GeneTex

Autophagy in cancer and disease

Fine tuning of cellular microenvironment

Chieh-Huei Wang, PhD

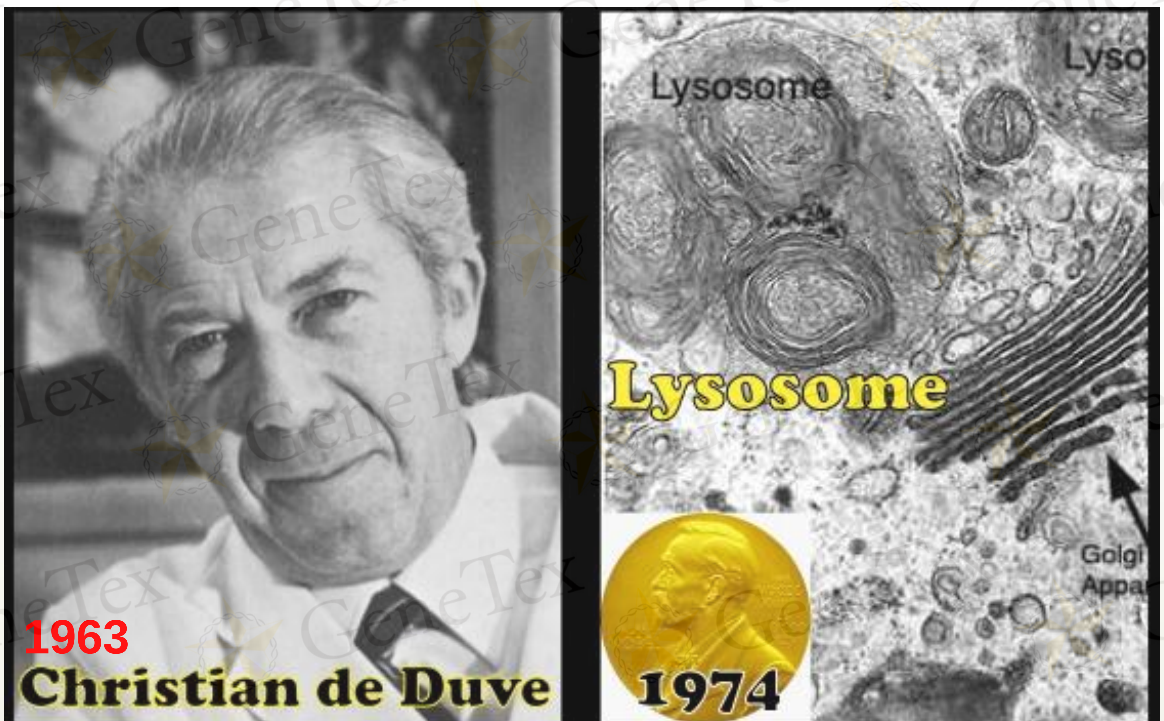
Autophagy

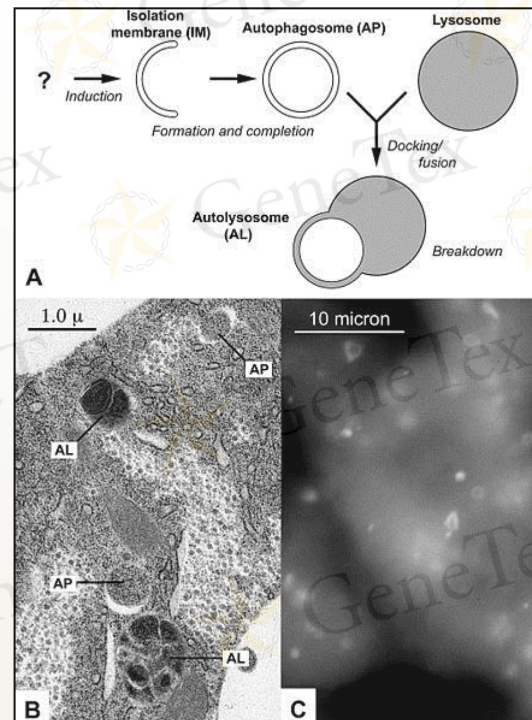
Autophagy: a basic cellular process in eukaryotes

Phagy = eating/lysosomal degradation

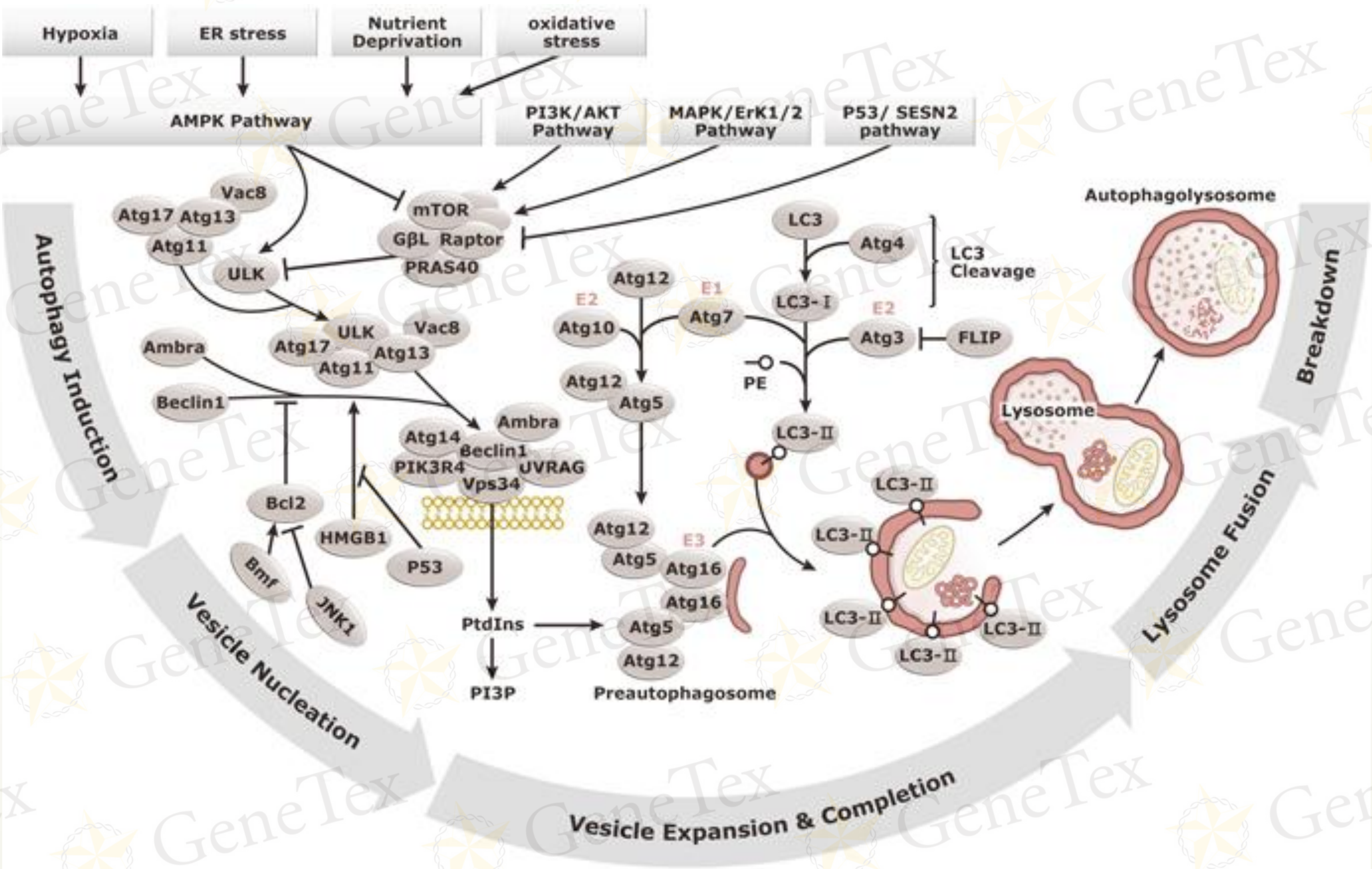
Autophagy = self-eating

Mechanism of breakdown of cytoplasm within the lysosome





Underlying Mechanisms of Autophagy



Autophagy

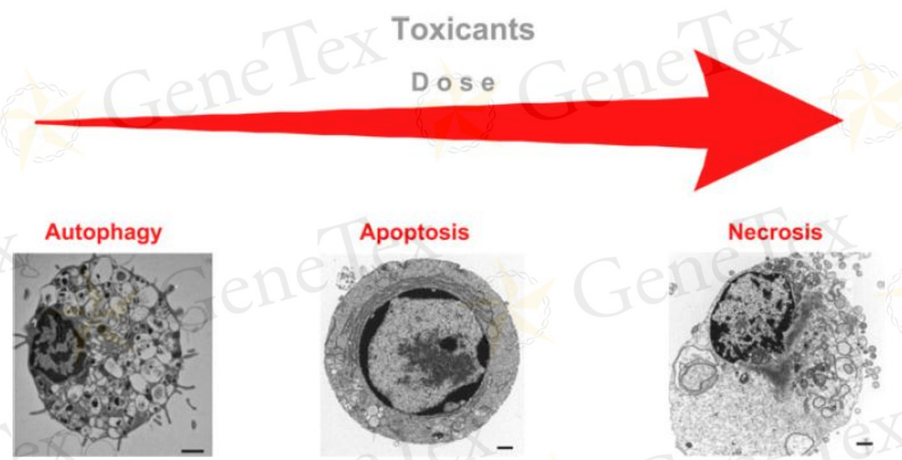


FIG. 1. Dose-response relationship of toxicant-induced modes of cell death. The mode of cell death triggered by some toxicants is dose dependent. Most often, exposure to low doses results in autophagy or apoptosis, whereas higher levels of the same toxicant might cause necrosis.

