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Review article

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Regulated cell death pathways in kidney disease

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Supplementary Table 1. Main forms of regulated cell death: similitudes and differences

	Apoptosis	**Necroptosis**	**Pyroptosis**	**Ferroptosis**
Morphology	Nuclear condensation, cell shrinkage, extensive membrane blebbing without loss of membrane integrity	cell swelling and rupture	cell swelling and rupture	cell swelling and rupture
Receptor triggers	TNFR	TNFR	DAMP/PAMP receptors	?
Key proteolytic enzymes	Regulated by caspases, caspase-dependent	Regulated by caspases, caspase-independent	Regulated by caspases, caspase-dependent, other proteolytic enzymes	Lipid metabolism enzymes
Other key enzymes	-	RIPK3 (RIPK1)	-	GPX4, FSP1 protect. Lipid synthesis (ACSL4), lipid oxidation enzymes (LOX)
Key impact of iron availability	-	-	-	Required
Cell integrity	Non-lytic	Lytic	Lytic	Lytic
Key pore-forming proteins	BAX/BAK (mitochondrial membrane)	P-MLKL (cell membrane)	Gasdermin-NT (cell membrane, mitochondrial membrane)	Oxidative lipid-cell membrane protein adducts??
Changes in membrane signal and release of intracellular contents	Eat-me signals, pannexin 1 channels: release of anti-inflammatory small molecules	-	-	Phospholipid peroxidation, membrane protein adducts
Key cell membrane rupture protein	NINJ-1 (secondary necrosis)	NINJ-1	NINJ-1	? (Not NINJ-1)
Membrane rupture prevention mechanisms	Cleared by efferocytosis.	ESCRT-III	ESCRT-III	ESCRT-III
Release of DAMPs	No	Non-specific DAMPs	Non-specific DAMPs Release mature IL-1β/IL-18	Non-specific DAMPs, lipid peroxides
Impact on inflammation	Anti-inflammatory	Pro-inflammatory	Pro-inflammatory	Pro-inflammatory
Impact on autoimmunity	Non-immunogenic, lymphoid cell apoptosis may downregulate autoimmunity	Potentially immunogenic	Potentially immunogenic	Potentially immunogenic

Supplementary Table 2. Necroptosis, ferroptosis and pyroptosis: examples of preclinical kidney disease models for which there is evidence of involvement of each regulated necrosis modality. Unless otherwise specified, benefit was reported for the intervention. The list is not exhaustive and is based on bona fide modulators of the diverse forms of cell death. For the purpose of this table, as for suppl table 1, Nec-1 was considered an inhibitor of necroptosis.

Pathway	Preclinical kidney disease	Reference
Necroptosis	AKI IRI Cytokine storm: CLP-sepsis, LPS-sepsis Toxic AKI: cisplatin, radiocontrast, myoglobinuria, gentamicin Crystal nephropathy: oxalate, folic acid, CKD Subtotal nephrectomy Diabetic nephropathy Adenine diet-induced CKD Crystal: folic acid AKI-to-CKD Polycystic kidney disease: more severe UUO ANCA-associated vasculitis, lupus nephritis	1-14
Ferroptosis	AKI IRI Cytokine storm: CLP-sepsis, LPS-sepsis Toxic AKI: cisplatin, myoglobinuria Crystal nephropathy: oxalate, folic acid CKD Diabetic nephropathy? (Rosiglitazone**) Crystal: oxalate Polycystic kidney disease: UUO	15-24
Pyroptosis*	AKI IRI: conflicting evidence: may increase severity. Cytokine storm: LPS-sepsis Toxic AKI: cisplatin: conflicting evidence: may increase severity. Crystal: oxalate: may increase severity, but NLRP3 inflammasome targeting beneficial CKD Subtotal nephrectomy Diabetic nephropathy UUO Lupus nephritis: conflicting evidence: may increase severity. G2APOL1 mice	25-35

* Only molecules or genetically modified mice targeting gasdermins are shown, since caspase inhibitors and drugs targeting inflammasomes and Il-1β may have actions dependent on regulation of apoptosis and inflammation and independent from pyroptosis

** Antidiabetic drug and ACSL4 inhibitor

Supplementary Table 3. Preclinical kidney diseases that respond to manipulation of genes encoding proteins involved in regulated necrosis or drugs targeting these proteins.

