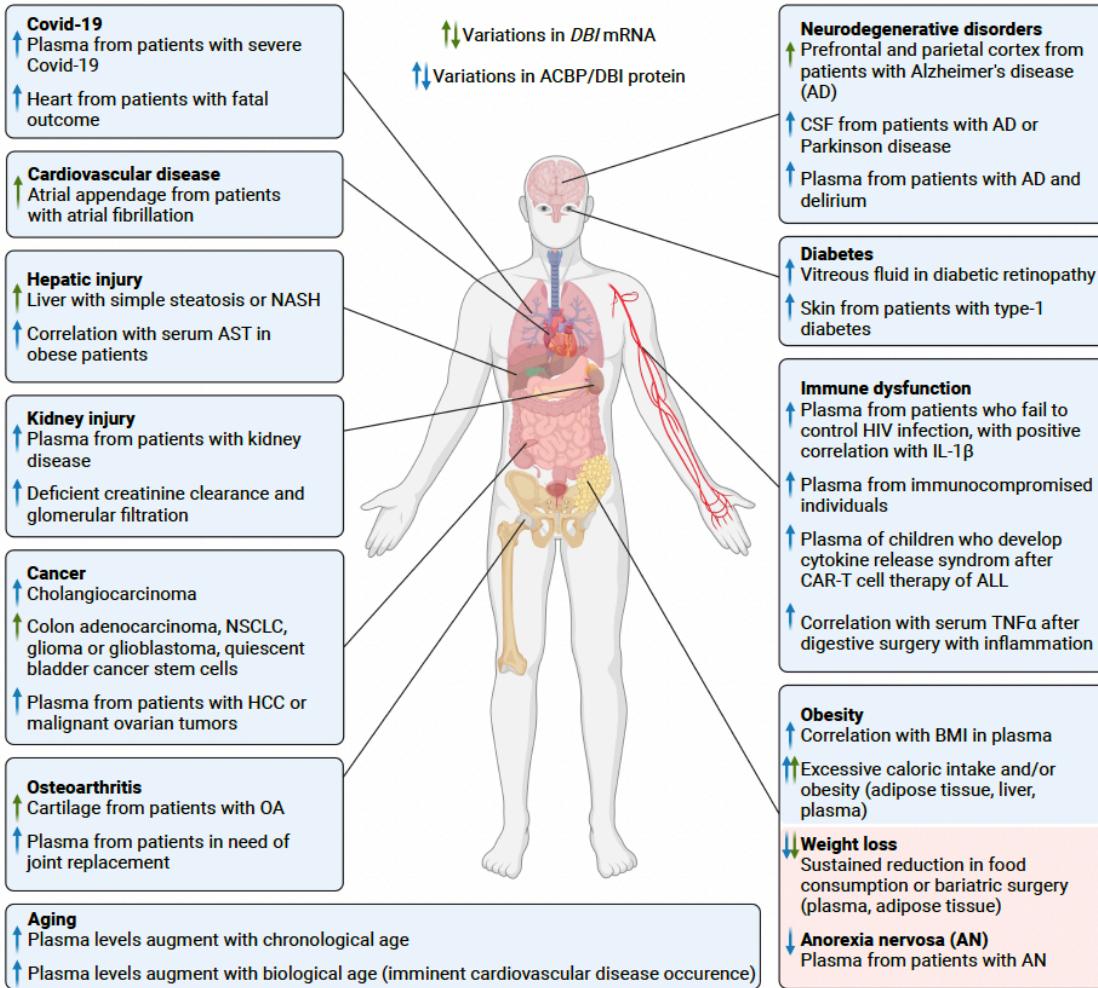
Reduced fibrosis and inflammation markers

Anti-obesity effects

- High-fat diet
- Hyperphagy of normal diet (Lep^{ob})
- Rosiglitazone
- Refeeding after fasting

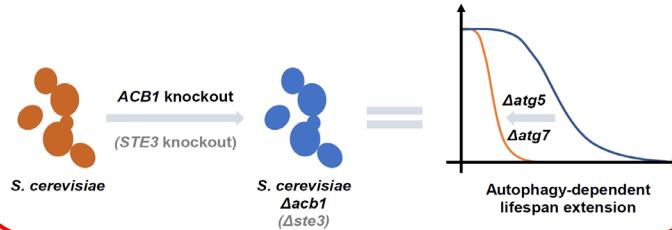
*Reduced food intake & weight gain
Avoidance of metabolic syndrome
Reduced inflammation markers*

Elevated ACBP/DBI mRNA and protein levels in human disease

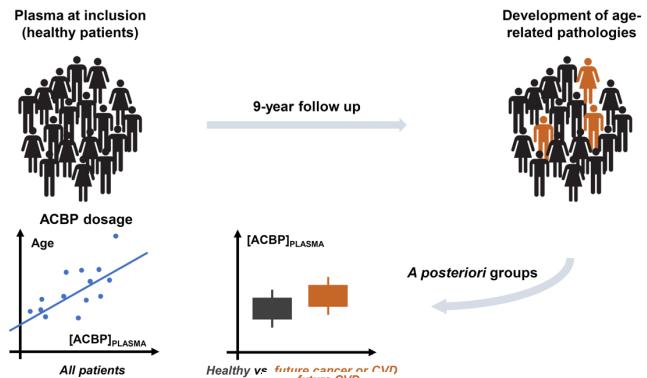


ACBP is a targetable autophagy checkpoint involved in aging and cardiovascular disease

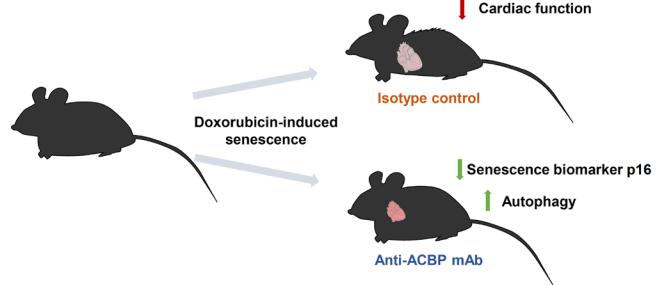
Lifespan extension in yeast



Prediction of future disease



Prevention of cardiac senescence



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