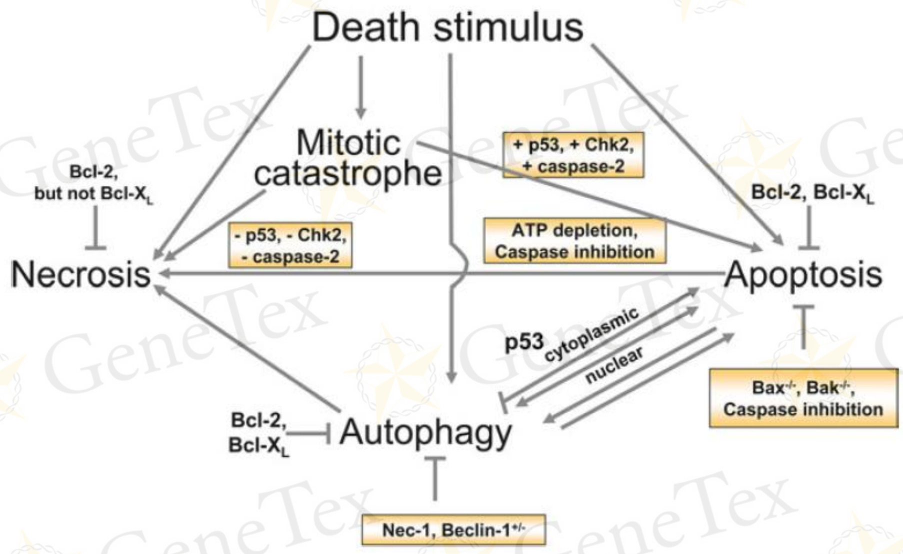
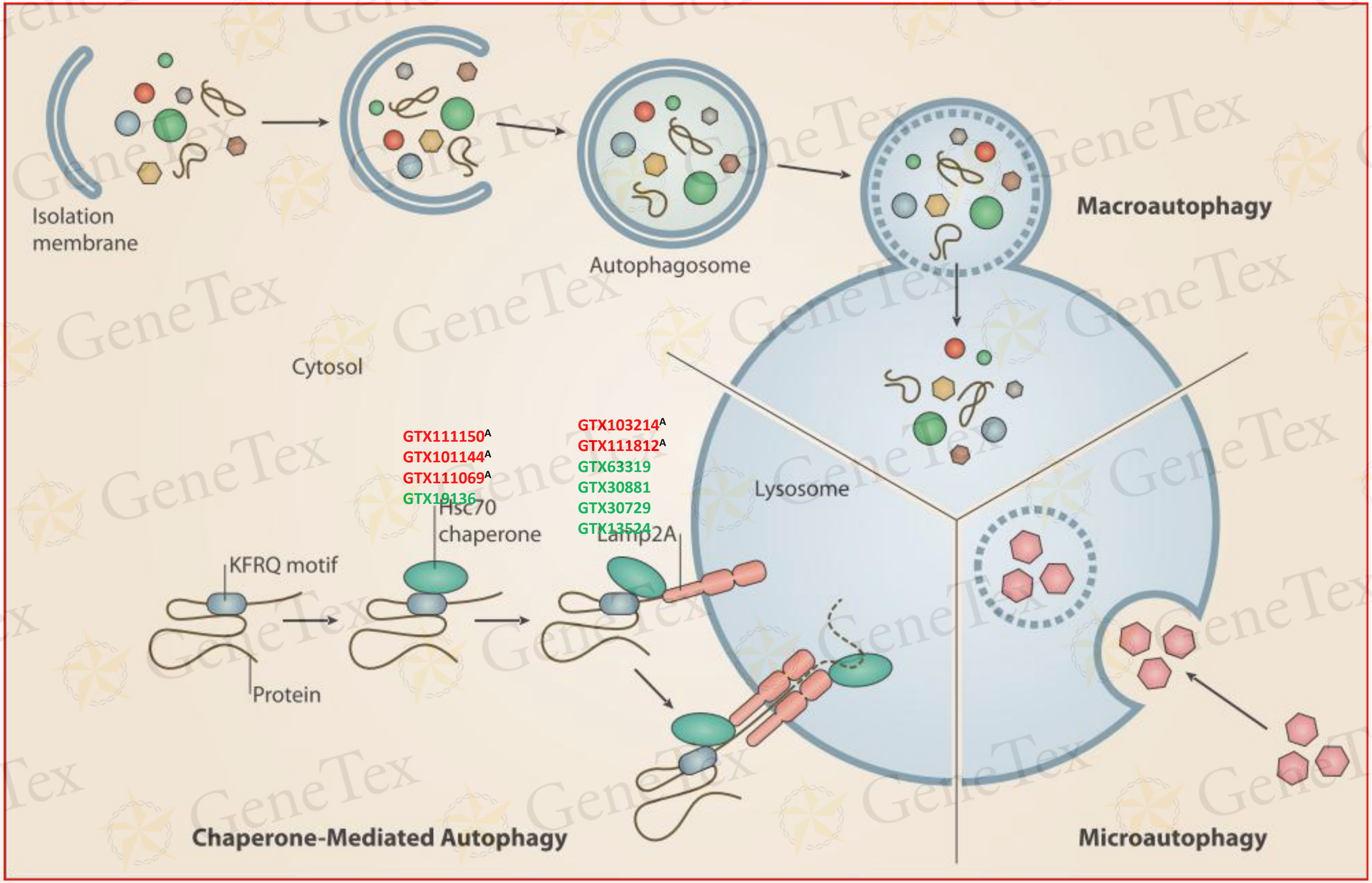


FIG. 4. Cross talk between different modes of cell death. Toxicants might trigger different modes of cell death depending on which pathways can be activated. Inhibition of one particular pathway might lead to cell death by a different mechanism. However, some inhibitors (Bcl-2) can block several cell death modalities. The p53 status of the cell is also important for the mode of cell death that is induced.

