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PROGRAMMED CELL DEATH AND LIVER DISEASES

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Cell death represents the most critical pathologic entity in liver disease, which dictates pathologic consequences such as inflammation, fibrosis, and cell transformation. We analyzed the conclusions of studies on the involvement of different types of programmed cell death (PCD) in the pathogenesis of liver diseases. Three main forms of PCD (autophagy, apoptosis, necrosis) and five additional, still insufficiently studied PCD – necroptosis, ferroptosis, pyroptosis, partanatosis and entosis – observed in the liver in various acute and chronic diseases are considered. The involvement of several PCD at once in the development of any one pathology and one type of PCD in different pathologies was established. This indicates the existence of cross-regulation of metabolism in the liver cells with different levels of damage in the formation of the main dominant type of PCD. Available results indicate the possibility of attenuation (correction) of functional and morphological manifestations of PCD in the organ by controlled blocking of effector-mediated PCD pathways, as well as targeted induction of autophagy, anti-apoptotic and anti-necrotic mechanisms in liver cells.

Keywords: programmed cell death, autophagy, apoptosis, necrosis, liver diseases.

The study of molecular mechanisms of diseases in order to improve their treatment has become the main focus of modern medical science. Development of ideas about active participation in adaptation, morphogenesis and cellular homeostasis of the evolutionarily developed mechanism of regulation of cell activity – programmed cell death (PCD) – has contributed to the expanded study of the role of PCD in pathological processes in the body [1–4]. This review assesses the role of different forms of PCD in the pathogenesis of acute and chronic liver diseases, as well as substantiates possible ways to correct them.

1. DIFFERENT FORMS OF PCD ACTIVATED IN LIVER DISEASES

Cell death represents the most critical pathologic entity in liver disease, which dictates pathologic consequences such as inflammation, fibrosis, and cell transformation [5]. Most of the described cell death mechanisms, except for direct physical or chemical destruction, are mediated by evolutionary mechanisms and therefore belong to a type of programmed cell death. Depending on the nature of the damaging effect and the mechanisms of death initiation, there are 3 main, most studied PCD types (autophagy, apoptosis, necrosis) and 5 types of additional, still insufficiently studied PCD (necroptosis, pyroptosis, ferroptosis, partanatosis, entosis) (see Table 1).

These different types of PCD can manifest and coexist simultaneously in hepatocytes, cholangiocytes or nonparenchymal liver cells. The degree of expression and involvement of each form of PCD depends on the etiology and stage of the pathological process, and on the degree of cross-effects of other types of PCD on them. It is also important to note that among all the listed forms of PCD, autophagy and apoptosis occupy a special place because in the early stages of their development, the cell death process can be stopped or even prevented. This means that autophagy and apoptosis can serve as mechanisms for therapeutic regulatory (regenerative) effects.

1.1. Autophagy and autophagic cell death

Autophagy is the process of lifelong intracellular degradation and utilization of altered cytoplasmic contents through formation of autophagosomes. Autophagy plays a key role in the processes of cell adaptation and survival [7], as it provides short-term maintenance of cellular and energy homeostasis [8–10] due to the release of nutrient and energy-intensive substances into the cytoplasm and subsequent utilization. That is why some authors [11] consider autophagy as a way of "predominantly programmed survival" of cells due to the fact that when activated, autophagy provides protective rather than cytotoxic effects [12]. As a result of stress, altered proteins of the cytoplasm, damaged mitochondria, endoplasmic reticulum and peroxisomes translocate to organelle membranes, where they form a protein complex involved in formation of an autophagosome with a double membrane. Autophagosome formation (D = 0.3–1.0 μm) occurs with the participation of Vps 34, Beclin-1, Atg4 – Atg12/Atg16L1 proteins, etc. Subsequent formation of an autophagolysosome occurs through fusion of the autophagosome with lysosomes

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[13]. Degradation (hydrolysis) of altered proteins and release of nutrient and energy-intensive substances that can support the life-support of these cells into the cytoplasm takes place in the autophagolysosome [10, 11, 13]. With excessive degradation of altered proteins in cells, autophagic death can be prevented only by inhibiting autophagy [14].

