Oxidative stress and cell death biology

緊迫與細胞死亡生物學

1.	9/11	課程簡介
2.	9/18	細胞緊迫誘導與粒腺體
3.	9/25	緊迫生物學與病毒和細菌之感染
4.	10/2	緊迫生物學與癌細胞生長
5.	10/9	細胞凋亡:Caspases pathway
6.	10/16	細胞凋亡: Bcl-2 family
7.	10/23	細胞凋亡: Pro-apoptotic pathway
8.	10/30	細胞凋亡與腦部疾病
9.	11/6	期中考
10.	11/13	細胞壞死與免疫反應
11.	11/20	細胞壞死與疾病
12.	11/27	細胞自噬誘導與功能
13.	12/4	細胞自噬與病毒
14.	12/11	細胞自噬與疾病
15.	12/18	Oral presentation
16.	12/25	Oral presentation
17.	1/1	開國紀念日(放假)
18.	1/8	Final Report

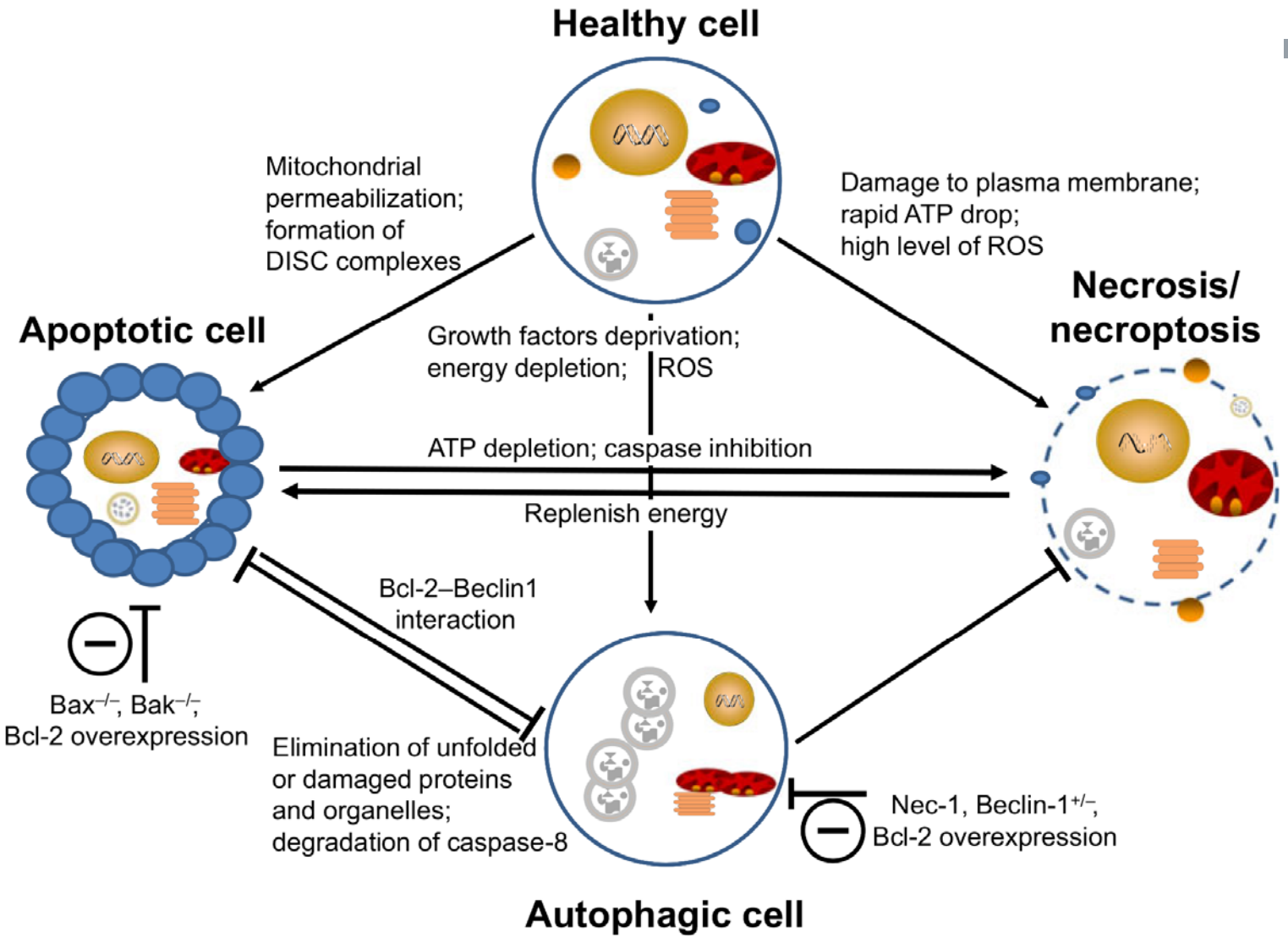
Textbooks:

1. Christopher Potten and James Wilson. Aug 16, 2004. First Ed. Apoptosis: The Life and Death of Cells (Developmental & Cell Biology). The press syndicate of the University of Cambridge.

2. Douglas R. Green. Sep 30, 2018. 2 nd. Cell Death: Apoptosis and Other Means to an End.

3. Donald Armstrong and Robert D. Stratton. Apr 11, 2016. First Ed. Oxidative Stress and Antioxidant Protection: The Science of Free Radical Biology and Disease. Wiley press.