Autophagy

Types of autophagy



The molecular machinery of autophagy

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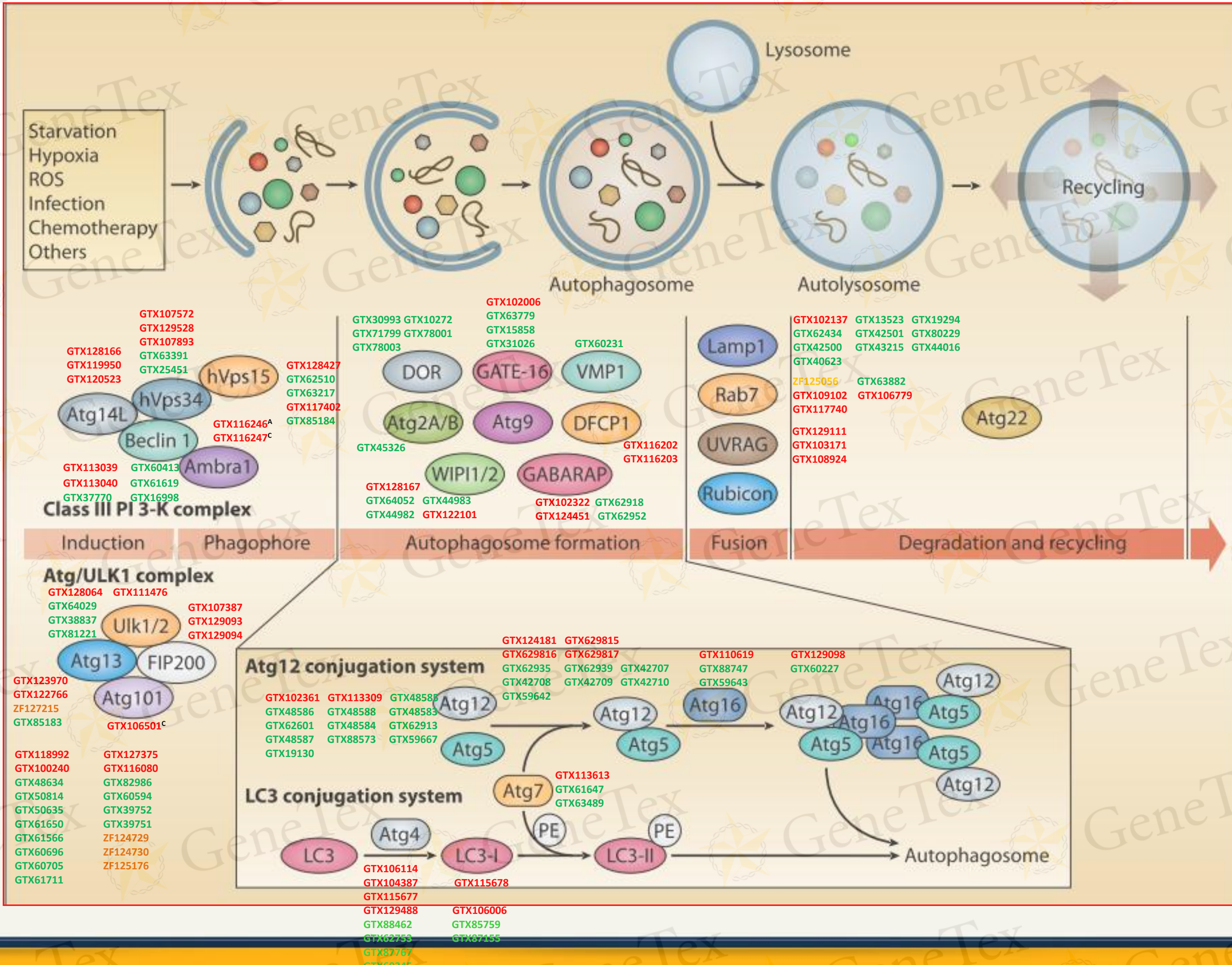
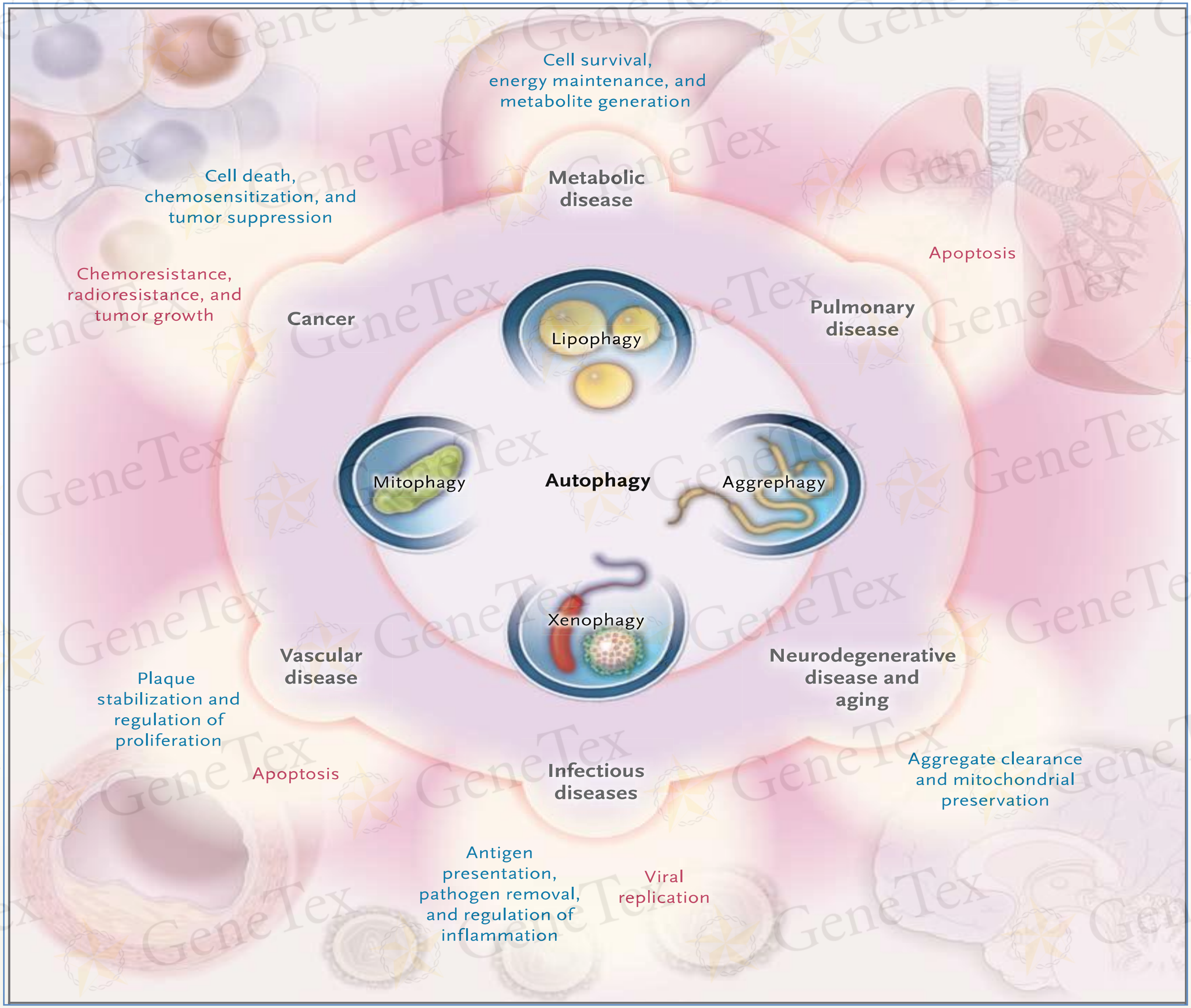
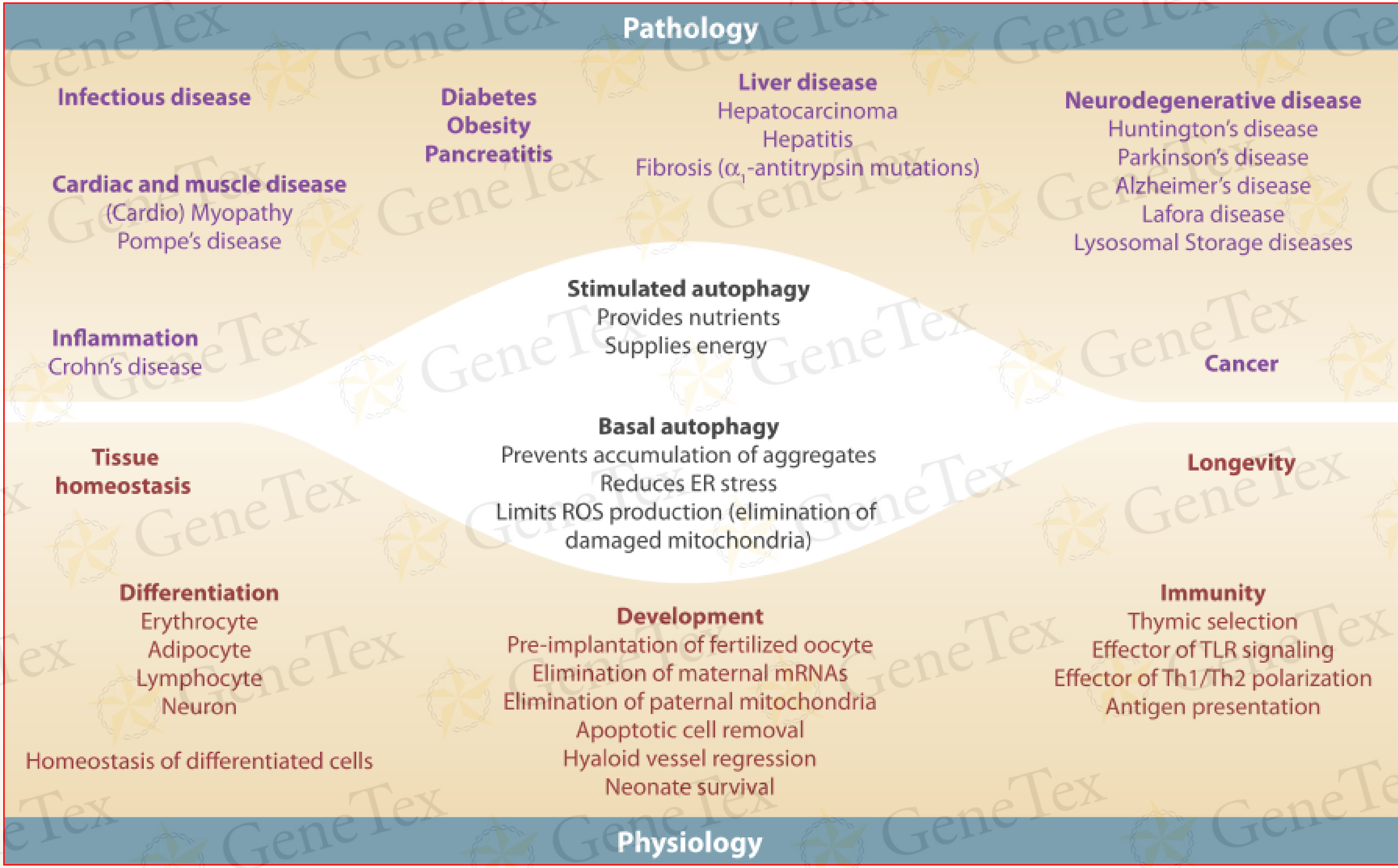