Condition	Necroptosis	Ferroptosis	Pyroptosis*
AKI			
IRI-AKI	Nec1, Nec1f: 48h AZD5423: 24h RIPK3-KO mice: 48h Primidone: 48h ALL: Protection	Fer1: 48h SRS 16-86: 48h Nec1f: 48h, 72 Vitamin K: K1, K2 MK4 : 48h ALL: Protection	GSDMD-KO mice: 48h, more injury GSDME-KO mice: 48h, more injury GSDME-KO: 24h, protection
Cisplatin	Nec1: 48h y 72h AZD5423, Cpd-71: 72h MLKL-KO and RIPK3-KO mice: 72h ALL: protection	Fer1, MIOX-KO mice, GW4064, 72h: protection MIOX-Tg mice and FXR-KO mice 72h: more injury	GSDMD-KO, and GSDME-KO mice: 72h protection. GSDMD-KO mice: 48h, more injury
FA-AKI	RIPK3-KO mice: 48h, not protection but less inflammation. Nec1, Nec1s, RIPK3-KO and MLKL-KO mice: 96h, protection. Dabrafenib: 28 days, protection.	Fer1: 48h, protection	ND
Myoglobinuria	Nec1 in rats: 24h, protection. RIPK3-KO mice: 24h, no protection.	Fer1: 24h, protection	ND
Calcium oxalate crystals	Nec1, Nec1s, Nec1f, MLKL-KO mice, RIPK3-KO mice: 24h, protection.	Fer1: 4 weeks in rats, protection. Nec1f: 24h, protection	GSDMD-KO mice: 20 d: more severe
LPS	GSK872: 24h, protection.	Fer1: 24h, protection	Disulfiram: decreased death
Cecal ligation-puncture	RIPK3-KO mice: 24h, protection MLKL-KO mice: 24h, NO protection	Fer1: 24h, protection	ND
CI-AKI	Nec1: 24h, protection.	ND	
Gentamicin	Nec1, RIPK3-KO mice: 24h, protection.	ND	ND
CKD			
UUO	GSK872, Nec1, RIPK3-KO mice: 7 days, protection. MLKL-KO mice: 7 days, NO protection.	Lpx1: 14 days, protection.	Gasdermin E deletion: protection Gasdermin D deletion: protection
Diabetic nephropathy	RIPK3-KO mice and dabrafenib: 24 weeks, protection.	(Rosiglitazone)**	ND
Subtotal nephrectomy	Nec1: 8 weeks, protection.	ND	Gasdermin E deletion: protection
Adenine	RIPK3-KO mice: 14 days, protection.	ND	ND
Lupus nephritis	GSK872: 18 weeks, protection.	ND	Gasdermin D deletion: increased severity Gasdermin E deletion: protection Disulfiram: protection
Polycystic kidney disease	Nec1: more severe disease	Fer1: protection	ND
G2APOL1 mice	ND	ND	Disulfiram: protection

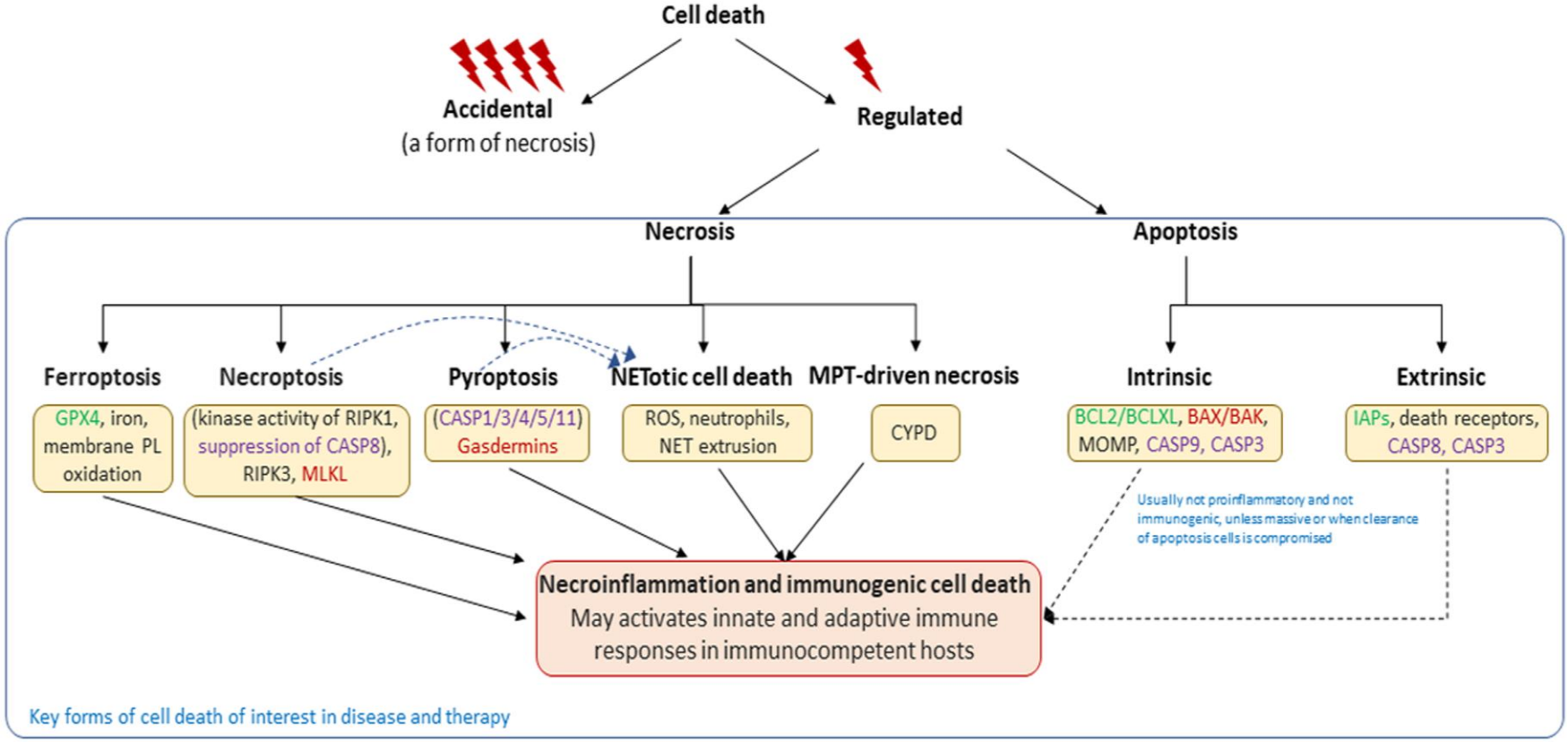
IRI: ischemia reperfusion injury; GSDME: gasdermin E; ND: no data; UUO: unilateral ureteral obstruction.
* Only molecules or genetically modified mice targeting gasdermins are shown, since caspase inhibitors and drugs targeting inflammasomes and Il-1β may have actions dependent on regulation of apoptosis and inflammation and independent from pyroptosis
** Beware that rosiglitazone is an antidiabetic drug and inhibitor of ACSL4