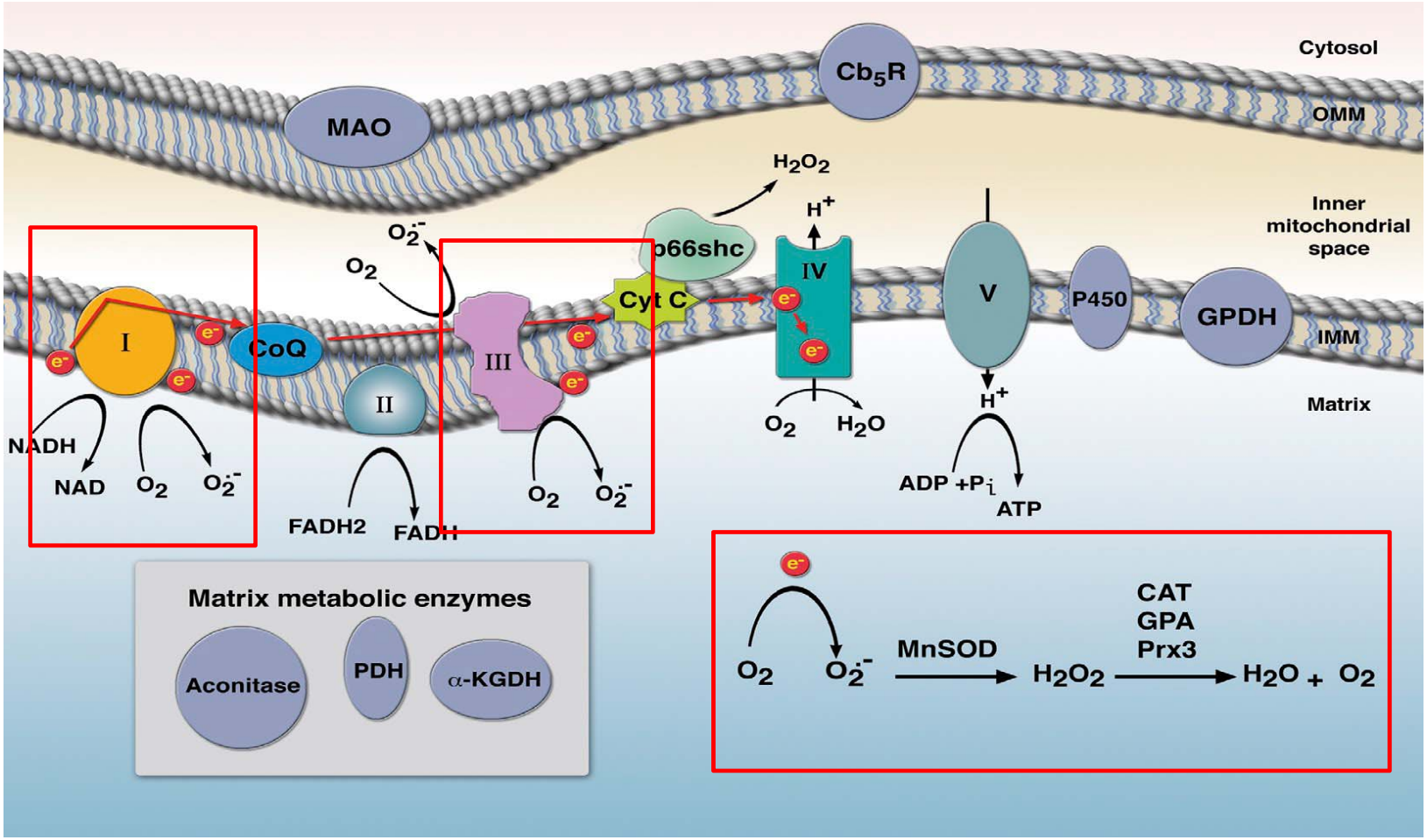
4. 生命科學相關期刊



Crosstalk between various cell death modalities. In response to various type of damage, different cell death mechanisms can be activated. Moreover, crosstalk exists between the different forms of cell death. ROS, reactive oxygen species; DISC, death-inducible signalling complex.

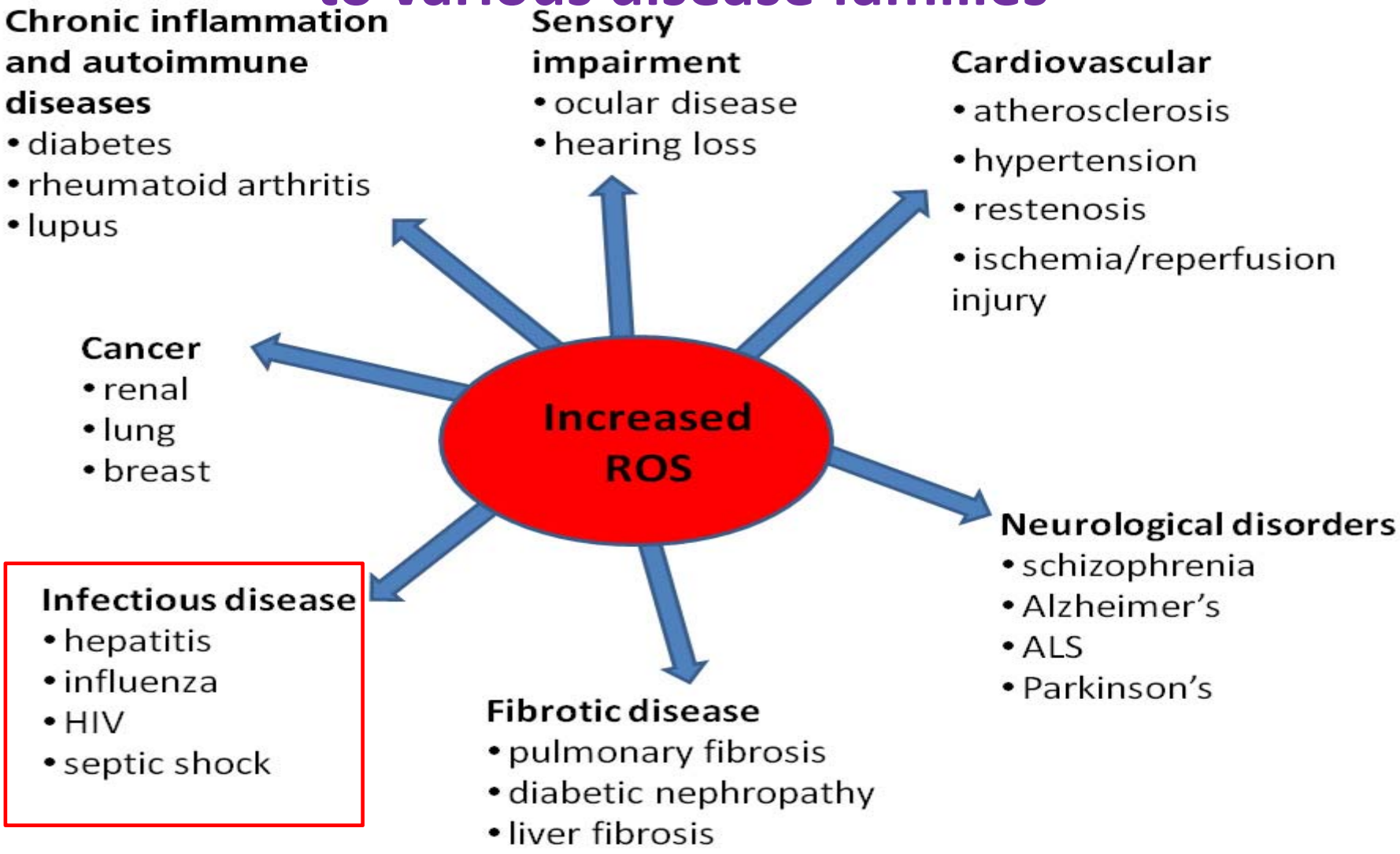
Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling