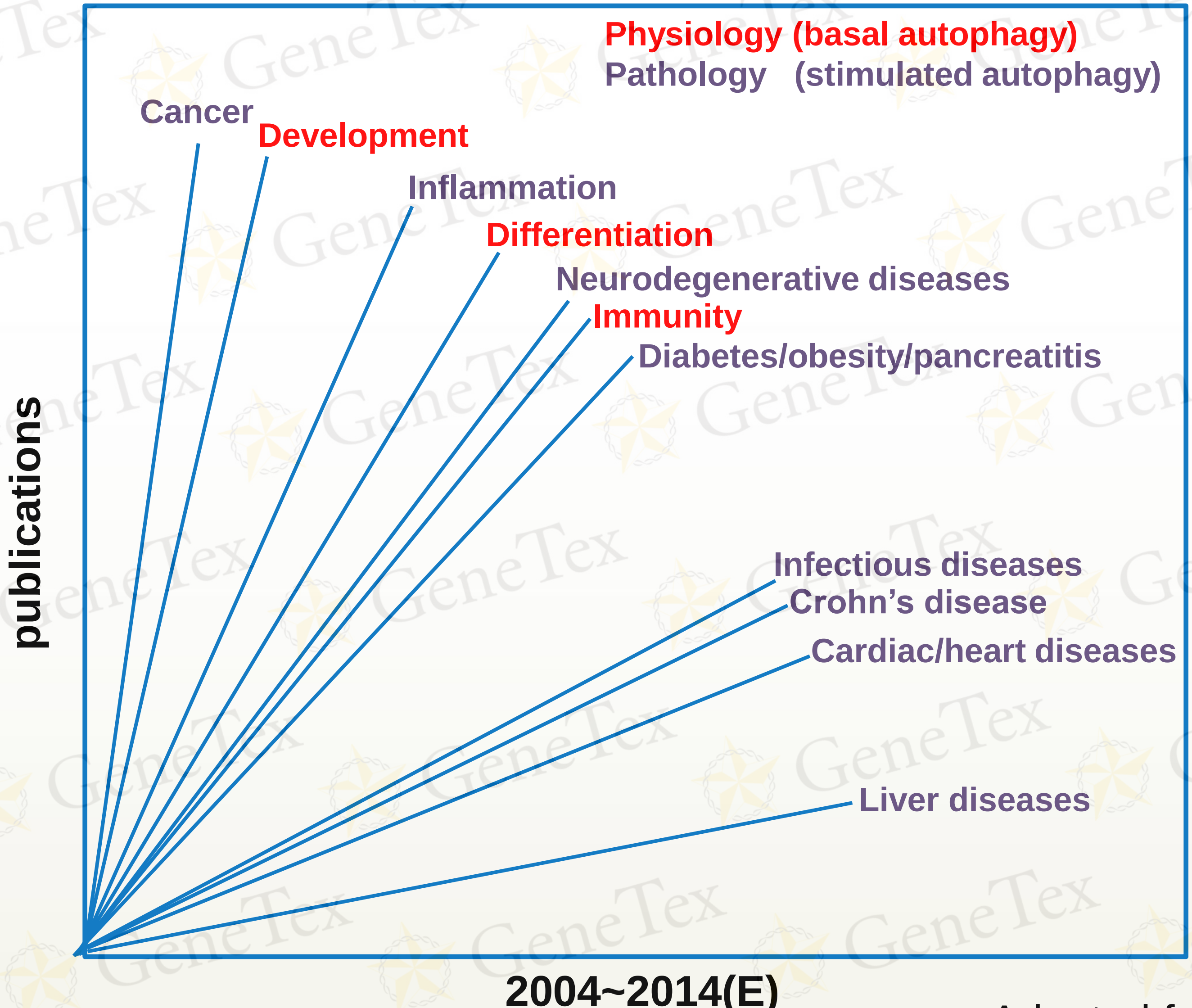
N Engl J Med 2013;368:651-62.