Supplementary Table 4. Drug targeting ferroptosis, necroptosis or pyroptosis in preclinical AKI.

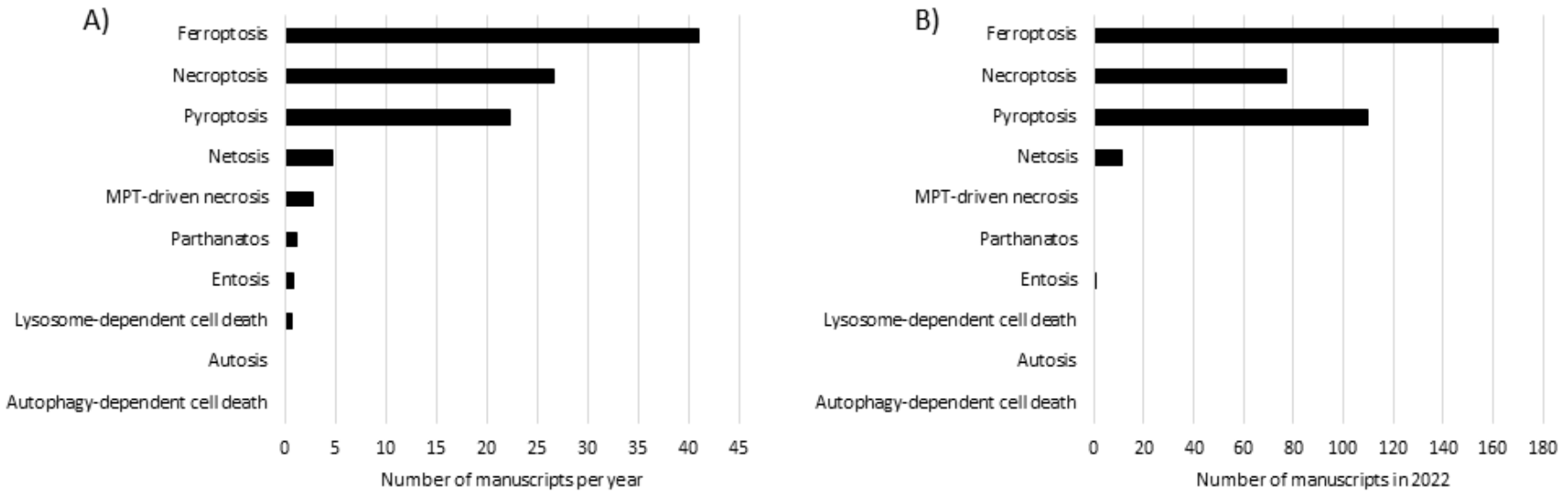
Target	Molecule	Kidney disease	Effect	Reference
Ferroptosis				
Scavenger of lipid peroxidation	Ferrostatin-1	IRI Cisplatin Folic acid-AKI (early injury) Rhabdomyolysis Polycystic kidney disease	↑ renal function ↓ tubular injury ↓ tubular cell death ↓ lipid peroxidation	6,15-18,20
	SRS 16-86	IRI	↑ renal function ↓ tubular injury	15
	Liproxstatin	$GPX4^{-/-}$ mice UUO	↑ survival, ↓ tubular cell death ↓ tubular injury, ↓ fibrosis	24,36
	Vitamin K1, K2 MK4	IRI	↑ renal function ↓ tubular injury	37,38
ACSL4 inhibitor	Rosiglitazone	$GPX4^{-/-}$ mice Diabetic nephropathy**	↑ survival ↑ renal function	39,40
Necroptosis				
RIPK3 inhibitor	Dabrafenib	Folic acid induced AKI-CKD transition and diabetic nephropathy	↓long-term fibrosis and inflammation (28 days)	41,42
	GSK`872	LPS-sepsis and lupus nephritis UUO	↑renal function ↓tubular injury ↓cell death	11,13,43
	AZD5423	IRI Cisplatin	↑renal function ↓tubular injury	44
	CPD42	Gentamicin-AKI	↑renal function ↓tubular injury	10
RIPK1 inhibitor	Necrostatin 1	IRI Cisplatin Folic acid-AKI (96h) Oxalate nephropathy UUO Gentamicin-AKI Subtotal nephrectomy	↑renal function ↓tubular injury	1,3,5,8,10,43,45
	Necrostatin 1s	Folic acid-AKI (96h) Oxalate nephropathy	↑renal function ↓tubular injury	3,46
	Primidone	IRI-AKI	↑renal function ↓tubular injury	47
	Cpd-71	Cisplatin	↑renal function ↓tubular injury	48
RIPK1 inhibitor Scavenger of lipid peroxidation	Necrostatin-1f	Oxalate nephropathy IRI	↑renal function ↓tubular injury	49
Pyroptosis*				
Block gasdermin D pore formation	Disulfiram	G2APOL1 mice LPS-AKI	lower albuminuria and improved kidney function Decreased death	50 51