Autophagy plays an important role in protecting the liver from toxic factors, particularly in alcoholic liver disease [15–17] and toxic effects of pharmaceuticals [18, 19]. The function of autophagy under these influences is to attenuate oxidative stress, to inhibit the excessive accumulation of altered proteins and damaged organelles in cells [20, 21]. Inhibition of autophagy by removal of

Table 1

Characteristics of various types of PCD [4–6]

Forms of PCD in liver	Mechanism of action	Effectors (markers)	Cell morphology	Liver diseases
1. Autophagy	Sequential formation in cytoplasm of phagophore, autophagosome, autophagosome lysosome	LC3-P, ULK1, Atg12, Atg4, GABA-RAP	Vacuolization of cell cytoplasm, formation of autophagosomes and autophagolysosomes	Toxic effects, viral hepatitis, alcoholic liver disease
2. Apoptosis (degradation of dying cells by phagocytosis without inflammation)	Caspase-dependent (receptor-mediated) and mitochondrial-dependent pathways	PS of outer membrane, FAS/ TNFR1, CASPs-3,7,8,9,10 BAX/BAK APAF1	Cell compaction, chromatin condensation, nuclear fragmentation, formation of apoptotic bodies	Cholestatic, autoimmune, diseases, viral hepatitis, alcoholic disease, non-alcoholic steatohepatitis, hepatocarcinoma
3. Necrosis mediated by increased mitochondrial permeability transition – mPT-driven necrosis – (cell destruction and inflammation)	ROS and RNS generation, cytosolic Ca accumulation in mitochondria (Mx).	CypD, BAX/BAK	Wrinkling and disorganization of cytoplasm and Mx structure, nuclear thickening and fragmentation, cytoplasmic membrane rupture, cell lysis	Ischemia-reperfusion injury, nonalcoholic fatty disease, alcoholic disease
4. Necroptosis (necrotoxic cell destruction)	Activation of FAS/ TNFR1, TLRs-3/4, ZBP1; CASP-8 inhibition, necrosome formation	RIPK1, RIPK3 MLKL	Cell lysis due to increased plasma membrane permeability	Drug toxicity, non-alcoholic steatohepatitis, alcoholic disease, autoimmune diseases
5. Ferroptosis (develops when the cell lacks glutathione)	Fe-catalyzed formation of ROS, lipid peroxidation (PL)	GPX4	Necrotic morphology, mitochondria destructured, loss of cristae, outer membrane ruptures	Drug toxicity, autoimmune hepatitis, alcoholic disease, non-alcoholic steatohepatitis
6. Pyroptosis (combines signs of apoptosis, necrosis and inflammation)	Removal of grand-tricellular pathogens (LPS and/ or bacteria) by inflammasome formation	NLRP1,-3; CASP-1, CASPs-4,-5,-11; GSDMD	Cell lysis due to formation of pores in the outer membrane;	Drug toxicity, cholestasis, autoimmune and viral hepatitis, non-alcoholic steatohepatitis, alcoholic disease
7. Partanatosis	Alkylating DNA damage, exposure to ROS, RNS, hypoxia	PARP-1	DNA fragmentation, nuclear condensation	Toxic drugs, hepatocarcinoma
8. Entosis	Disappearance of integrin signaling from matrix; cancer cell competition	Myosin/ Rho A/ ROCK	Invasion, engulfment of some cells by others (cell cannibalism)	Hepatocarcinoma, fibrosis progression