Reactive oxygen species generation (ROS) and disposal in the mitochondria



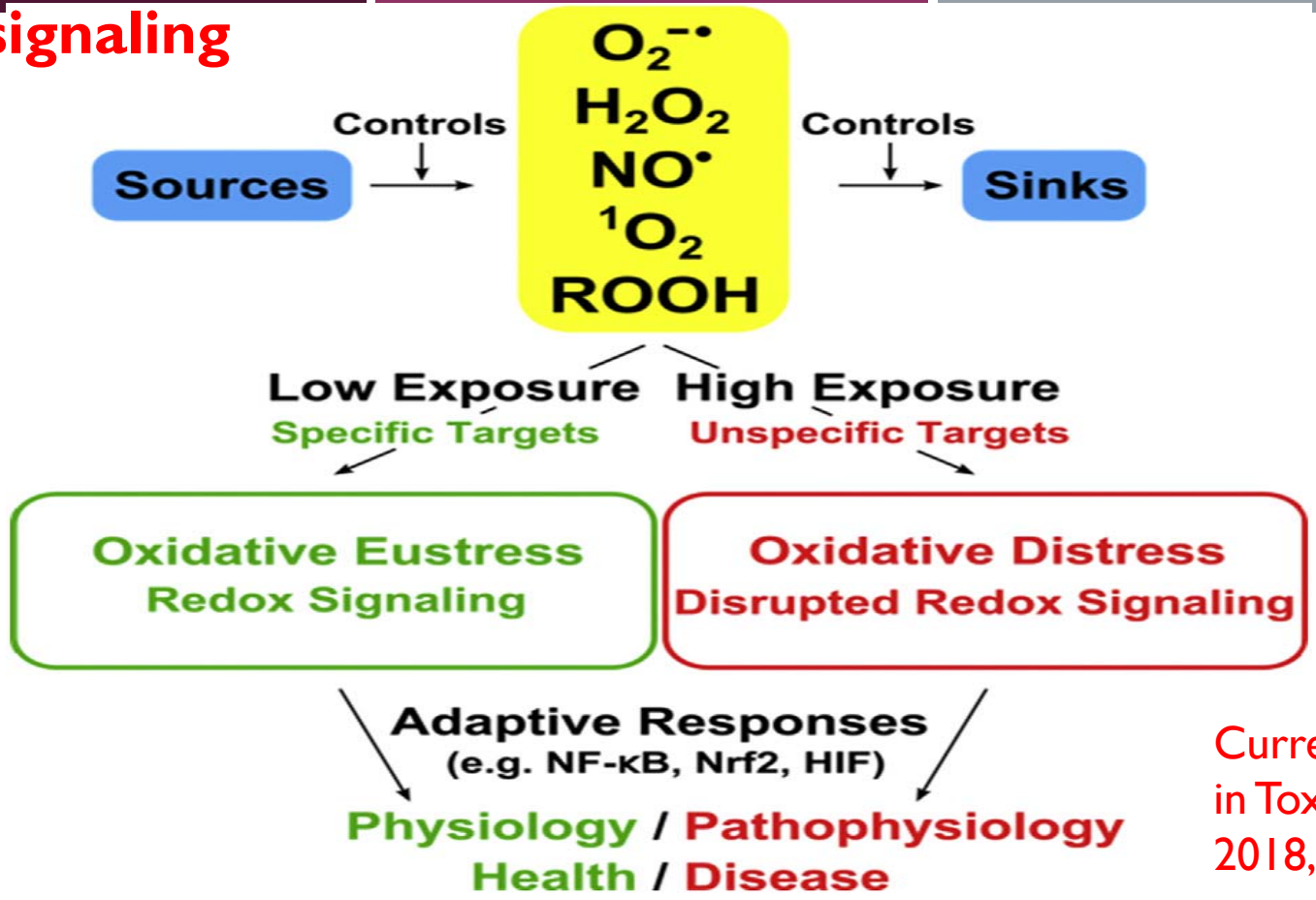
Primary sources of ROS occur from the transfer of electrons (e) to molecular oxygen at either Complex I or III in the mitochondria.

Overproduction of ROS and its contribution to various disease families



Swiss Med Wkly. 2012;142:w13659

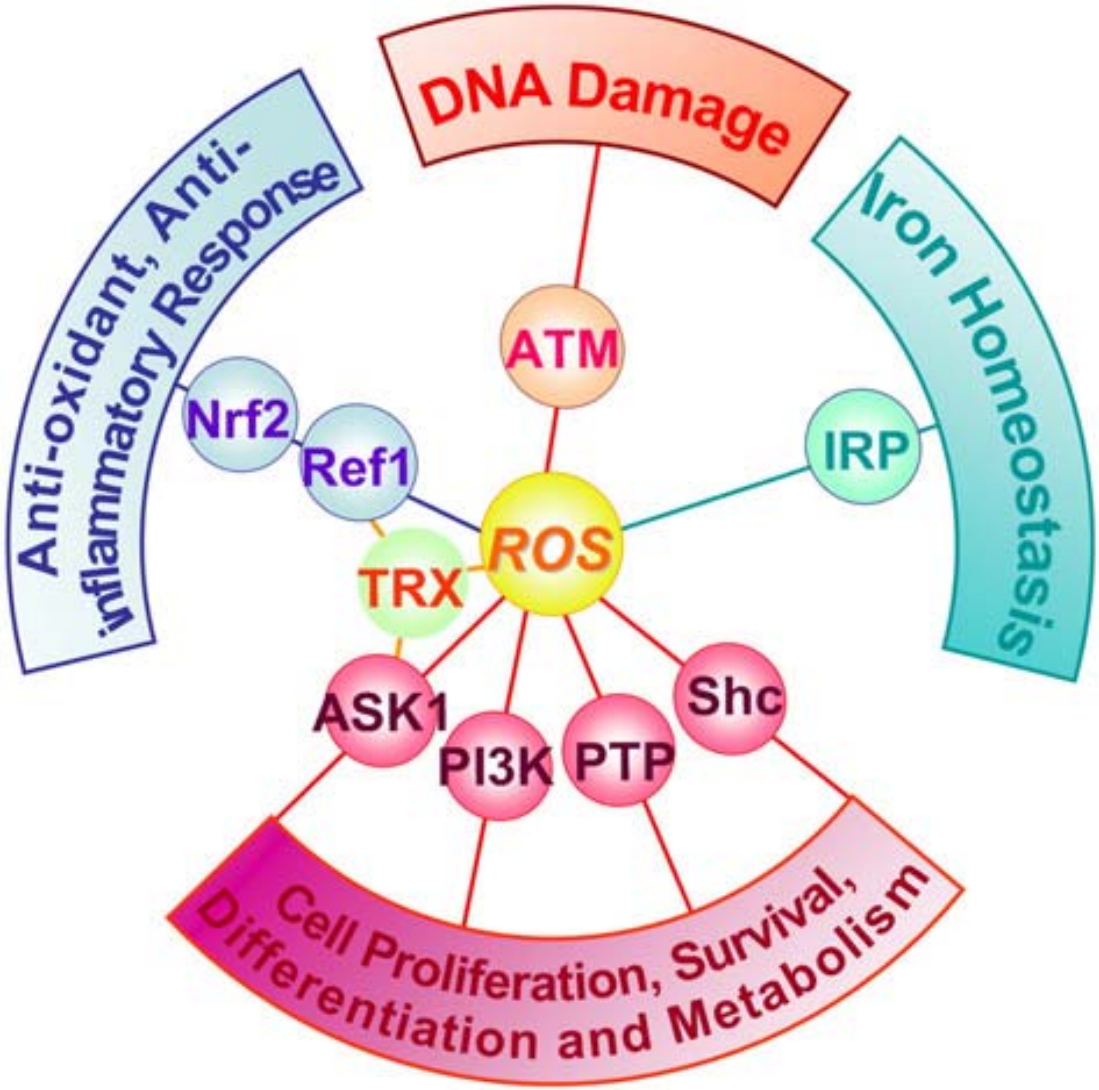
Oxidative stress and its relationship to redox signaling



Current Opinion in Toxicology 2018, 7:122–126

Various oxidantsare produced by endogenous or exogenous sources. Their steady state levels are also controlled by removal reactions (sinks). Low oxidant exposure allows for addressing specific targets in the use for redox signaling (oxidative eustress良性壓力), whereas high exposure leads to disrupted redox signaling and/or damage to biomolecules (oxidative distress). Adaptive responses modulate and counteract. The outcome contributes to health and disease processes.