Current trending of autophagy research

Physiology and pathology

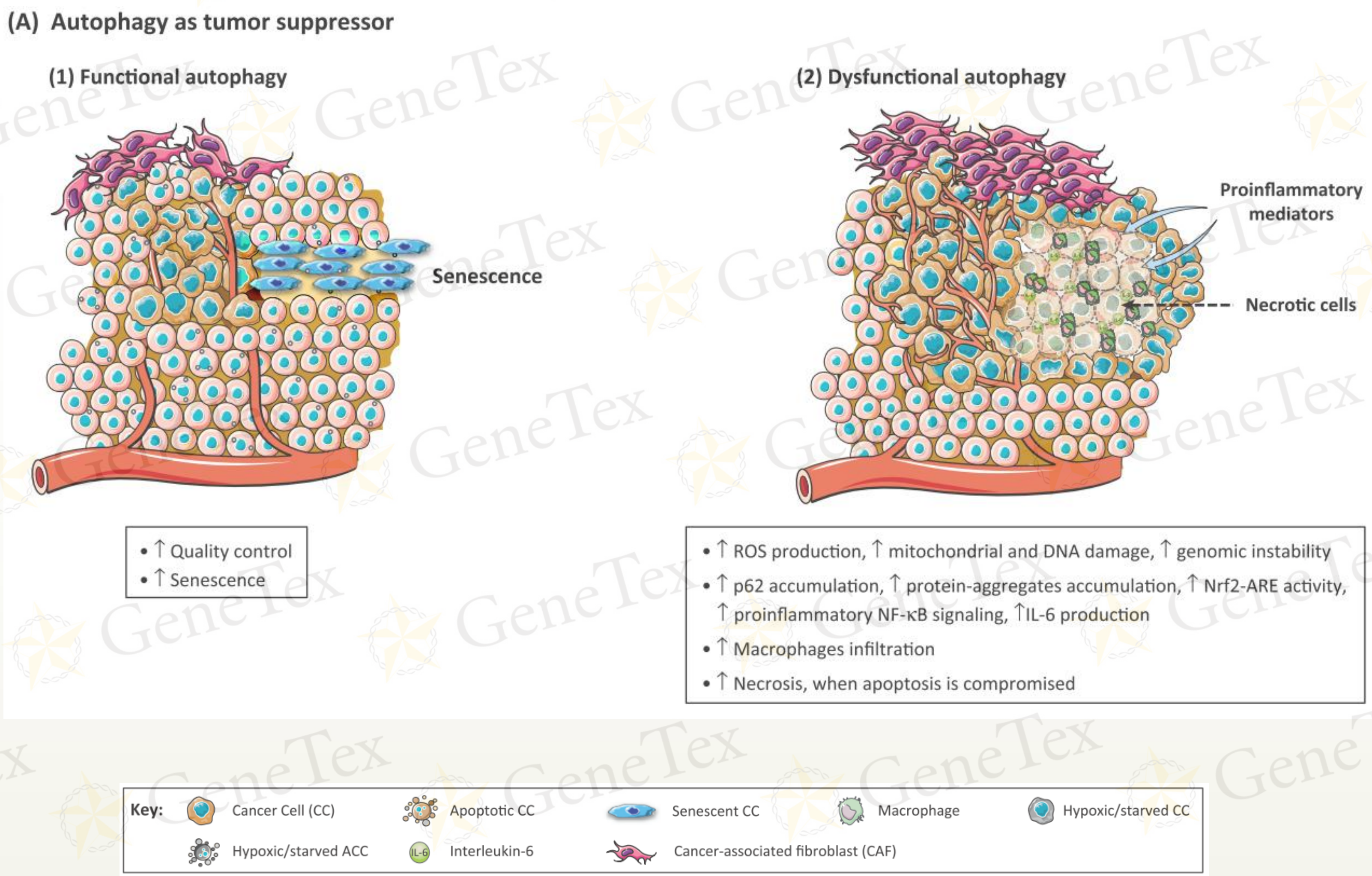


Current trending of autophagy research



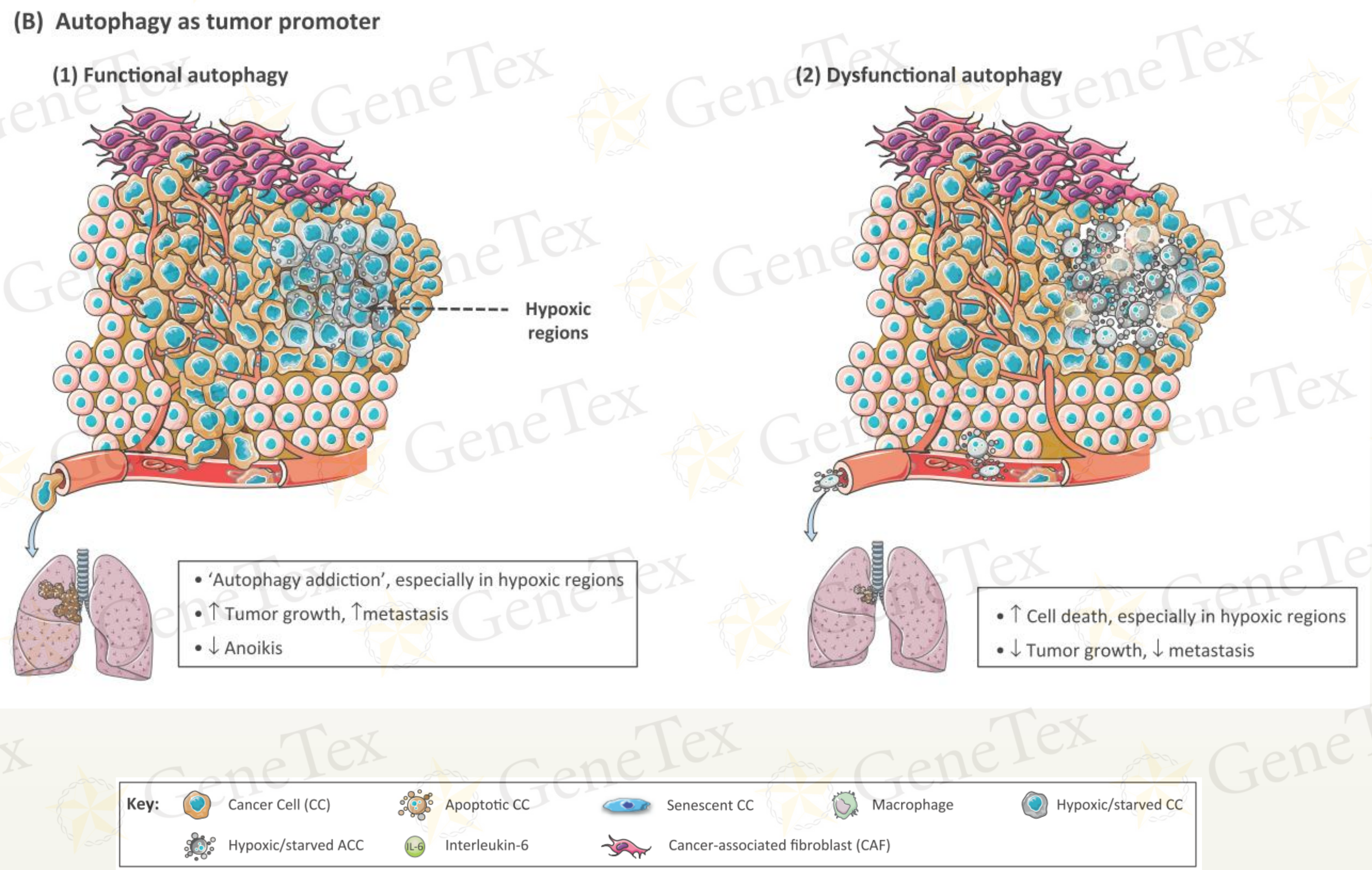
Adapted from GoPubMed

Dual Roles of Cancer-associated Autophagy



Trends Mol Med. 2013 Jul;19(7):428-46.

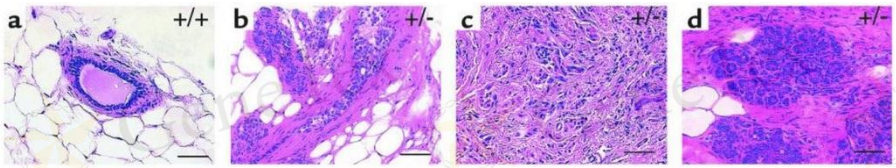
Dual Roles of Cancer-associated Autophagy

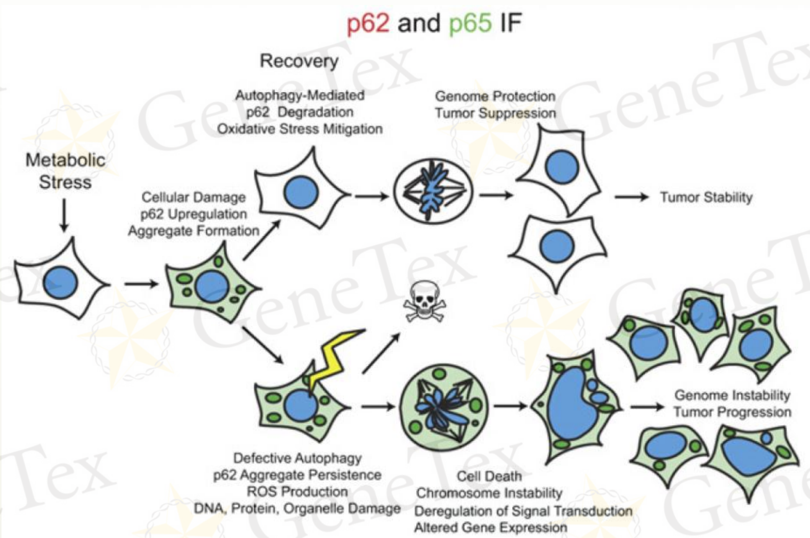


Autophagy in oncology

➢ Tumor suppressor

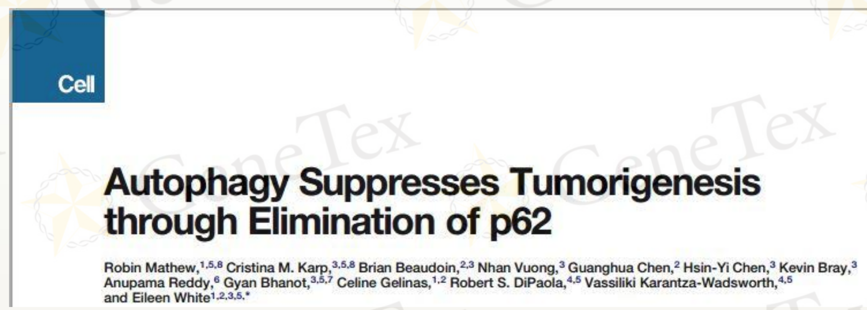
- Isolate damaged proteins & organelles to limit instable cell growth
- Promote cell death of cancerous cells





✓ Loss of Beclin1 renders mice tumor-prone

✓ Defects in autophagy result in sustained p62 (SQSTM1) expression and ROS production, which is sufficient to promote tumorigenesis



Cell

Autophagy Suppresses Tumorigenesis through Elimination of p62

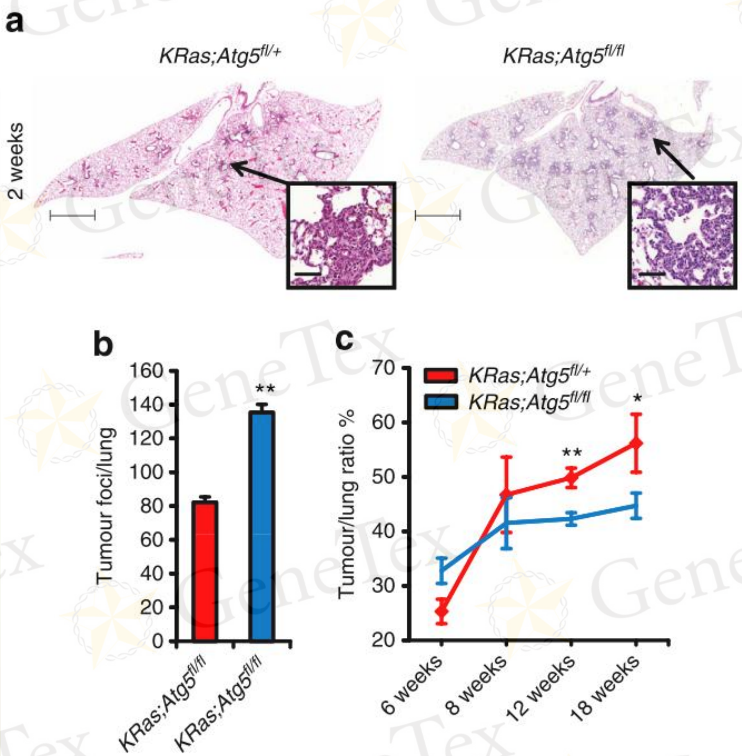
Robin Mathew,[1,5,8] Cristina M. Karp,[3,5,8] Brian Beaudoin,[2,3] Nhan Vuong,[3] Guanghua Chen,[2] Hsin-Yi Chen,[3] Kevin Bray,[3] Anupama Reddy,[6] Gyan Bhanot,[3,5,7] Celine Gelinas,[1,2] Robert S. DiPaola,[4,5] Vassiliki Karantza-Wadsworth,[4,5] and Eileen White[1,2,3,5,*]

Cell. 2009 Jun 12;137(6):1062-75.