Note. APAF1, apoptotic protease activating factor 1; ROS, reactive oxygen species; RNS, reactive nitrogen species; LP, lipid peroxidation; BAK, Bcl-2 homologous antagonist killer; BAX, Bcl-2-associated X protein; CASPs, cysteine-dependent aspartate-directed proteases; CypD, Cyclophilin D; Fas TNF, ligand TNF cell death receptor encoded by the FAS gene; TNFR1, tumor necrosis factor receptor 1; GABA-RAP, Gamma-aminobutyric acid receptor-associated protein, encoded by the GABARAP gene, which takes part in autophagosome formation; GPX4, Glutathione peroxidase 4; GSH, Glutathione; GSDMD, Gasdermin D; LC3, soluble microtubular-associated protein 1A/1B – light chain-3, which is conjugated in the autophagosome with phosphatidylethanolamine to form LC3-II, an autophagy marker; MLKL, mixed lineage kinase domain like pseudokinase; mPT-driven necrosis, necrosis caused by increased mitochondrial (Mt) membrane permeability; NLRP1,-3, NOD-like receptor (NLR) family, pyrin domain-containing proteins; PS, phosphatidylserine (marker of apoptosis); PARP-1, Poly (ADP-ribose) polymerase 1; RIPK1,-3, receptor-interacting serine/threonine-protein kinase 1 and 3; Rho A/ROCK, Rho-associated protein kinase (ROCK); TLRs $^{3}/_{4}$, toll-like receptors $^{3}/_{4}$; TNFR1, tumor necrosis factor receptor 1; ULK1, Unc-51 like autophagy activating kinase; ZBP1, Z-DNA-binding protein.

proteins involved in the formation of autophagosomes (Atg5 knockout gene) leads to liver cell death, inflammation and fibrosis in a mice alcohol stress model [22]. At the same time, activation of autophagy by removal of lipid peroxidation products, lipid droplets and aggregates of altered protein – adenosine monophosphate-activated protein kinase (AMPK or AMP-activated protein kinase) – promotes protection of mitochondria against apoptosis when modeling alcoholic disease [16, 23].

It was found that ethanol induces autophagy through oxidative stress mechanisms, which are associated with AMPK activation and suppression of the mammalian target of rapamycin complex 1 (mTORC-1) pathway [17, 21]. Indeed, autophagy activation by rapamycin, an inhibitor of mTORC-1, reduced ethanol-induced liver damage, whereas inhibition of autophagy by chloroquine exacerbated the damage [17]. A single alcohol intake activates autophagy; with chronic intake and in high doses, alcohol can suppress autophagy [17, 21] and exacerbate liver damage through toxic effects.

Liver cell death during toxic exposure to acetaminophen (paracetamol) – (APAP) – does not occur as a result of their autophagic death. Studies in mice have shown that activation of autophagy actually protects liver cells from APAP-induced death, whereas inhibition of autophagy aggravates APAP toxicity [24–27]. Mitochondrial dysfunction, mitochondrial protein breakdown products, accumulation of reactive oxygen species (ROS) and adenosine triphosphate (ATP) depletion all contribute to cell necrosis, but also serve as a catalyst for autophagy initiation upon APAP exposure [18, 24]. Autophagy initiation limits ROS generation by damaged mitochondria, and the autophagosomes that form create a barrier to the expansion of necrosis. Consequently, the resulting changes contribute to activation of mitochondrial biogenesis and liver regeneration [18, 19].

1.2. Apoptosis

Apoptosis, like autophagy, is an active player in morphogenesis and regulation of cell count in the body; it supports cell homeostasis and stimulates physiological cell regeneration [28]. Meanwhile, apoptosis is also triggered under various pathological conditions, which leads to death of cells that are undesirable for the body [29]. Cell death and its removal in apoptosis is carried out by phagocytosis without inflammation. Produced apoptotic cells are utilized by neighboring parenchymal and nonparenchymal cells, fibroblasts, macrophages and dendritic cells [30, 31]. Mediators released by apoptotic cells selectively inhibit neutrophil migration [31, 32]. At the same time, there is increased chemotaxis of macrophages, which, using their numerous receptors, detect the appearance of expression of phosphatidylserine (PS) and other oxidized lipids on the surface of apoptotic cells, which are markers of early apoptosis, and quickly remove them.