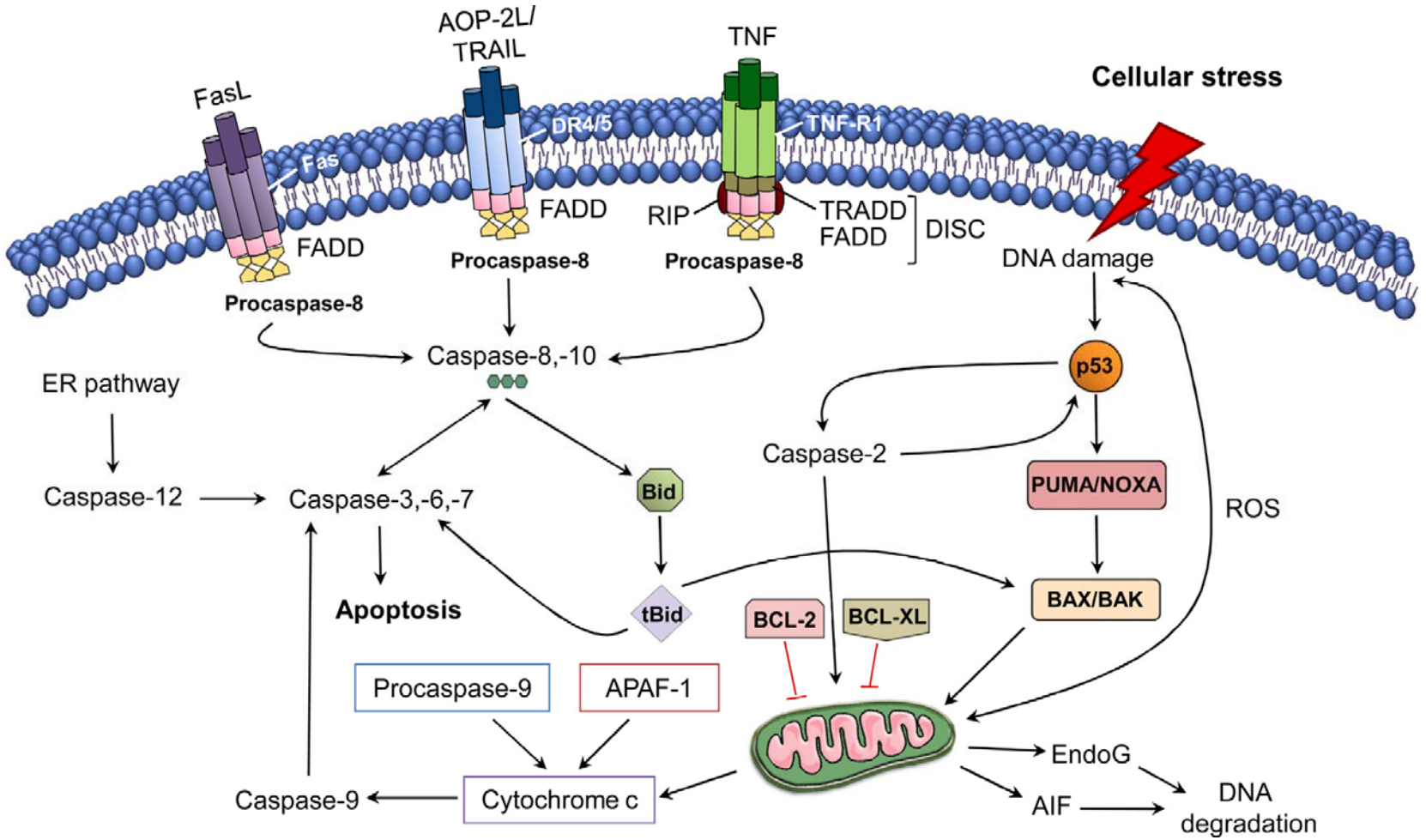
Cellular signaling pathways regulated by ROS



Reactive oxygen species (ROS) regulate several signaling pathways through interaction with critical signaling molecules, affecting a variety of cellular processes, such as proliferation, metabolism, differentiation, and survival (apoptosis signal-regulated kinase 1 (ASK1), PI3 kinase (PI3K), protein tyrosine phosphatase (PTP), and Src homology 2 domain-containing (Shc)); antioxidant and anti-inflammatory response (thioredoxin (TRX), redox-factor 1 (Ref-1), and NFE2-like 2 (Nrf-2)); iron homeostasis (iron regulatory protein (IRP)); and DNA damage response (ataxia–telangiectasia mutated (ATM)).

Apoptosis triggered by internal (intrinsic) or external (extrinsic) stress signals

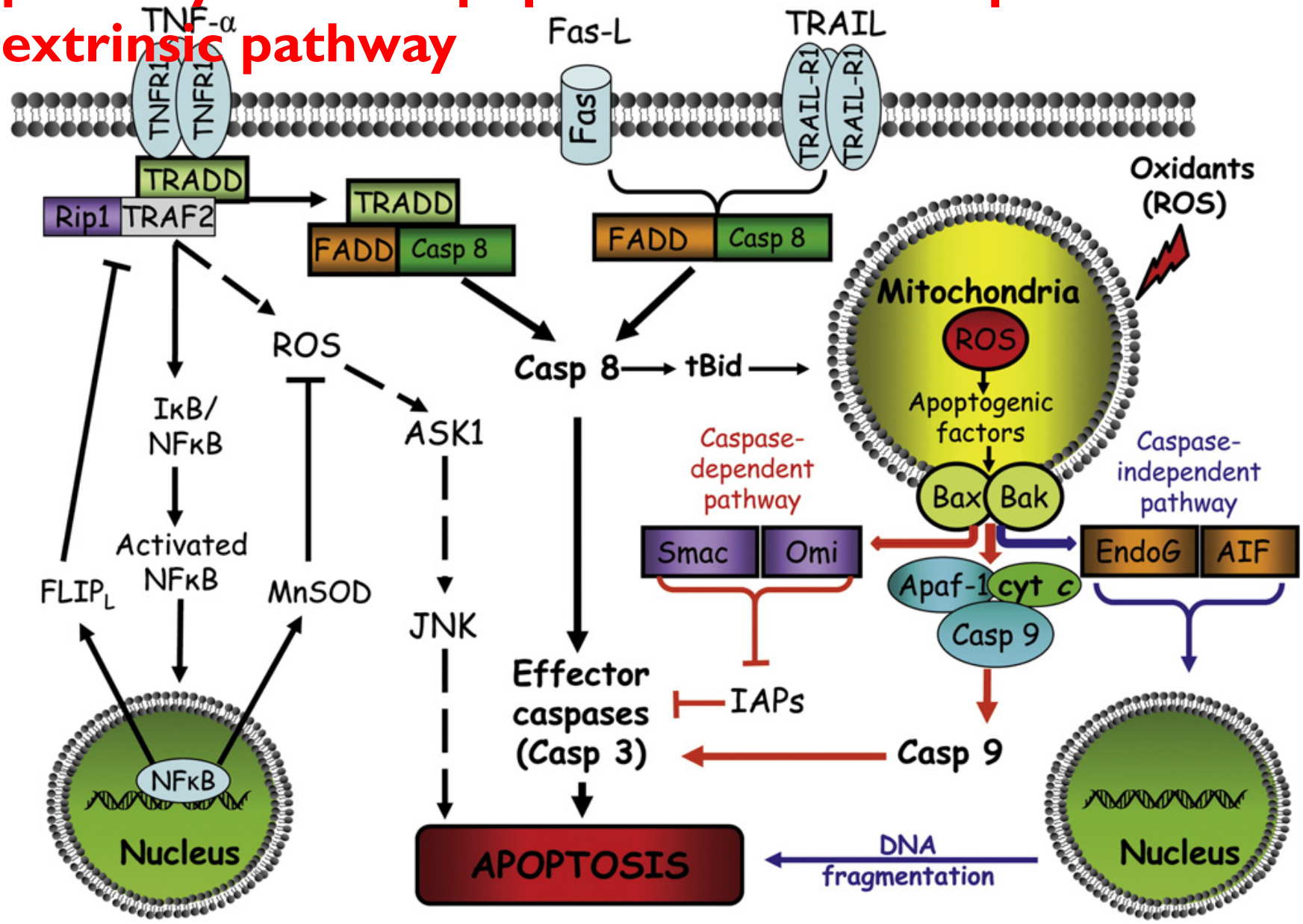
Schematic representation of apoptotic pathways