Autophagy in oncology

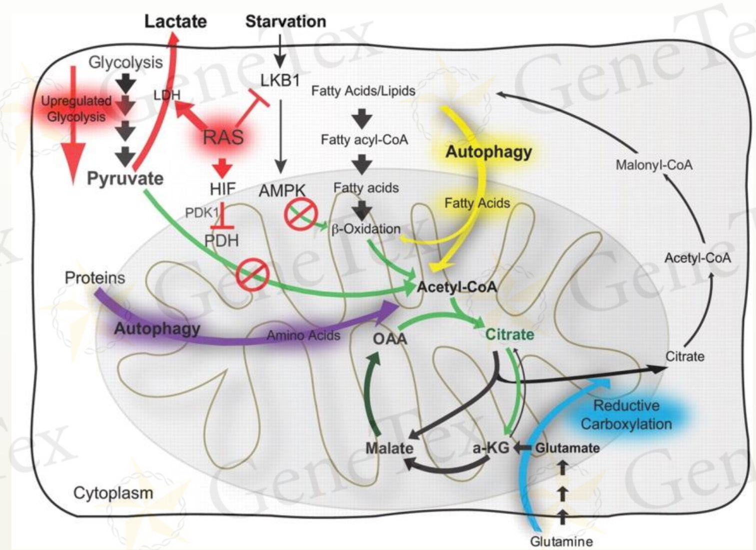
➢ Tumor survival

- Favor tumor cells to survive metabolic stress



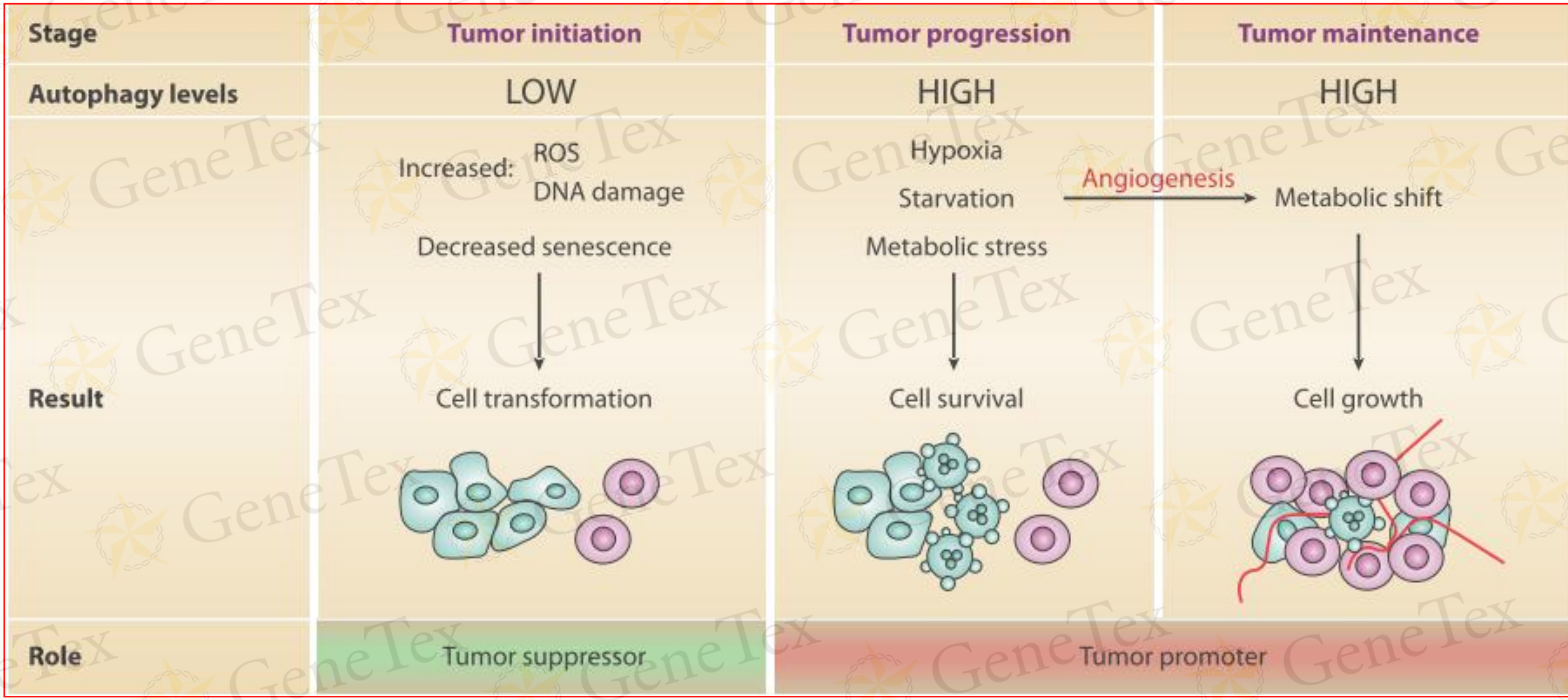
✓ The increase in metabolic stress is offset by autophagy functions

✓ Inactivate Atg5 accelerates the onset of $Kras^{G12D}$-driven lung cancer, but markedly impairs the tumor progression.

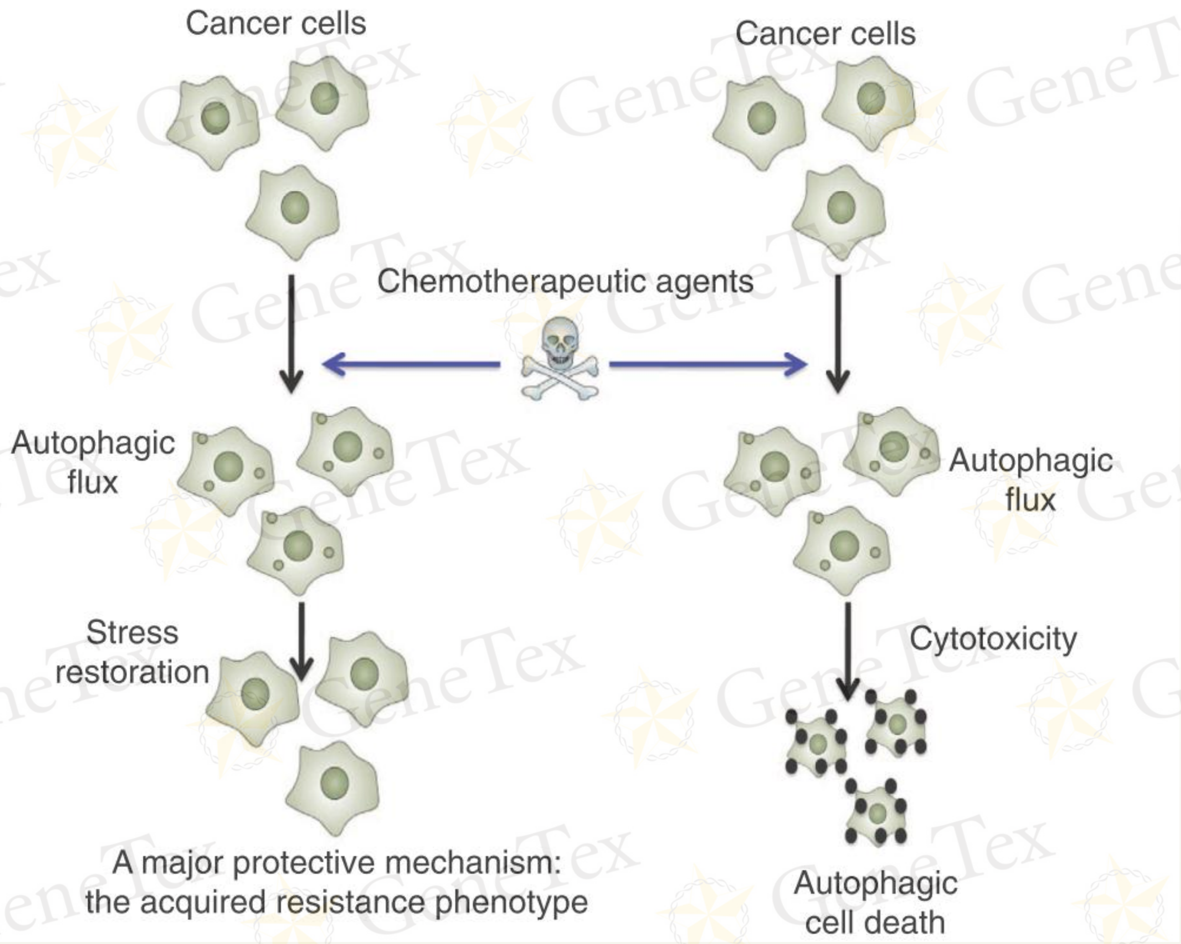


Nat Commun. 2014;5:3056;
Cold Spring Harb Symp Quant Biol. 2011;76:389-96.