Apoptosis includes 3 phases: signaling (induction phase), effector (realization phase) and degradation (destruction phase). The signaling phase can be accomplished via two pathways: extrinsic (involving cell death receptors – caspase-dependent pathway) and intrinsic (involving mitochondria) [5, 28]. Both pathways eventually lead to activation of initiating caspases (CASPs-8,-9,-10,-12) and subsequent activation of effector caspases (CASPs 3,6,7,14), which results in proteolysis, nuclear fragmentation and apoptotic cell death by phagocytosis [28].

In the extrinsic caspase-dependent pathway, the apoptosis signal is triggered by extracellular microenvironment factors: hypoxia, ischemia/reperfusion, exposure to physical and chemical agents, disturbances in cell cycle signaling, etc. These factors stimulate transmembrane cell receptors of two types: type 1 – Tumor necrosis factor (TNF)-family death receptors (TNF receptors or DRs), such as, FAS (CD 95, APO-1), TNFR-1 (p55, CD 120A) and others; type 2 – pattern recognition receptors (PRR) [12], which include toll-like receptors (TLRs). TLRs are part of a multiprotein complex containing Receptor-interacting protein kinase 1 (RIPK1), cellular inhibitor of apoptosis proteins 1 and 2 (cIAP-1 and cIAP-2) and several other proteins [5], which can participate in cell death prevention.

The apoptosis triggering process occurs through interaction of a specific TNF-family death receptor with its adaptor, which further interacts with effectors, procaspases, inactive precursors that initiate caspases [28]. As a result of the interaction of ligand, receptor, adaptor and procaspases, apoptosomes are formed in which cell death processes are initiated due to autolytic activation of caspases [33]. First, the initiating caspases, CASPs-2,-8,-9,-10,-12, are activated in apoptosomes, which further participate in activation of effector caspases, CASPs-3,-7, etc. [5, 34], which leads to proteolysis, nuclear fragmentation, and apoptotic cell death.

The intrinsic or mitochondrial apoptosis signaling pathway is initiated by stressor or cytotoxic DNA damage that activates nuclear protein p53. Induction of p53 increases the activity of the Bcl-2 family regulatory proteins: Bcl-2, BID (BH3 – interacting-domain death agonist BH3) and tBID (BID – after the post-transcriptional modification). These activated proteins, moving into mitochondria, interact with the mitochondrial pool of pro-apoptotic proteins of the Bcl-2 family: with the Bcl-2 associated X apoptosis regulator BAX (BAX) and/or BAK, Bcl-2 homologous antagonist killer (BAK) [12]. Such interaction leads to conformational changes in mitochondrial proteins, pore formation in the outer mitochondrial membrane and release of mitochondrial apoptotic components – cytochrome C, procaspases-2,-3,-9 and apoptotic protease activating factor 1 (APAF1), which

are involved in apoptosome formation [35]. Further, as in the extrinsic apoptosis pathway, procaspase-9 is initiated in the apoptosome, which interacts with the effector procaspase-3, activates it to caspase-3, and triggers the caspase cascade of the effector phase of apoptosis.

Apoptosis, being a regulated process, can be cancelled in the inducer phase (reversible apoptosis phase). The ability to cancel apoptosis is regulated by multidomain protein RIPK1, which is part of the multiprotein type 2 transmembrane receptor complex (see above). RIPK1 has a direct effect on the outcome of type 1 TNF-death receptor activation and causes the affected cell to survive or die, depending on its posttranslational modifications [36, 37]. It is known that E3-ubiquitin (a protein involved in regulation of the functioning and degradation of intracellular proteins), when interacting with cIAP, catalyzes RIPK1 polyubiquitination and promotes activation of nuclear factor kappa B (NF-kB). This interaction leads to gene transformation, ensuring survival and prevention of cell death (cancellation of the irreversible apoptosis phase) [38, 39].

Cellular structures are destroyed (cytoskeleton destruction, cleavage of adhesive proteins, hydrolysis of the nuclear membrane) in the effector phase of apoptosis. In the degradation phase of apoptosis, deep morphological and biochemical changes occur, leading to formation of apoptotic cells, 0.2 μm in diameter, which leave the apoptosis zone, appear in blood and are subsequently phagocytosed [40]. In the degradation phase, apoptosis acquires secondary necrosis features, in which the release of damage-associated molecular patterns (DAMPs), including nucleosomes, from cells, occurs. Nucleosomes contain fragments of genomic DNA, nuclear protein HMGB-1, heat shock proteins HSP and other autoantigens that induce an antigen-specific immune response [32, 41].