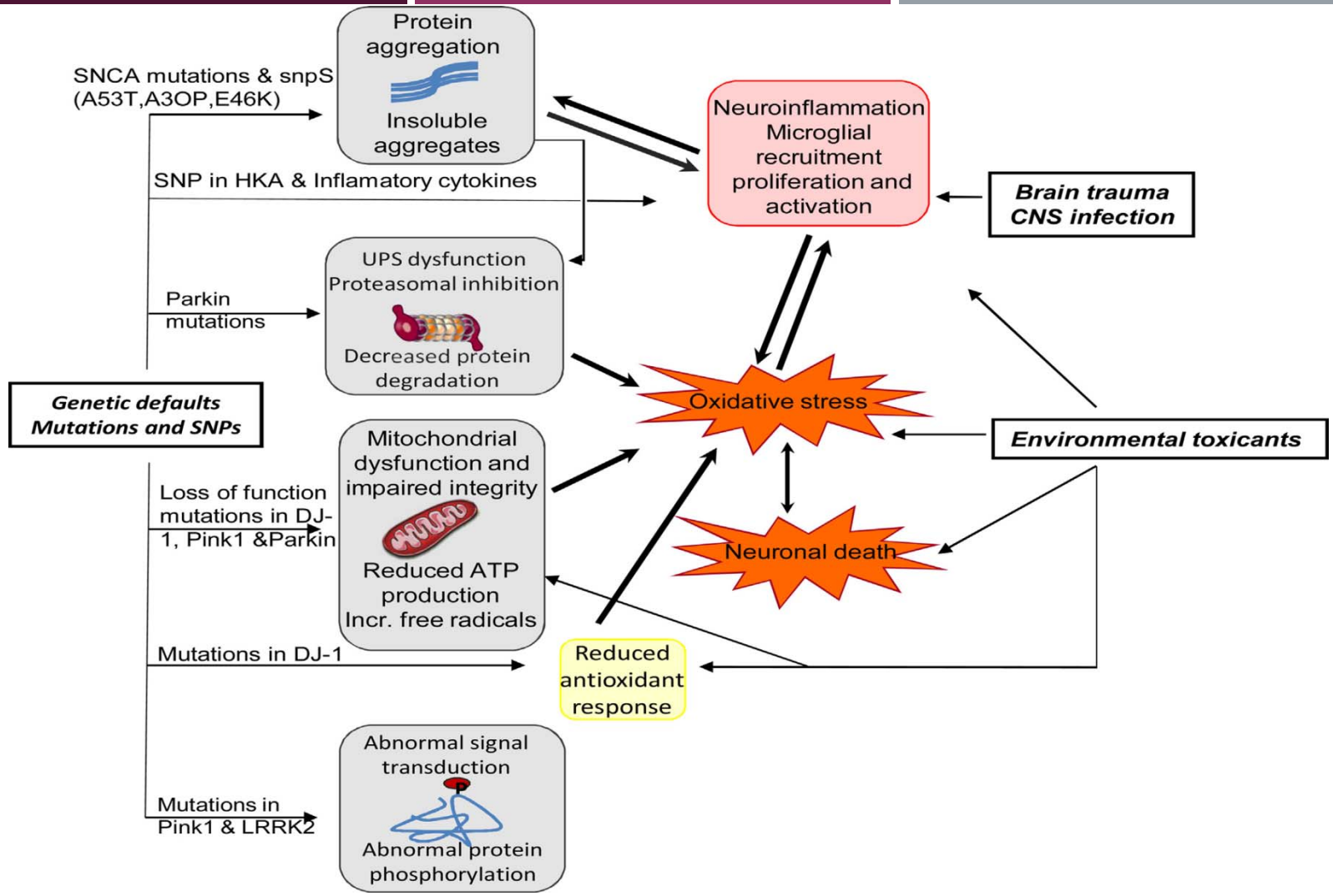
Apoptosis triggered by internal (intrinsic) or external (extrinsic) stress signals that is activated by binding of ligands (e.g. FasL, APO-2L, TRAIL, TNF) to cell surface receptors (e.g. Fas, DR4, DR5, TNF-R1). The intrinsic apoptosis pathway might be triggered by p53 upon DNA damage following exposure to cellular stress.

Progress in Neurobiology 112 (2014) 24–49

Death-receptor-mediated and mitochondrial pathways of cell apoptosis. Death receptor extrinsic pathway



Role of genetic factors and environmental factors in PD



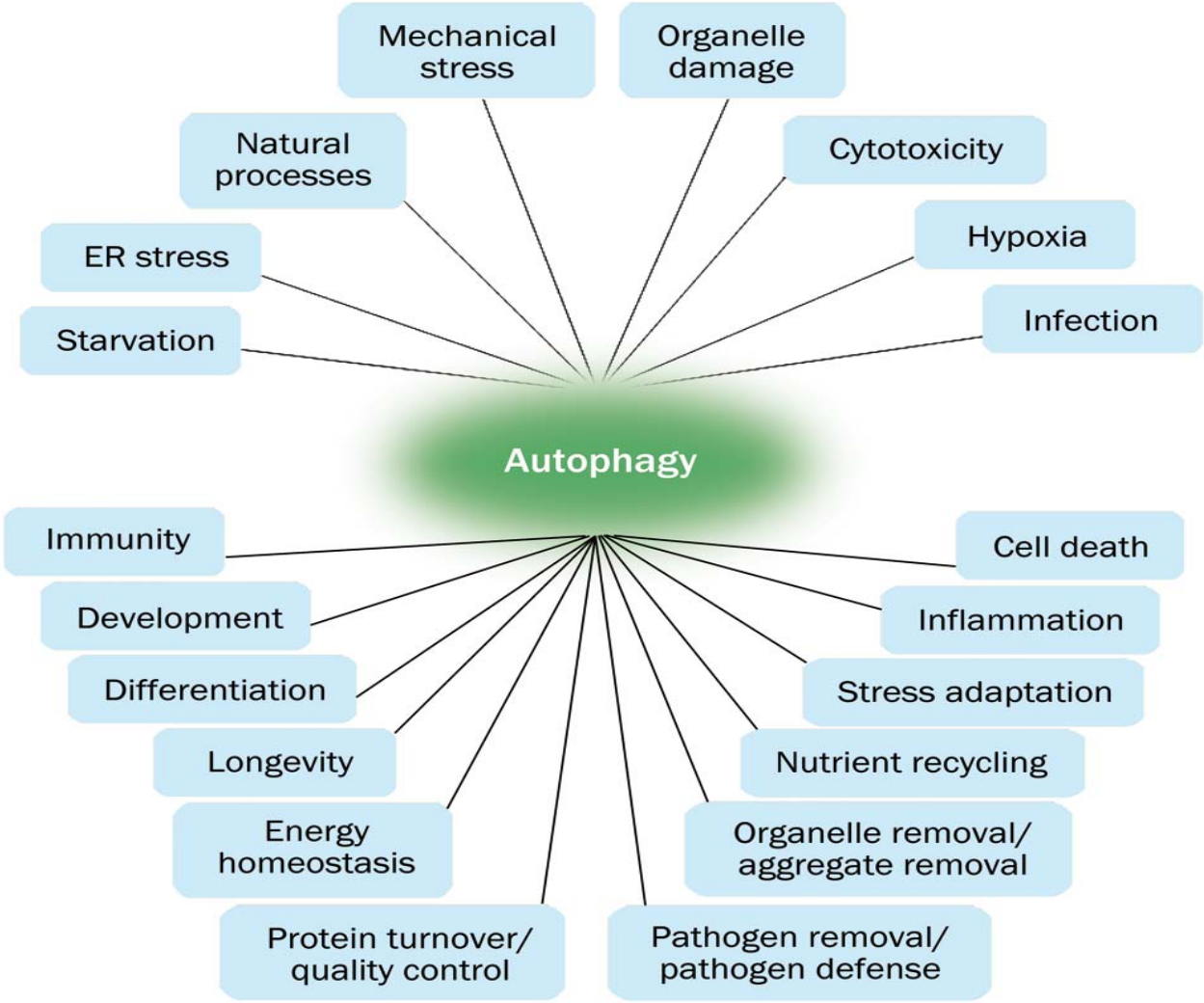
In dopaminergic neurons oxidative stress can occur due to defects of genes known to play a role in the etiology of PD, such as PINK1, LRRK2. Oxidative stress and other cellular-stress stimuli may lead to neuronal cell death by disrupting the function of PD related gene products such as Parkin, DJ-1 or PINK 1. This may lead to the interference with the function of mitochondria or induction of inflammatory processes within