***** Only molecules targeting gasdermins are shown, since caspase inhibitors and drugs targeting inflammasomes and Il-1β may have actions dependent on regulation of apoptosis and inflammation and independent from pyroptosis

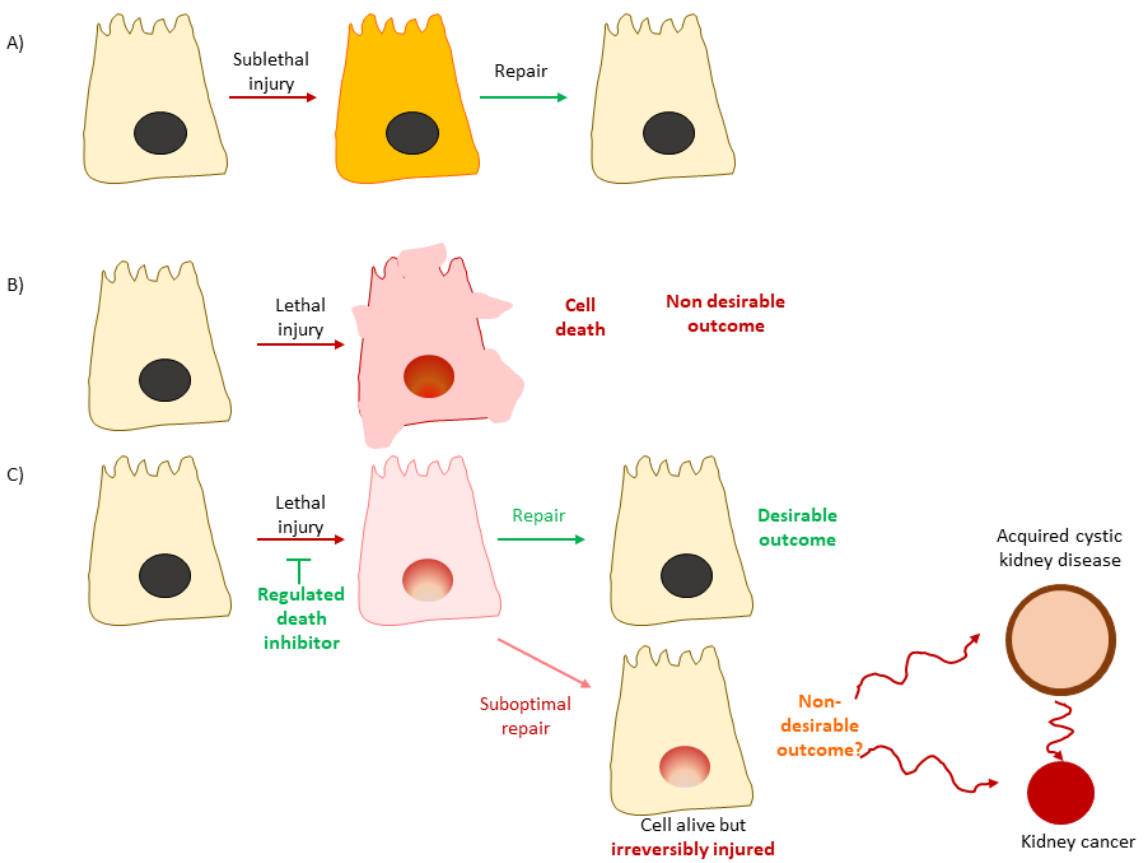
** Beware that rosiglitazone is an antidiabetic drug