Both intrinsic and extrinsic pathways of apoptosis are usually involved in cholestatic and autoimmune liver damage, alcoholic and non-alcoholic steatohepatitis, mild hepatotoxic liver injury and viral hepatitis [42–44].

It has been shown in animal models and in vitro experiments that ethanol causes metabolic, toxic and inflammatory damage to liver cells. Cell damage leads to dysfunction of mitochondria and other organelles, ROS formation, BAX (proapoptotic Bcl-2 protein) translocation into mitochondria, cytochrome C release, caspase activation [45–47] and apoptotic cell death [42]. It is known that acute and chronic alcohol exposure increases intestinal permeability to bacterial products such as lipopolysaccharides (LPS) and this leads to inflammation, Kupffer cells stimulation, increased TNF production by them [48] and TNF expression of apoptosis receptors FAS and TNFR1 [49].

In vitro and in vivo studies using pan-caspase inhibitor showed a significant attenuation of alcohol-induced hepatocyte apoptosis without transition to necroptosis (i.e. without induction of RIPK1 and RIPK3 markers) [50, 51]. Despite the lack of influence of pan-caspase inhibitor on inflammatory markers, less pronounced liver fibrosis was observed when the damage was modeled with combined use of alcohol and CCl_4 [52].

In non-alcoholic steatohepatitis, the pathological process in the liver proceeds against the background of detection of caspase-3,-7 and an increased number of TUNEL*-positive cells in liver biopsy specimens, which proves the inflammatory nature of apoptosis. Such results were obtained in a study of CASP3 and CASP-8 knockout mice that were fed a diet deficient in methionine and choline. These mice were protected against apoptosis, had decreased activity of proinflammatory cytokines, and reduced expression of morphological signs of inflammation and liver fibrosis [53–55]. Meanwhile, mice fed a high-fat diet demonstrated increased ROS levels and signs of apoptosis – increased caspase-3 and caspase-8 activity – as well as increased content of TUNEL*-positive cells in liver biopsy specimens [56]. The importance of apoptosis in non-alcoholic steatohepatitis is also supported by other studies. Thus, it was shown [57] that along with caspase-3 and -7 in nonalcoholic steatohepatitis, caspase-6 is activated, which begins to play an important role in the progression of this disease due to the disturbance of regulatory interaction of metabolic sensor AMPK and apoptotic process participants. In a healthy liver, AMPK is known to phosphorylate proapoptotic caspase-6 and inhibit its activation.

Meanwhile, when non-alcoholic steatohepatitis was simulated in mice on a choline-deficient diet in combination with a high-fat diet, AMPK activity was suppressed; at the same time, simultaneous use of a caspase-6 inhibitor attenuated the morphological signs of apoptosis and liver fibrosis and decreased the level of transaminases[57].

It was also shown that hepatocyte swelling in non-alcoholic steatohepatitis [58] causes stress in cells and their organelles, which induces apoptosis, release of cellular degradation products from damaged molecular patterns (DAMPs, damage-associated molecular patterns) and activation of TLRs. In turn, TLRs activation turns the inflammation and cell death signals into a permanent damaging factor. This is facilitated by interaction of hepatocytes with liver macrophages (Kupffer cells) and leukocytes (natural killers), which, by supplying

* TUNEL (terminal deoxyribonucleotide transferase – mediated dUTP nick end labeling) is a method of recording free 3'-OH DNA ends in a condensed chromatin nucleus using light, laser, confocal or transmission electron microscopy. In apoptosis, DNA fragmentation leads to a significant increase in the number of 3'-OH DNA ends (TUNEL-positive cells) in both intrinsic and extrinsic pathways of apoptosis.

TNF to the body, maintain inflammation in nonalcoholic steatohepatitis [59].