List of some of the potential apoptotic drugs used for treatment of neurodegenerative diseases.

Drug	Mechanism of action	References
Minocycline	It prevents release of cytochrome *c* from mitochondria Increases the expression anti-apoptotic protein Bcl-2 and inhibits the activity of caspases-1 and -2	Kim and Suh (2009) and Seidl and Potashkin (2011)
CEP-1347	Inhibits the mixed lineage kinase (MLK) family, thereby preventing apoptosis	Wang et al. (2004)
Rasagiline	Selective and irreversible inhibitor of MAO-B Inhibits apoptosis by activating protein kinase C and by down regulating FAS and Bax family of proteins	Youdim et al. (2005)
Selegiline	Selective inhibitor of MAO-B Inhibits apoptosis by up-regulating regulating Bcl-2 protein Minimize loss of mitochondrial potential Inhibit the activity of caspases	Tatton and Chalmers-Redman (1996)
Coenzyme Q 10	Protect neurons from oxidative stress by scavenging reactive oxygen species	Choi et al. (2012)
Melatonin	It is a chemical compound secreted by pineal gland Prevents the oxidative stress by stimulating the synthesis of antioxidant enzymes such as super oxide dismutase and glutathione peroxidase	Pandi-Perumal et al. (2012)
Resveratrol	A chemical compound present in grapes, red wine and other fruits. Inhibits the oxidative stress by up regulating the anti-oxidant system	Khan et al. (2010)
Lithium	It rescues spinal cord mitochondria in ALS Facilitates the clearance of SOD1 and ubiquitin in ALS motor neurons	Pandi-Perumal et al. (2012)

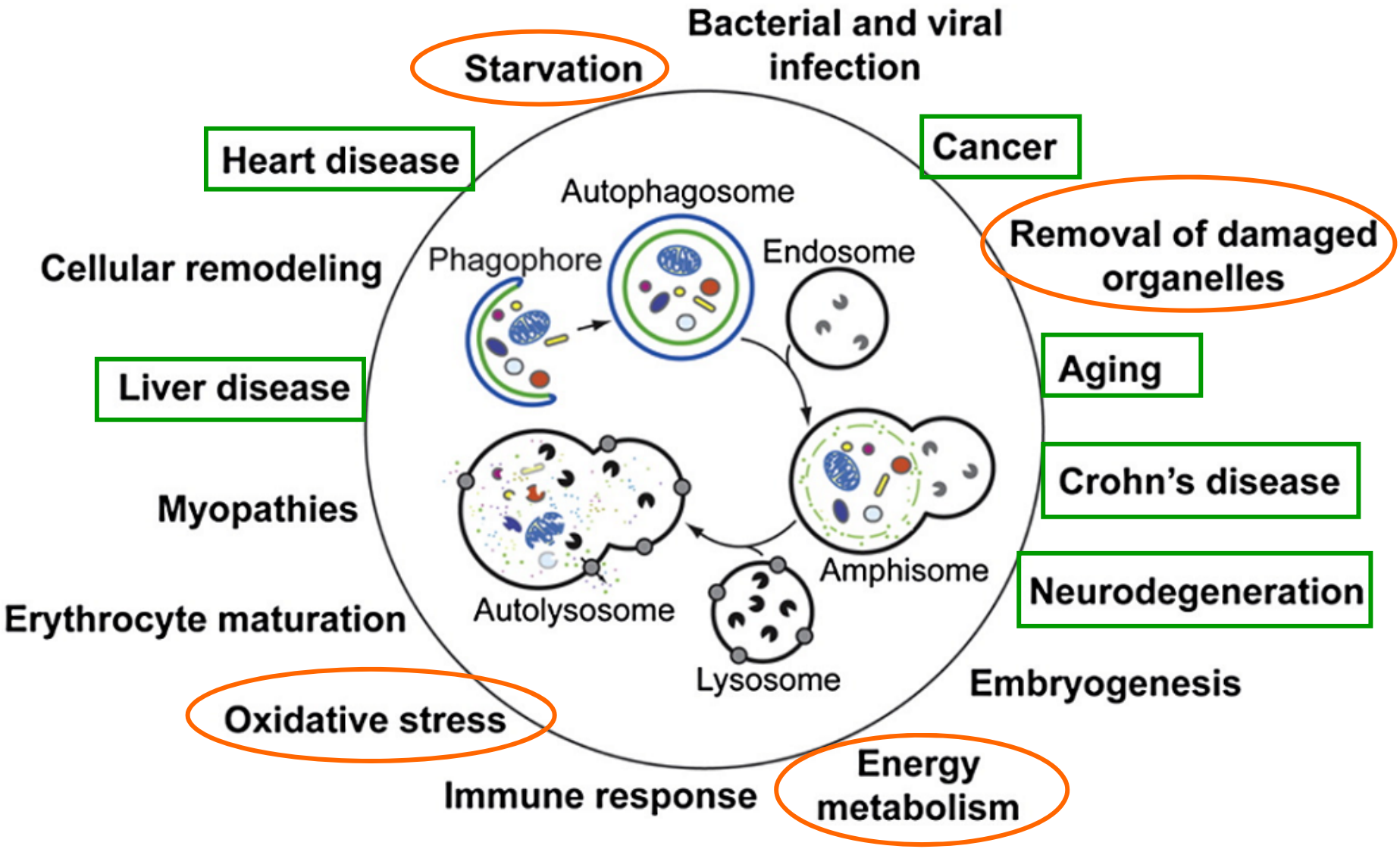
Autophagy regulation, function and diseases