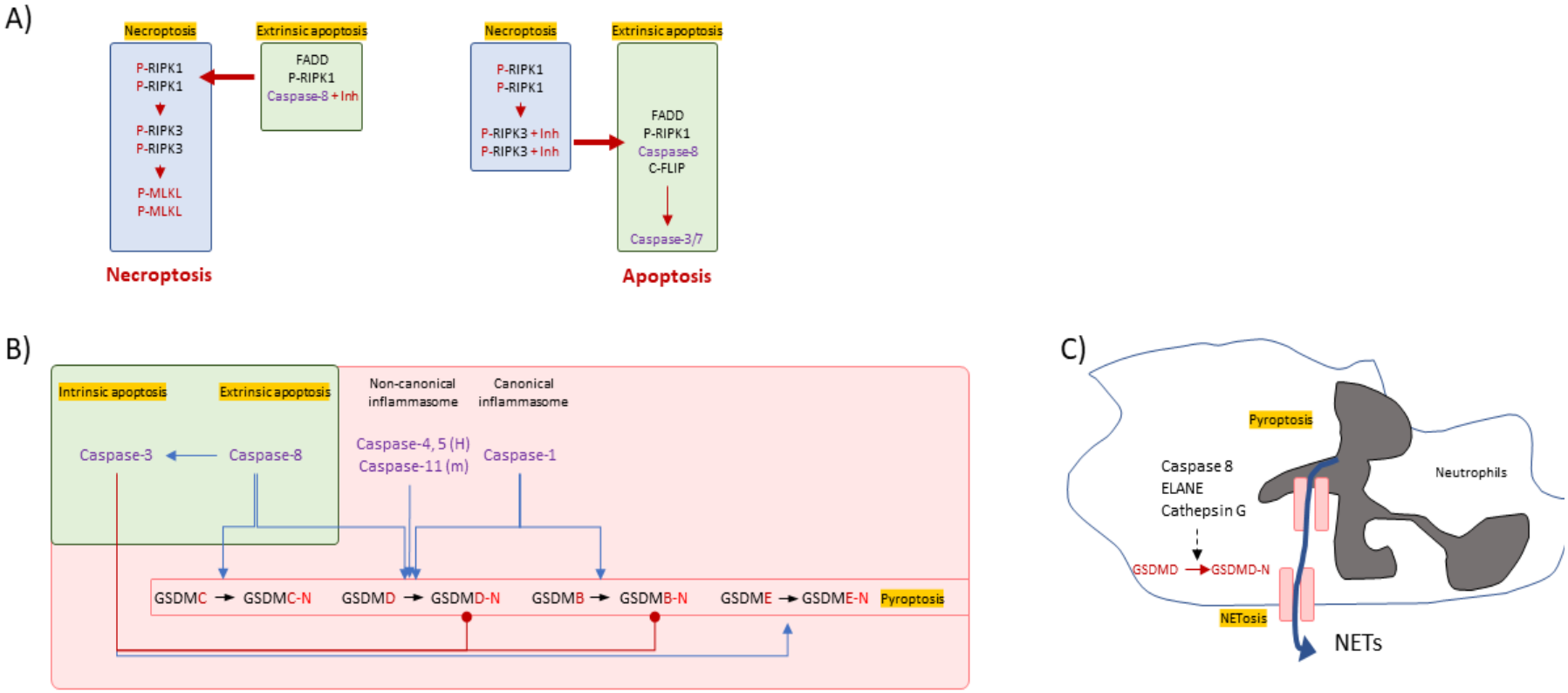
Supplementary Figure 1. **Main forms of cell death of interest in disease and therapy and relationship to immunogenic cell death.** Extreme physical, chemical, or mechanical cues may cause instant cell death (Accidental cell death). However most often cell death occurs in response to less intense cues and is regulated by intracellular molecules. Key components for each form of cell death are indicated. Apoptosis is the main form of programed cell death occurring physiologically, e.g., during development. During tissue injury, both regulated necrosis and apoptosis may occur, the later having a lesser impact as an immunogenic form of cell death unless excessive or when clearance is suboptimal. Key protective proteins for each pathway in green, caspases in purple, pore-forming proteins in red. Note that caspase-8 promotes apoptosis but protects from necroptosis. GPX4: Glutathione peroxidase 4; MLKL: Mixed Lineage Kinase Domain Like Pseudokinase, RIPK3: Receptor-interacting serine/threonine-protein kinase 3, RIPK1: Receptor-interacting serine/threonine-protein kinase 1, MPT: Mitochondrial permeability transition (MPT), MOMP: Mitochondrial outer membrane permeabilization, CASP3: Caspase-3, ROS: reactive oxygen species, hematopoietic cells, NET: Neutrophil extracellular trap, PL: phospholipids. Adapted from ref.52, Springer Nature Limited.



Supplementary Figure 2. **Publications on regulated necrosis and the kidney**. **A)** Number of manuscripts per year on diverse forms of cell death defined by the Nomenclature Committee on Cell Death 2018 [52] and the kidney. The number was obtained by dividing the total number of references between the number of years elapsed from the first report of that cell death and the kidney. As a comparator, the number of manuscripts per year on apoptosis and kidney were 595. **B)** Number of manuscripts in 2022. As a comparator, the number of manuscripts in 2022 on apoptosis and kidney were 1615. Forms of cell death with at least one kidney-related publication are shown. Among the most represented forms of regulated necrosis, the first kidney related publication for mitochondrial permeability transition-induced regulated necrosis (MPT-RN) dates from 2009, netosis from 2010, necroptosis, pyroptosis and entosis from 2012, ferroptosis from 2014, parthanatos from 2017 and autosis from 2020.
The following searches were performed on October 21, 2022: (necroptosis OR necroptotic) AND kidney; (ferroptosis OR ferroptotic) AND kidney; (netosis OR netotic) AND kidney; Anoikis AND kidney; Autophagy-dependent cell death AND kidney; (Pyroptosis or pyroptotic) AND kidney; autosis AND kidney; (entosis OR entotic) AND kidney; "Lysosome-dependent cell death" AND kidney; “mitochondrial permeability transition-induced regulated necrosis (MPT-RN)” AND kidney; OR ("Mitochondrial permeability transition" OR MPT) AND necrosis) AND kidney; Parthanatos AND kidney; (Apoptosis OR apoptotic) AND kidney