Consequently, apoptosis in nonalcoholic steatohepatitis and nonalcoholic fatty liver disease is the predominant mode of cell death. It involves both extrinsic (via cell surface receptors) and intrinsic pathways of apoptosis activation (via lipotoxicity and organelle stress).

In cholestatic liver diseases accompanied by impaired bile excretion and cholangiopathy, apoptotic death of cholangiocytes is also noted [60]. In liver biopsy specimens from patients with primary biliary cholangitis, cholangiocyte apoptosis, in which cytoplasm thickening and nuclear condensation are observed in cells, is detected [61]. It is believed that apoptosis in these patients is mediated by TNF receptor FAS (CD95), since FAS expression in the cytoplasm of bile duct cells is accompanied by increased FasL expression in the surrounding lymphocytes and other immune cells [61, 62]. FAS-mediated apoptosis of hepatocytes in cholestasis is accompanied by activation of hepatic stellate cells (HSCs) and development of fibrosis, which indicates a connection between apoptosis and formation of fibrosis in the liver [63]. FAS (apoptosis antigen 1) is not the only cell death receptor involved in cholangiocyte apoptosis. Takeda et al. [64] showed that expression of DR5 (death receptor-5) gene was also increased in the liver of patients with primary biliary cholangitis and primary sclerosing cholangitis, and DR5 knockout mice were resistant to cholestatic cell death after bile duct ligation [64]. Cubero et al. [65] reported increased expression of activated proteolytic enzymes caspase-3 and -8 as well as RIPK3 protein in liver biopsy specimens of patients with primary biliary cholangitis, indicating activation of apoptosis and association of apoptosis with other forms of PCD. Using a model of bile duct ligation in CASP-3 knockout mice, the researchers reported a decrease in transaminases AST and ALT, a decrease in caspase-3 activity and RIPK1 and RIPK3 protein levels [65], i.e. a concomitant inhibition of necroptosis mechanisms. Other works [66, 67] have shown the association between decreased apoptosis and decreased caspase-3 and -7 -positive cells, decreased inflammation, hepatic stellate cell (HSC) activity, fibrosis, portal hypertension and improved survival with pan-caspase inhibitors. These data support the importance of apoptosis in cholestatic liver disease.

Liver cell apoptosis is also thought to play an important role in the pathogenesis of hepatitis B and C virus (HCV and HBV) [68, 69]. By histological markers (cell cytoplasm thickening, DNA fragmentation and detection of TUNEL-positive cells), apoptosis has long been detected in liver biopsy specimens of patients with viral hepatitis [70]. Increased expression of FAS receptors in hepatocytes detected by increased FASL expression in lymphocytes in HBV and HCV suggests that apoptosis is the main cause of liver cell death during active hepatitis [70, 71].

1.3. Necrosis caused by increased mitochondrial membrane permeability (mPT-driven necrosis)

Necrosis is the final state of a severe pathological process in cells, which is accompanied by cell swelling, membrane rupture, release of DAMPs and subsequent development of inflammatory response. mPT-driven necrosis described for liver is characterized by pore formation and increased permeability of inner and outer mitochondrial membranes, decreased membrane potential, cessation of ATP synthesis, osmotic destruction of both membranes and cell death [12, 72]. The exact mechanisms of mPT-driven necrosis are not yet known. It has been suggested that a decrease in mitochondrial membrane potential leads to pore enlargement due to disruption of the interaction between the ATP synthase of the pores and mitochondrial protein cyclophilin D (CypD) involved in their formation [73]. The involvement of mPT-driven necrosis in a number of liver diseases, in which oxidative stress and mitochondrial Ca^{2+} overload play an important pathogenetic role, has been proved [12]. For example, it has been shown that in APAP toxicity, APAP is converted into toxic metabolite NAPQI (N-acetyl-p-benzoquinone imine) by direct oxidation involving cytochromes; then NAPQI is effectively detoxified by glutathione (GSH) to form APAP-GSH conjugates [74]. However, when GSH and cysteine reserves in cells are depleted, the toxic metabolite NAPQI binds to thiol (-SH) protein groups, and the resulting NAPQI degradation products cause stress damage to the endoplasmic reticulum and mitochondria [75]. Subsequent mitochondrial damage occurs as a result of ROS formation, nitric oxide (RNS) accumulation in mitochondria [76] and developing Ca^{2+} overload. Continued ROS generation increases mitochondrial stress, which leads to activation of mitogen-activated protein kinases (MAPK) that leads cells to mPT-driven necrosis [77]. mPT-driven necrosis develops as a consequence of mitochondrial membrane rupture, translocation of apoptosis-inducing factor (AIF) into the nucleus and release of endonuclease, followed by DNA fragmentation [78]. The importance of mPT-driven necrosis in the development of APAP toxicity, nonalcoholic steatohepatitis and nonalcoholic fatty liver disease has been confirmed in a number of works [79–81].