Autophagy is vital in a range of physiological and pathological situations



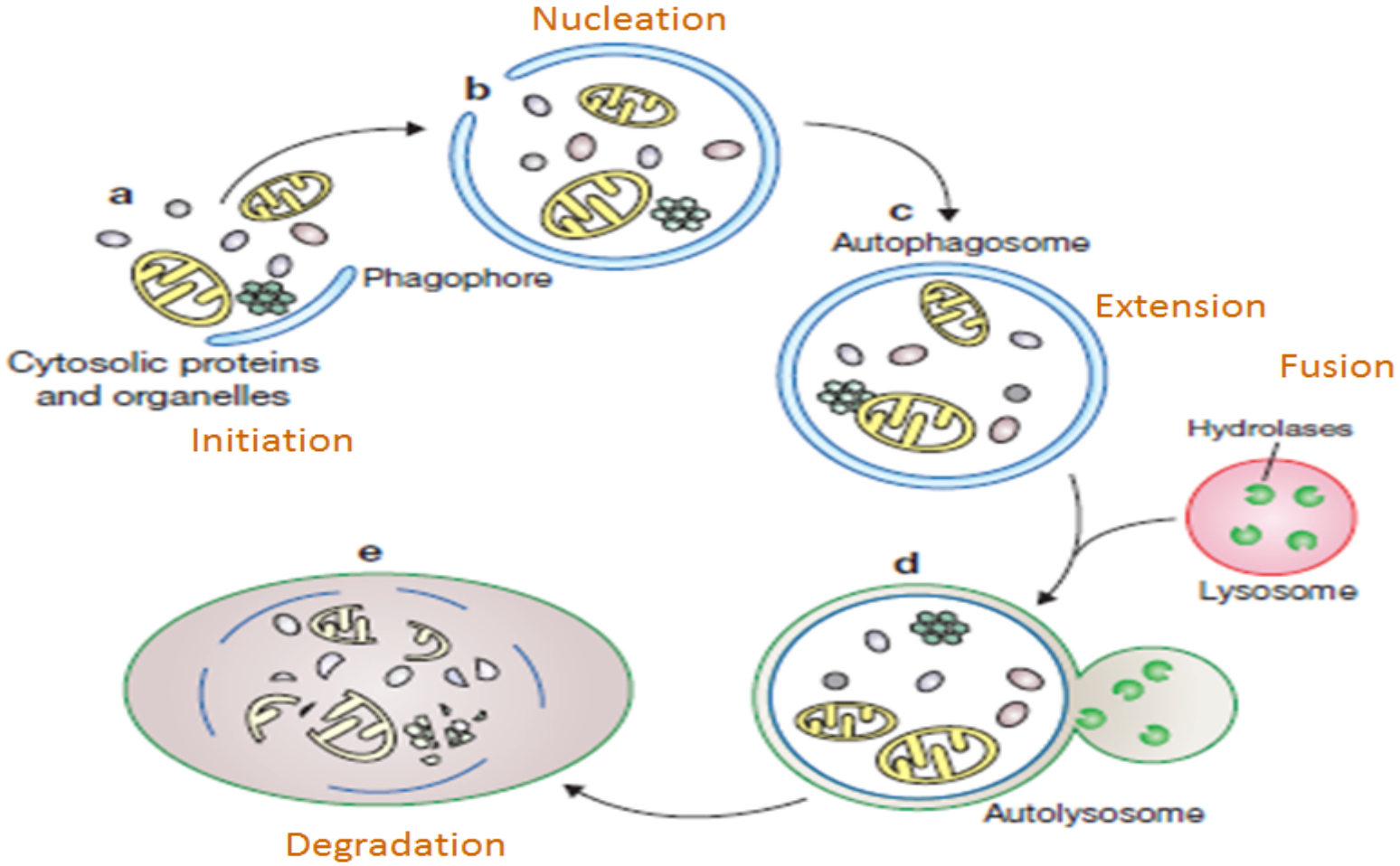
Acta Pharmacologica Sinica (2013) 34: 585–594

The Autophagy induction



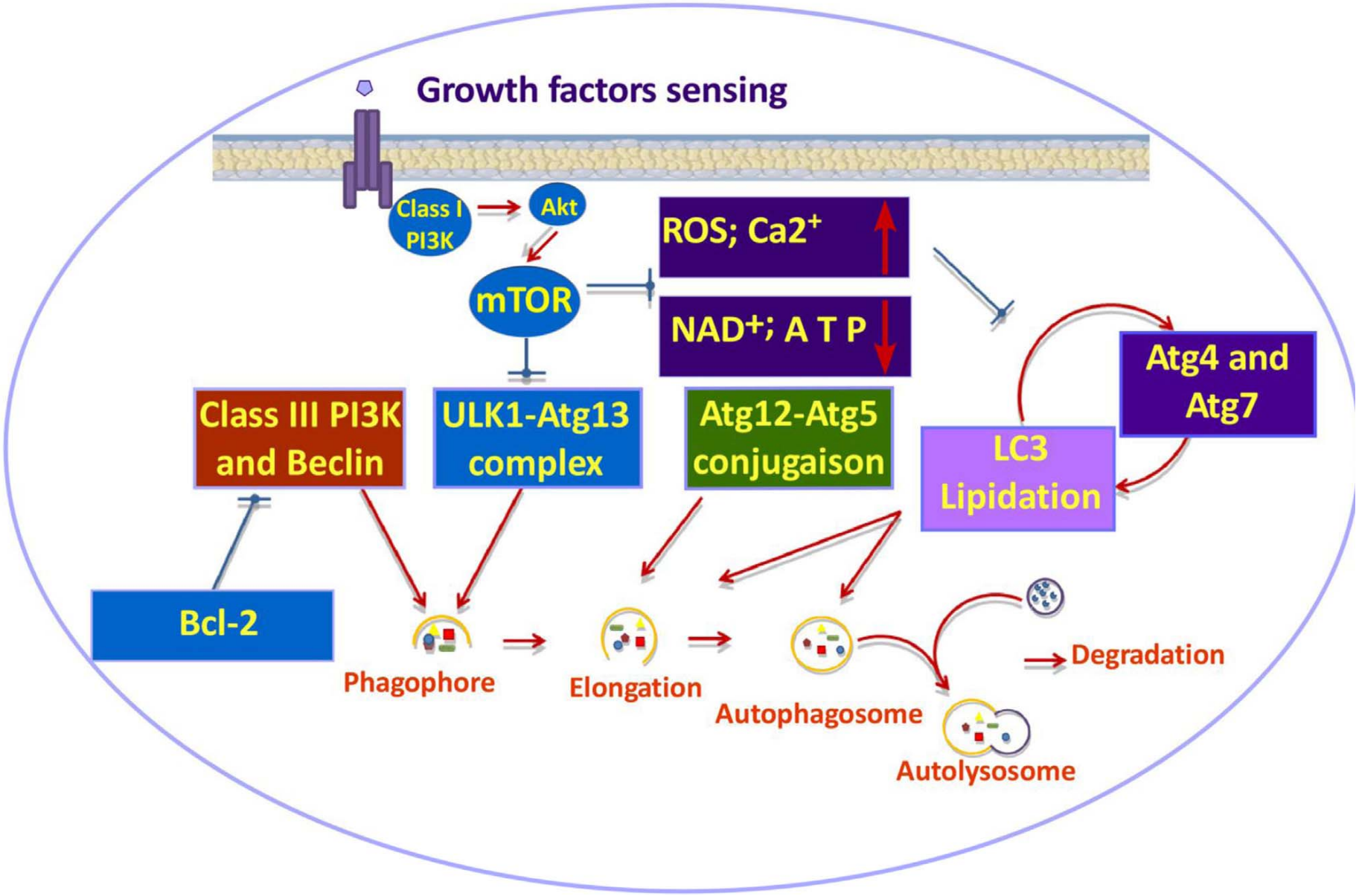
Klionsky, D.J. (2010). *Dev Cell 19*, 11-12.