Supplementary Figure 3. Potential adverse consequences of preventing cell death in kidney injury. A) In the course of disease, cells may be stressed, resulting in sublethal injury that is rapidly repaired. **B)** More severe stressors may cause cell death, potentially causing cell depletion, organ failure and delaying or even preventing tissue repair. **C)** The expected outcome of the therapeutic use of inhibitors of regulated necrosis is to prevent cell death, resulting in fully functional and healthy surviving cells. However, there is the concern that therapeutic approaches that inhibit cell death may also impair the clearance of irreversibly damaged cells. Of special concern are those who have suffered DNA damage. In this regard, acquired somatic mutations are involved in the pathogenesis of autosomal dominant polycystic kidney disease and, although less studied, likely in acquired kidney cystic disease associated with CKD [53]. Acquired mutations may also lead to malignancy. Regulated necrosis has evolved as a means of protecting organisms from pathogens such as intracellular pathogens.



Supplementary Figure 4. Molecular interactions between different forms of regulated cell death. **A)** Extrinsic apoptosis and necroptosis are interconnected. Inhibition of caspase-8 may convert apoptosis into necroptosis by facilitating the interaction between RIPK1 and RIPK3. By contrast, inhibitors of RIPK3, such as GSK'872 promote apoptosis by interacting with RIPK3 to activate caspase-8 via recruitment of RIPK1 to assemble a novel multiprotein complex [54]. This is also observed for certain kinase-dead mutants of RIPK3. **B)** Molecular links between apoptosis and pyroptosis. Caspase-3 or caspase-8 activation in the course of apoptosis may activate certain gasdermins, such as gasdermin-C, -D and -E, triggering pyroptosis. By contrast, caspase-3 may also degrade gasdermin-B-NT and gasdermin-D-NT, protecting from pyroptosis. **C)** Pyroptosis and NETosis. NETosis mainly refers to neutrophil death triggering the release of DNA and nuclear components into neutrophil extracellular traps (NETs). Molecular pathways consistent with both necroptosis and pyroptosis have been shown to result in NETosis. In neutrophils, endogenous proteases may process gasdermin-D to gasdermin-D-NT that inserts protein pores into the nuclear and plasma membranes, facilitating the release of nuclear material.

REFERENCES

1 Linkermann, A. *et al.* Two independent pathways of regulated necrosis mediate ischemia-reperfusion injury. *Proc Natl Acad Sci U S A* **110**, 12024-12029 (2013). https://doi.org:10.1073/pnas.1305538110

2 Linkermann, A. *et al.* The RIP1-kinase inhibitor necrostatin-1 prevents osmotic nephrosis and contrast-induced AKI in mice. *J Am Soc Nephrol* **24**, 1545-1557 (2013). https://doi.org:10.1681/ASN.2012121169

3 Martin-Sanchez, D. *et al.* TWEAK and RIPK1 mediate a second wave of cell death during AKI. *Proc Natl Acad Sci U S A* **115**, 4182-4187 (2018). https://doi.org:10.1073/pnas.1716578115

4 Homsi, E., Andreazzi, D. D., Faria, J. B. & Janino, P. TNF-α-mediated cardiorenal injury after rhabdomyolysis in rats. *Am J Physiol Renal Physiol* **308**, F1259-1267 (2015). https://doi.org:10.1152/ajprenal.00311.2014

5 Mulay, S. R. *et al.* Cytotoxicity of crystals involves RIPK3-MLKL-mediated necroptosis. *Nat Commun* **7**, 10274 (2016). https://doi.org:10.1038/ncomms10274

6 Xu, Y. *et al.* A Role for Tubular Necroptosis in Cisplatin-Induced AKI. *J Am Soc Nephrol* **26**, 2647-2658 (2015). https://doi.org:10.1681/ASN.2014080741

7 Xiao, X. *et al.* Inhibition of Necroptosis Attenuates Kidney Inflammation and Interstitial Fibrosis Induced By Unilateral Ureteral Obstruction. *Am J Nephrol* **46**, 131-138 (2017). https://doi.org:10.1159/000478746

8 Zhu, Y., Cui, H., Xia, Y. & Gan, H. RIPK3-Mediated Necroptosis and Apoptosis Contributes to Renal Tubular Cell Progressive Loss and Chronic Kidney Disease Progression in Rats. *PLoS One* **11**, e0156729 (2016). https://doi.org:10.1371/journal.pone.0156729

9 Schreiber, A. *et al.* Necroptosis controls NET generation and mediates complement activation, endothelial damage, and autoimmune vasculitis. *Proc Natl Acad Sci U S A* **114**, E9618-E9625 (2017). https://doi.org:10.1073/pnas.1708247114

10 Hu, B. F. *et al.* Protective effect of inhibiting necroptosis on gentamicin-induced nephrotoxicity. *FASEB J* **36**, e22487 (2022). https://doi.org:10.1096/fj.202200163R

11 Guo, C. *et al.* Pathogenesis of lupus nephritis: RIP3 dependent necroptosis and NLRP3 inflammasome activation. *J Autoimmun* **103**, 102286 (2019). https://doi.org:10.1016/j.jaut.2019.05.014