Autophagy and Cancer



Dual Roles of Autophagy for Chemotherapy



Autophagy and Cancer

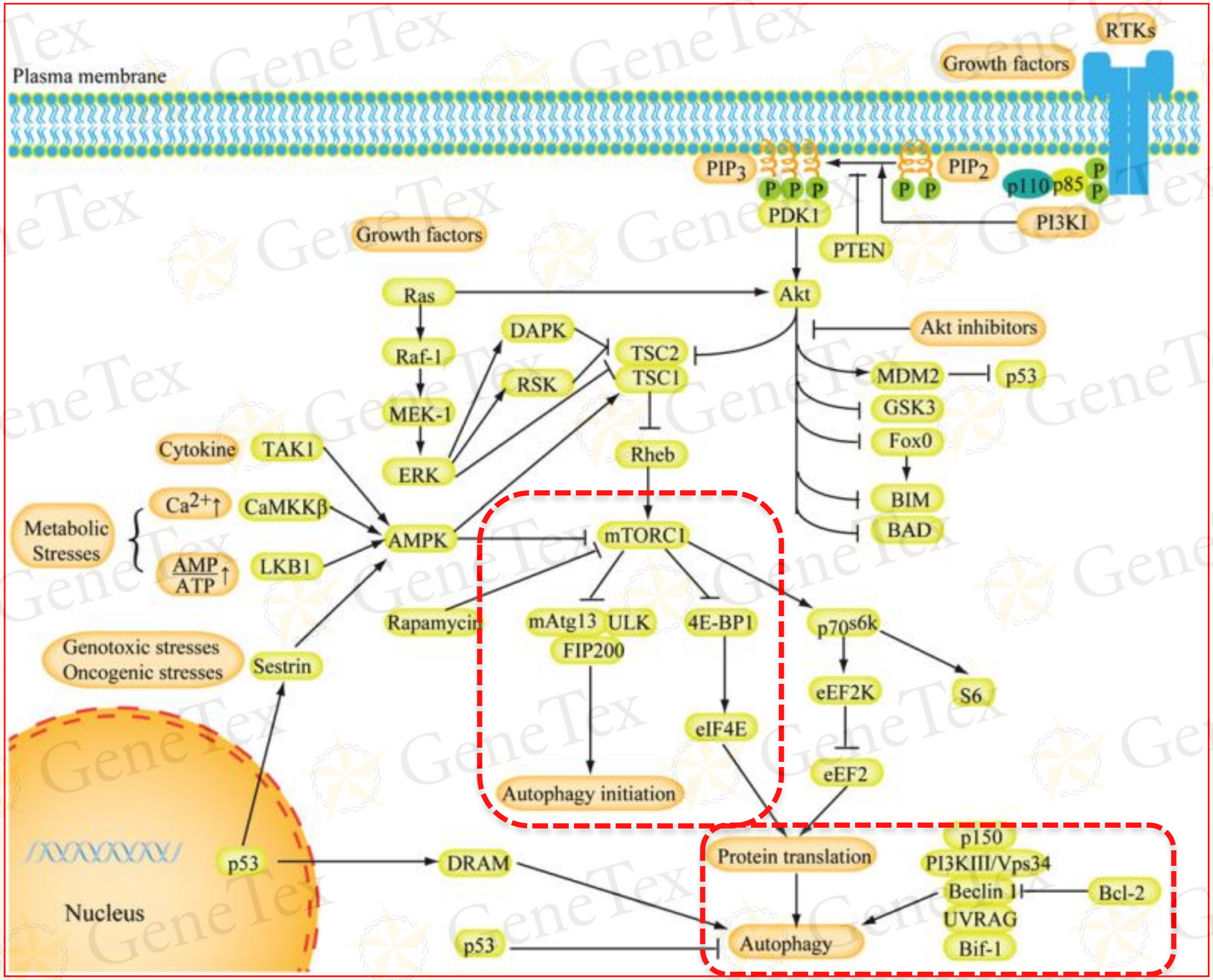


Table 1 Human diseases associated with defective autophagy

Genes	Functions in autophagy	Associated human diseases
ATG5	Autophagosome formation	Genetic polymorphisms are associated with asthma [132, 133] and enhanced risk of systemic lupus erythematosus [134, 135]
ATG16L1	Autophagosome formation	T300A mutation is associated with increased risk of Crohn's disease [90, 91, 136]
BECN1	Autophagosome formation	Monoallelic deletion is associated with risk and prognosis of human breast, ovarian, prostate, and colorectal cancers [70-73, 75]
EI24/PIG8	Autophagosome formation and/or degradation	Mutations and deletions are associated with human early onset breast cancers [32, 84,137]
EPG5	Autophagosome maturation and degradation	Recessive mutations are associated with Vici syndrome [27]
IRGM	Phagosome degradation	Single-nucleotide polymorphisms (SNPs) and deletion mutation are associated with enhanced risk of Crohn's disease [101-103, 136]
NOD2/CARD15	Xenophagy induction	SNPs and mutational variants are associated with enhanced risk of Crohn's disease [104-106, 136]
PARK2/Parkin	Mitophagy induction	Mutations are associated with autosomal recessive or sporadic early-onset Parkinson's disease [51, 52]
PARK6/PINK1	Mitophagy induction	Mutations are associated with autosomal recessive or sporadic early-onset Parkinson's disease [51, 53, 54]
SMURF1	Selective autophagy	SNP is associated with enhanced risk of ulcerative colitis [138]
SQSTM1/p62	A selective substrate An adaptor protein for selective autophagy	Mutations are associated with Paget disease of bone [139] and amyotrophic lateral sclerosis [140, 141]
TECPR2	Autophagosome formation	A frameshift mutation is associated with an autosomal-recessive form of hereditary spastic paraparesis [35]
UVRAG	Autophagosome degradation	Deletion mutation is associated with human colorectal cancer [88]
WDR45/WIPI4	Autophagosome formation	Heterozygous mutations are associated with static encephalopathy of childhood with neurodegeneration in adulthood (SENDA) [12, 13]
ZFYVE26/SPG15	Autophagosome maturation	Mutations are associated with hereditary spastic paraparesis type 15 [44, 45]

Table 2. Association of Autophagy-Related Factors and Human Disease.*

Gene	Association
BECN1	Monoallelically deleted at high frequency in human breast, ovarian, and prostate cancers[5,7-10] Altered expression found in many human tumors[11,12]
UVRAG	Deleted at high frequency in human colon cancers[13]
ATG5	SNPs associated with risk of systemic lupus erythematosus[14] SNPs associated with risk of childhood and adult asthma and decline in lung function[15,16]
ATG16L1	SNPs associated with increased risk of Crohn's disease[17-19]
NOD2	SNPs associated with increased risk of Crohn's disease and susceptibility to *Mycobacterium leprae* infection[14,19,20]
IRGM	SNPs associated with increased risk of Crohn's disease[19,21]; one SNP associated with increased resistance to *M. tuberculosis* infection[22]
LAMP2	X-linked deletion associated with Danon's cardiomyopathy[23]
PARK2	Mutations associated with Parkinson's disease and colon, lung, and brain cancers[7,24]
p62/SQSTM1	Mutations associated with Paget's disease[25]
SMURF1	SNP associated with increased risk of ulcerative colitis[26]

* SNP denotes single-nucleotide polymorphism.

Current trending of autophagy research

Keystone Symposia on Molecular and Cellular Biology

Autophagy : Fundamentals to Disease (E2)

May 23-28, 2014 Hyatt Regency Austin, Austin, Texas, USA

Scientific Organizers: Christina H. Eng, Daniel J. Klionsky, Guido Kroemer and Li Yu

(Sponsored by Cell Research and Shire Human Genetic Therapies)

Impact of Autophagy in Cancer

Guido Kroemer :	Autophagy vs. anticancer immune response
Ravi K. Amaravadi :	Targeting autophagy vs. cancer therapy
Jayanta Debnath :	Autophagy vs. secretion and cancer
Eileen P. White :	Autophagy vs. cancer metabolism

Pharmacological Manipulation of Autophagy

Christina H. Eng :(Pfizer)	Autophagy components vs. oncology drug targets
Natalie D'Amore :	Targeting autophagy for cancer therapy
Junying Yuan :	Chaperone-mediated autophagy vs. mutant p5

Autophagy and disease

Beth Levine :	Autophagy and immunity
Andrea Ballabio :	Transcriptional control of autophagy in health and disease
Ken H. Cadwell :	Anti-inflammatory functions of autophagy in Crohn's Disease
Junichi Sadoshima :	Autophagy vs. Cardiomyopathy

Interplay between Autophagy, Metabolism and aging

Ana Maria Cuervo :	Selective autophagy vs. metabolism in aging
Frank Madeo :	Spermidine vs. age associated disease
Myung-shik Lee :	Autophagy vs. obesity and diabetes