Formation and expansion of the isolation membrane

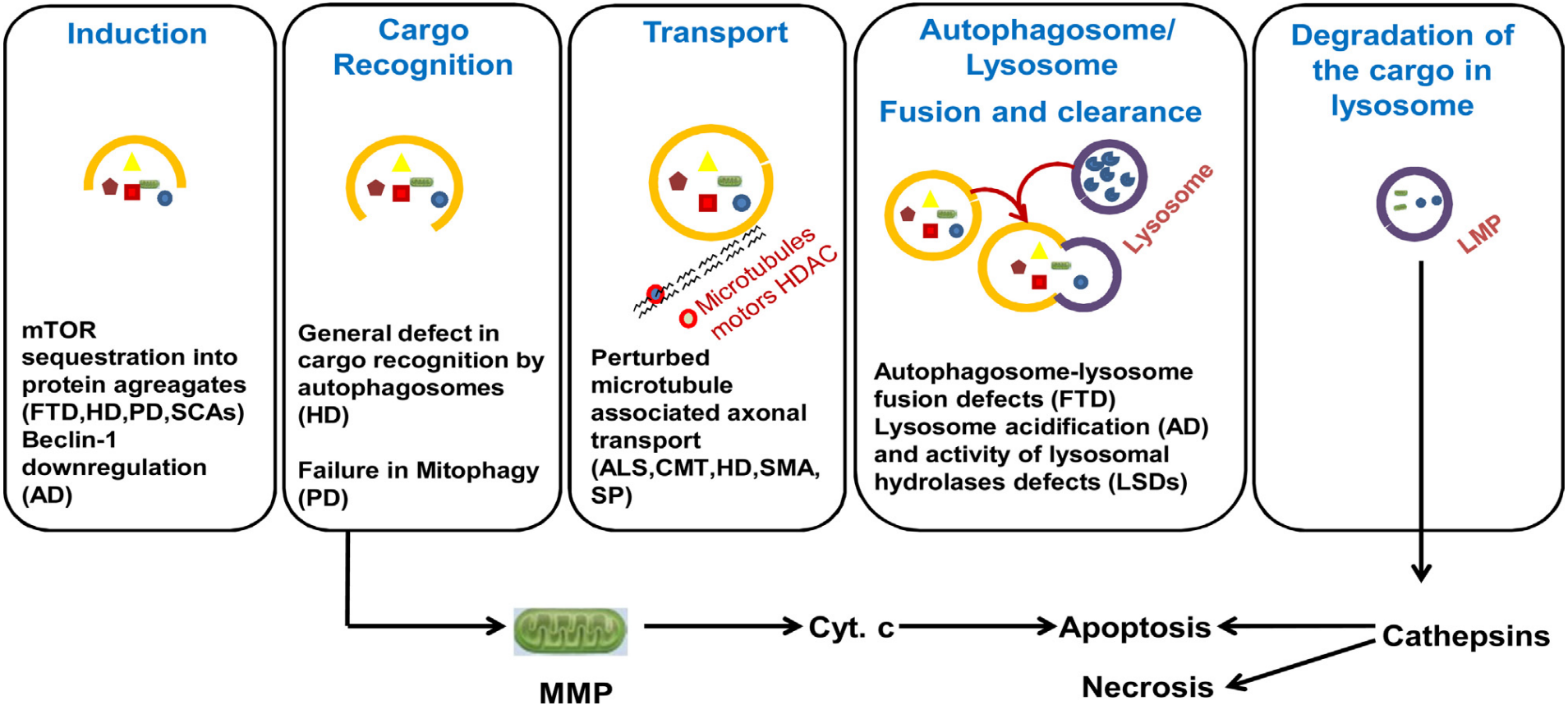


Autophagy functions to balance cellular metabolism and promote cell survival during stressful conditions.

Summary of basic autophagy signaling events



Distinct steps of the autophagic pathway can be altered in a variety of neurodegenerative disorders and possible links to neuronal cell death



AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; CMT, Charcot–Marie–Tooth disease; FTD, fronto-temporal dementia; HD, Huntington's disease; LSDs, lysosomal storage disorders; PD, Parkinson's disease; SCAs, spino-cerebelar ataxias; SMA, spinal muscular atrophy; SP, spastic paraplegia.

Macroautophagy in proteopathic neurodegenerative diseases and their therapeutic modulators.

Proteopathic neurodegenerative disorders	Macroautophagy	Chaperon-mediated autophagy	Potential therapeutic modulators
Alzheimer's disease	Macroautophagy is transcriptionally up-regulated (Lipinski et al., 2010) Autophagosome maturation is impaired (Yu et al., 2005) Macroautophagy is inhibited by mutated presinilin-1 in a familial form of AD (Cataldo et al., 2004)	CMA degrades regulator of calcineurin-1 (RCAN1) (Liu et al., 2009) CMA degrades Tau proteins (Wang, 2009)	Raprmycin (Mendelsohn and Larrick, 2011; Spilman et al., 2010) Resveratrol (Kim et al., 2007; Vingtdeux et al., 2011) Nicotinamide (Liu et al., 2013a) Latrepirdine (Steele and Gandy, 2013)
Parkinson's disease	Macroautophagy degrades wild-type and mutated α-syn (Vogiatzi et al., 2008)	CMA degrades wild-type α-syn (Cuervo et al., 2004; Vogiatzi et al., 2008) CMA is inhibited by mutated α-syn (Cuervo et al., 2004) CMA activity is reduced in the brain of PD patient (Alvarez-Erviti et al., 2010)	Rapamycin (Dehay et al., 2010; Mendelsohn and Larrick, 2011) Trehalose (Sarkar et al., 2007) Kaempferol (Filomeni et al., 2012) Resveratrol (Wu et al., 2011) Isorhynchophylline (Lu et al., 2012)
Huntington's disease	Macroautophagy is debilitated to cargo recognition (Martinez-Vicente et al., 2010) Macroautophagy degrades Htt43Q (Carra et al., 2008) Macroautophagy is impaired in early stages of HD (Koga et al., 2011)	CMA degrades mutated Htt (Bauer et al., 2010) CMA is up regulated in early stage of HD (Koga et al., 2011)	Trehalose (Sarkar et al., 2007) Rapamycin (Mendelsohn and Larrick, 2011; Ravikumar et al., 2002) Rilmenidine (Rose et al., 2010)
Amyotrophic lateral sclerosis	Macroautophagy degrades mutated and wild type SOD1 (Hetz et al., 2009; Kabuta et al., 2006) Macroautophagy degrades TDP-43 (Johnson et al., 2010) Macroautophagy is induced by mutated SOD1 (Crippa et al., 2010b; Li et al., 2008)	No available data	Litium (Fornai et al., 2008) Resveratrol (Kim et al., 2007) Trehalose (Gomes et al., 2010)