12 Sureshbabu, A. *et al.* RIPK3 promotes sepsis-induced acute kidney injury via mitochondrial dysfunction. *JCI Insight* **3** (2018). https://doi.org:10.1172/jci.insight.98411

13 Zhang, S. *et al.* RIPK3 mediates renal tubular epithelial cell apoptosis in endotoxin-induced acute kidney injury. *Mol Med Rep* **20**, 1613-1620 (2019). https://doi.org:10.3892/mmr.2019.10416

14 Imamura, M. *et al.* RIPK3 promotes kidney fibrosis via AKT-dependent ATP citrate lyase. *JCI Insight* **3** (2018). https://doi.org:10.1172/jci.insight.94979

15 Linkermann, A. *et al.* Synchronized renal tubular cell death involves ferroptosis. *Proc Natl Acad Sci U S A* **111**, 16836-16841 (2014). https://doi.org:10.1073/pnas.1415518111

16 Martin-Sanchez, D. *et al.* Ferroptosis, but Not Necroptosis, Is Important in Nephrotoxic Folic Acid-Induced AKI. *J Am Soc Nephrol* **28**, 218-229 (2017). https://doi.org:10.1681/ASN.2015121376

17 Wenzel, S. E. *et al.* PEBP1 Wardens Ferroptosis by Enabling Lipoxygenase Generation of Lipid Death Signals. *Cell* **171**, 628-641.e626 (2017). https://doi.org:10.1016/j.cell.2017.09.044

18 Guerrero-Hue, M. *et al.* Curcumin reduces renal damage associated with rhabdomyolysis by decreasing ferroptosis-mediated cell death. *FASEB J* **33**, 8961-8975 (2019). https://doi.org:10.1096/fj.201900077R

19 He, Z. *et al.* Role of ferroptosis induced by a high concentration of calcium oxalate in the formation and development of urolithiasis. *Int J Mol Med* **47**, 289-301 (2021). https://doi.org:10.3892/ijmm.2020.4770

20 Deng, F., Sharma, I., Dai, Y., Yang, M. & Kanwar, Y. S. Myo-inositol oxygenase expression profile modulates pathogenic ferroptosis in the renal proximal tubule. *J Clin Invest* (2019). https://doi.org:10.1172/JCI129903

21 Kim, D. H. *et al.* Farnesoid X receptor protects against cisplatin-induced acute kidney injury by regulating the transcription of ferroptosis-related genes. *Redox Biol* **54**, 102382 (2022). https://doi.org:10.1016/j.redox.2022.102382

22 Qiu, W. *et al.* Melatonin suppresses ferroptosis via activation of the Nrf2/HO-1 signaling pathway in the mouse model of sepsis-induced acute kidney injury. *Int Immunopharmacol* **112**, 109162 (2022). https://doi.org:10.1016/j.intimp.2022.109162

23 Zhang, X. *et al.* Ferroptosis Promotes Cyst Growth in Autosomal Dominant Polycystic Kidney Disease Mouse Models. *J Am Soc Nephrol* **32**, 2759-2776 (2021). https://doi.org:10.1681/ASN.2021040460

24 Zhang, B. *et al.* Liproxstatin-1 attenuates unilateral ureteral obstruction-induced renal fibrosis by inhibiting renal tubular epithelial cells ferroptosis. *Cell Death Dis* **12**, 843 (2021). https://doi.org:10.1038/s41419-021-04137-1

25 Ye, Z. *et al.* Caspase-11 Mediates Pyroptosis of Tubular Epithelial Cells and Septic Acute Kidney Injury. *Kidney Blood Press Res* **44**, 465-478 (2019). https://doi.org:10.1159/000499685

26 Yang, J. R. *et al.* Ischemia-reperfusion induces renal tubule pyroptosis via the CHOP-caspase-11 pathway. *Am J Physiol Renal Physiol* **306**, F75-84 (2014). https://doi.org:10.1152/ajprenal.00117.2013

27 Miao, N. *et al.* The cleavage of gasdermin D by caspase-11 promotes tubular epithelial cell pyroptosis and urinary IL-18 excretion in acute kidney injury. *Kidney Int* (2019). https://doi.org:10.1016/j.kint.2019.04.035

28 Tonnus, W. *et al.* Gasdermin D-deficient mice are hypersensitive to acute kidney injury. *Cell Death Dis* **13**, 792 (2022). https://doi.org:10.1038/s41419-022-05230-9

29 Li, Y. *et al.* Activation of GSDMD contributes to acute kidney injury induced by cisplatin. *Am J Physiol Renal Physiol* **318**, F96-F106 (2020). https://doi.org:10.1152/ajprenal.00351.2019

30 Xia, W. *et al.* Gasdermin E deficiency attenuates acute kidney injury by inhibiting pyroptosis and inflammation. *Cell Death Dis* **12**, 139 (2021). https://doi.org:10.1038/s41419-021-03431-2

31 Zhang, Z. *et al.* Caspase-11-mediated tubular epithelial pyroptosis underlies contrast-induced acute kidney injury. *Cell Death Dis* **9**, 983 (2018). https://doi.org:10.1038/s41419-018-1023-x

32 Lv, D. *et al.* Treatment of Membranous Nephropathy by Disulfiram through Inhibition of Podocyte Pyroptosis. *Kidney Dis (Basel)* **8**, 308-318 (2022). https://doi.org:10.1159/000524164