Autophagy

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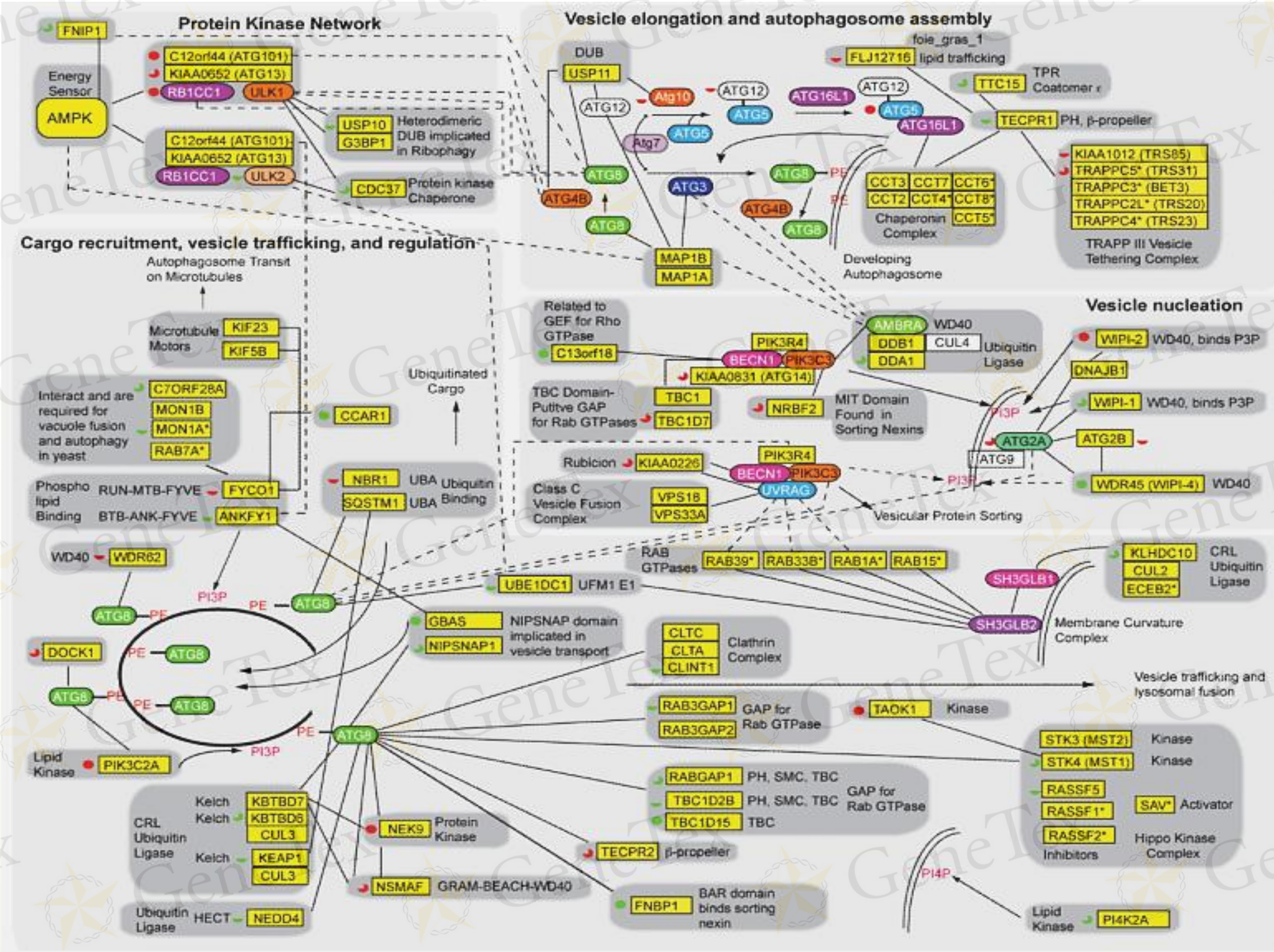
Functional integration of the Autophagy Interaction Network



Autophagy

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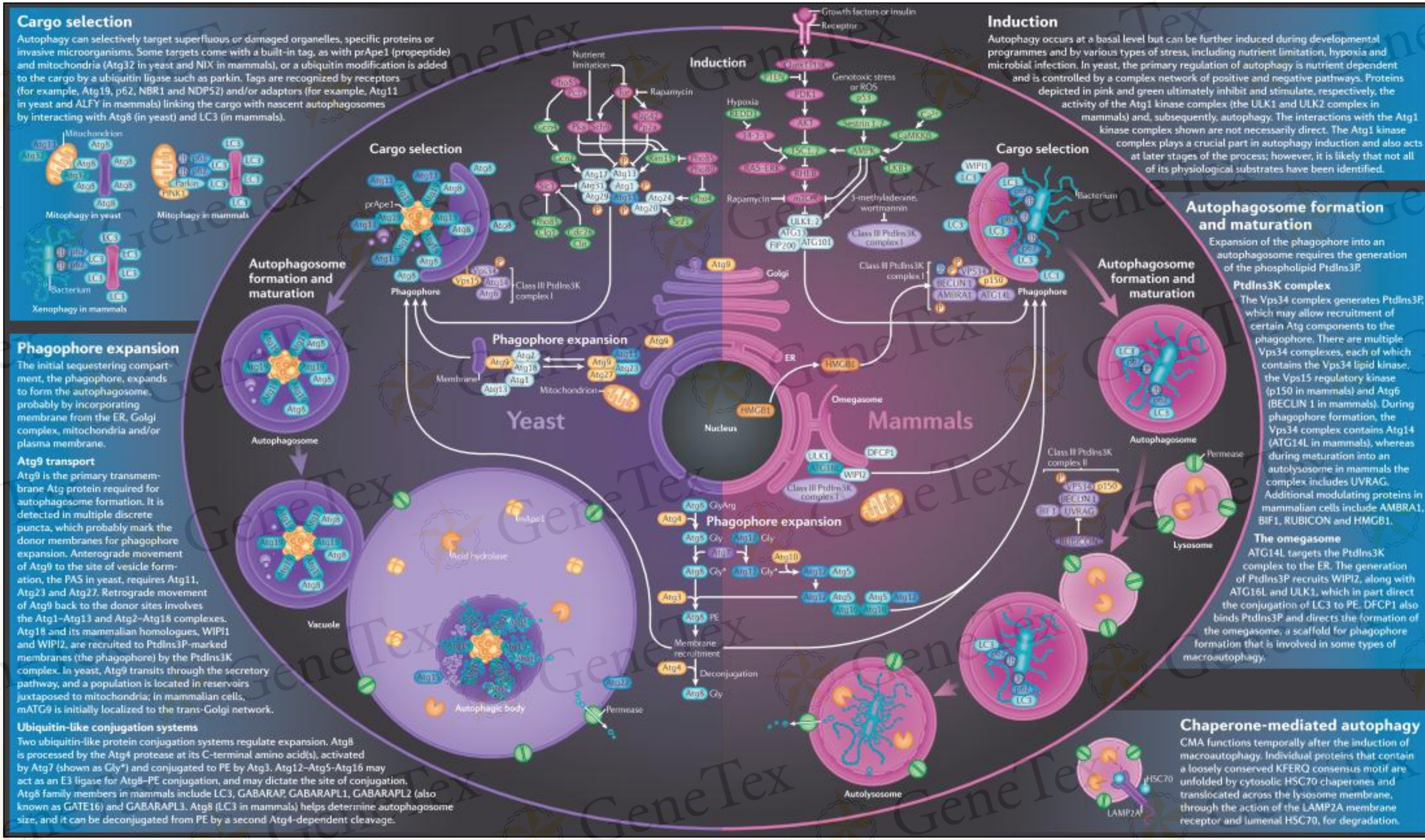

Daniel J. Klionsky and Vojo Deretic
April 2010 (http://www.nature.com/nrm/posters/autophagy)

Autophagy

Autophagy in health and disease

Disease or process	Role of autophagy*
Cancer[1,2]	✓ Functions in tumour suppression
	✗ Used by cancer cells for cytoprotection
Neurodegenerative diseases[3,4]	✓ Basal levels clear toxic protein aggregates in neurons; selectively removes damaged mitochondria by mitophagy
	✗ Amyloid precursor protein in autophagosomes can generate pathology-associated peptides
Myopathies; lysosomal storage diseases[5]	✓ Removes proteins and organelles to prevent the accumulation of protein aggregates or dysfunctional organelles and maintain cellular homeostasis
	✗ Accumulation of autophagosomes when maturation is impeded can compromise cellular physiology; excessive levels cause muscle wasting
Microbial infection[6,7]	✓ Helps eliminate invasive microorganisms and regulates innate immunity and the protective inflammatory response to microbial products
	✗ Some pathogens have adaptations that counter autophagy or use it to promote their own growth
Immune response; inflammatory bowel disease[8]	✓ Processes endogenous antigens for MHCII presentation; regulates naive T cell repertoires, T cell maturation and B cell and T cell homeostasis; counters damaging inflammation
	✗ May promote excess inflammatory cytokines when defective
Liver disease[9]	✓ Role in organelle homeostasis allows portions of the ER to be removed when protein misfolding overloads the UPR and ERAD
	✗ Excessive autophagic removal of the ER can cause liver damage
Heart, vascular and renal diseases[10–12]	✓ Its homeostatic properties are essential to cardiomyocytes and podocytes; protective during ischaemia and pressure overload; may protect against apoptosis in plaques; prevents glomerular disease
	✗ Can be harmful during reperfusion
Diabetes[13,14]	✓ Basal levels maintain normal islet structure and function; involved in the response of β-cells to a high-fat diet; may affect neutral lipid metabolism
	✗ Exposure to free fatty acids can lead to excessive autophagy and pancreatic β-cell death
Development[15–19]	✓ Removal of mitochondria by mitophagy in reticulocytes is key to erythrocyte differentiation
	✗ Unknown
Embryogenesis[20,21]	✓ Required for embryo implantation; allows neonates to survive after termination of the transplacental supply of nutrients; involved in the removal of dead cells during programmed cell death
	✗ Unknown
Ageing[22]	✓ Removes damaged organelles and oxidized or aggregated macromolecules to increase health and prolong life
	✗ Increased levels may lead to muscle and organ wasting in progeria

Daniel J. Klionsky and Vojo Deretic
April 2010 (http://www.nature.com/nrm/posters/autophagy)

Thank You

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