1.4. Necroptosis

Necroptosis, as a necrotoxic type of PCD, is involved in most chronic liver diseases, including viral hepatitis, autoimmune hepatitis, nonalcoholic steatohepatitis and alcoholic liver disease [82, 83]. Necroptosis has been shown to be initiated by TNF-family receptors (FAS

and TNFR1), pattern recognition receptors (PRRs)-, (TLRs) or intracellular sensor Z-DNA binding protein 1 (ZBP1). Necroptosis is activated when caspase-8 is inhibited, when receptors for interacting protein kinase-1 and -3 – (RIPK1 and RIPK3) are activated, and when a mixed lineage kinase domain-like protein (MLKL) is activated. Necroptosis is manifested by the formation of necrosomes, a rapid increase in cell membrane permeability and release of DAMPs from cells into the extracellular space [84–86]. The role of RIPK1 and RIPK3 proteins, MLKL and other participants in necroptotic liver cell damage has been actively studied in recent years [87–90]. In a model of autoimmune hepatitis using concanavalin-A (ConA), it was observed that administration of NEC-1, a RIPK1 inhibitor, protects the liver from damage [91–93]. Mice with the MLKL knockout were also protected against ConA damage [90]. However, additional studies on mice with ConA – liver damage and MLKL knockout – failed to reveal differences in the liver condition in the control and experimental groups. The studies could not also confirm the involvement of necroptosis [90, 94]. In a study of patients with HBV and patients with chronic viral hepatitis, increased serum RIPK3 and MLKL levels in the liver were found when compared to controls (healthy controls) [95, 96]. However, the authors could not relate these results to necroptosis, since it is known that RIPK1 and RIPK3 acquire functions that are independent of necroptosis in inflammation [5]. Besides, the results obtained may be a consequence of cross-influence of other PCD types activated under these conditions.

1.5. Pyroptosis

Cell pyroptosis has features of apoptosis and necrosis and is designed to remove intracellular pathogens. Pyroptosis is characterized by formation of an inflammasome containing a complex of caspases activated in the cell and producers of proinflammatory cytokines – IL-1β, IL-18. It is classified as an inflammatory necrosis coding type, which closely interacts with innate immunity [97]. There are two distinct pathways through which pyroptosis can occur – canonical and non-canonical. The canonical pathway is triggered if inflammasome sensors belonging to the NOD-like receptor (NLR) family, pyrin domain-containing proteins 1 and 3 (NLRP1 and NLRP3) are stimulated by PAMPs (pathogen-associated molecular patterns) pathogens and DAMPs. These sensors use caspase-1 to activate intracellular protein Gasdermin-D (GSDMD), which forms pores in the cytoplasmic membrane and promotes cell death [12]. When pyroptosis is activated via the non-canonical pathway, cytosolic lipopolysaccharides (LPS) and PAMPs are directly stimulated by caspases -4, -5 and -11. These caspases in turn activate GSDMD, which, by binding membrane phospholipids, initiates pore formation and leads to cell death [98–100].

Involvement of pyroptosis in liver diseases such as alcoholic disease [101–103], nonalcoholic steatohepatitis [104–107], APAP-induced toxic liver injury [108–110], autoimmune hepatitis [111–113], cholestatic liver diseases [114–117], and viral hepatitis [118, 119], has been proven mainly by examining the activation of key mediators of pyroptosis, NLRP3 inflammasome activity, and GSDMD protein.