33 Wang, H. *et al.* Complement induces podocyte pyroptosis in membranous nephropathy by mediating mitochondrial dysfunction. *Cell Death Dis* **13**, 281 (2022). https://doi.org:10.1038/s41419-022-04737-5

34 Cao, H. *et al.* Novel Effects of Combination Therapy Through Inhibition of Caspase-1/Gasdermin D Induced-Pyroptosis in Lupus Nephritis. *Front Immunol* **12**, 720877 (2021). https://doi.org:10.3389/fimmu.2021.720877

35 Li, Y. *et al.* GSDME-mediated pyroptosis promotes inflammation and fibrosis in obstructive nephropathy. *Cell Death Differ* **28**, 2333-2350 (2021). https://doi.org:10.1038/s41418-021-00755-6

36 Friedmann Angeli, J. P. *et al.* Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice. *Nat Cell Biol* **16**, 1180-1191 (2014). https://doi.org:10.1038/ncb3064

37 Kolbrink, B. *et al.* Vitamin K1 inhibits ferroptosis and counteracts a detrimental effect of phenprocoumon in experimental acute kidney injury. *Cell Mol Life Sci* **79**, 387 (2022). https://doi.org:10.1007/s00018-022-04416-w

38 Mishima, E. *et al.* A non-canonical vitamin K cycle is a potent ferroptosis suppressor. *Nature* **608**, 778-783 (2022). https://doi.org:10.1038/s41586-022-05022-3

39 Doll, S. *et al.* ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. *Nat Chem Biol* **13**, 91-98 (2017). https://doi.org:10.1038/nchembio.2239

40 Wang, Y. *et al.* Ferroptosis involves in renal tubular cell death in diabetic nephropathy. *Eur J Pharmacol* **888**, 173574 (2020). https://doi.org:10.1016/j.ejphar.2020.173574

41 Shi, Y. *et al.* RIPK3 blockade attenuates kidney fibrosis in a folic acid model of renal injury. *FASEB J* **34**, 10286-10298 (2020). https://doi.org:10.1096/fj.201902544RR

42 Shi, Y. *et al.* RIPK3 blockade attenuates tubulointerstitial fibrosis in a mouse model of diabetic nephropathy. *Sci Rep* **10**, 10458 (2020). https://doi.org:10.1038/s41598-020-67054-x

43 Piao, S. G. *et al.* Inhibition of RIP1-RIP3-mediated necroptosis attenuates renal fibrosis via Wnt3α/β-catenin/GSK-3β signaling in unilateral ureteral obstruction. *PLoS One* **17**, e0274116 (2022). https://doi.org:10.1371/journal.pone.0274116

44 Xu, C. H. *et al.* RIPK3 inhibitor-AZD5423 alleviates acute kidney injury by inhibiting necroptosis and inflammation. *Int Immunopharmacol* **112**, 109262 (2022). https://doi.org:10.1016/j.intimp.2022.109262

45 Linkermann, A. *et al.* Rip1 (receptor-interacting protein kinase 1) mediates necroptosis and contributes to renal ischemia/reperfusion injury. *Kidney Int* **81**, 751-761 (2012). https://doi.org:10.1038/ki.2011.450

46 Mulay, S. R. *et al.* Mitochondria Permeability Transition versus Necroptosis in Oxalate-Induced AKI. *J Am Soc Nephrol* (2019). https://doi.org:10.1681/ASN.2018121218

47 Riebeling, T. *et al.* Primidone blocks RIPK1-driven cell death and inflammation. *Cell Death Differ* **28**, 1610-1626 (2021). https://doi.org:10.1038/s41418-020-00690-y

48 Wang, J. N. *et al.* RIPK1 inhibitor Cpd-71 attenuates renal dysfunction in cisplatin-treated mice via attenuating necroptosis, inflammation and oxidative stress. *Clin Sci (Lond)* **133**, 1609-1627 (2019). https://doi.org:10.1042/CS20190599

49 Tonnus, W. *et al.* Dysfunction of the key ferroptosis-surveilling systems hypersensitizes mice to tubular necrosis during acute kidney injury. *Nat Commun* **12**, 4402 (2021). https://doi.org:10.1038/s41467-021-24712-6

50 Wu, J. *et al.* The key role of NLRP3 and STING in APOL1-associated podocytopathy. *J Clin Invest* **131** (2021). https://doi.org:10.1172/JCI136329

51 Hu, J. J. *et al.* FDA-approved disulfiram inhibits pyroptosis by blocking gasdermin D pore formation. *Nat Immunol* **21**, 736-745 (2020). https://doi.org:10.1038/s41590-020-0669-6

52 Galluzzi, L. *et al*. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. *Cell Death Differ* **25**, 486-541 (2018). https://doi.org:10.1038/s41418-017-0012-4

53 Zhang, Z. *et al*. Detection of. *J Am Soc Nephrol* **32**, 3114-3129 (2021). https://doi.org:10.1681/ASN.2021050690

54 Mandal, P. *et al.* RIP3 induces apoptosis independent of pronecrotic kinase activity. *Mol Cell* **56**, 481-495 (2014). https://doi.org:10.1016/j.molcel.2014.10.021