1.6. Ferroptosis

Ferroptosis is a type of PCD, which depends on intracellular iron content that catalyzes ROS formation and subsequent oxidative cell damage. Ferroptosis is activated upon depletion of cellular GSH, which promotes activation of iron-dependent lipid peroxidation (LPO) of cell membranes [120, 121]. Ferroptosis develops independently of apoptosis, necrosis, autophagy, and pyroptosis, and has subcellular characteristics of necrosis that are caused by the release of DAMPs [12]. The small size of compressed-density mitochondria, absence of cristae in them, and ruptures of the outer cell membrane, are morphological signs of ferroptosis [122, 123]. GSH-dependent enzyme glutathione peroxidase 4 (GPX4) is the main endogenous inhibitor of ferroptosis due to its ability to limit PL processes [124]. Inhibition of GPX4 activity leads to accumulation of ROS and LPO, and therefore reduced GPX-4 activity is considered a marker of ferroptosis. Reducing the accumulation of ROS and PL products can be achieved by the use of iron chelates (deferroxamine) and LPO inhibitors – (ferrostatin) [125]. The role of ferroptosis in the pathogenesis of liver disease has been investigated in alcohol disease [126–128], non-alcoholic steatohepatitis [128, 129], APAP toxicity [128, 130–132], and autoimmune hepatitis [133, 134]. It has been suggested that ferroptosis plays a role in various liver diseases and, therefore, it can coexist in cells along with other types of PCD (apoptosis, mPT-driven necrosis, necroptosis, etc.) [6].

1.7. Partanatosis

Partanatosis is a type of PCD caused by excessive cell response to DNA damage mediated predominantly by poly (ADP-ribose) polymerase 1 (PARP-1). Partanatosis occurs after severe and prolonged alkylating DNA damage, oxidative stress, hypoglycemia or inflammation [12]. Reactive nitrogen species (RNS), such as NO, are a trigger for PARP-1 activation, which causes depletion of nicotinamide adenine dinucleotide (NAD) and ATP in cells; RNS also contribute to the accumulation of poly (ADP-ribose) polymerase and poly (ADP-ribosylation) proteins, causing loss of mitochondrial membrane potential. In addition, poly (ADP-ribose) polymerases bind AIF and promote AIF nuclear translocation, causing

DNA fragmentation and nuclear condensation. It has recently been shown that a factor that inhibits macrophage migration in various liver diseases can bind AIF and catalyze DNA breakdown [135]. These data suggest that there is a cross-linkage between some necrotic types of PCD (mPT-driven necrosis, necroptosis) and parthenatosis. This is confirmed by the ability of activated RIPK1 and RIPK3 – markers of necroptosis – to stimulate the enzymatic activity of PARP-1, as well as contribute to ATP depletion and AIF release [136]. The role of partanatosis in liver diseases has not yet been studied; however, it is known that PARP-1 is involved in liver cell death [6].

1.8. Entosis

Entosis is a type of PCD related to cell cannibalism, which occurs in healthy and malignant tissues, involving the engulfment of viable cells by non-phagocytic cells of the same (homotypic) or a different (heterotypic) type [12]. Entosis of epithelial cells usually occurs when the cells lose integrin signaling as a result of detachment from the extracellular matrix. Enthosis is accompanied by cell invasion which depends on the activity of E-cadherin, catenin alpha 1, RhoA and Rho-associated kinase (ROCK). Entosis occurs under conditions of cancer cell competition and downregulation of myosin, a component of cytoplasmic membranes in engulfing cells, which allows penetration into these target cells [137]. Cells displaying high AMRK activity due to a lack of nutrients, succumb to entosis, designed to restore their nutrition [138]. In chronic liver diseases such as chronic hepatitis B and autoimmune hepatitis, entrainment of activated T-lymphocytes by hepatocytes occurs, indicating the involvement of entolysis in liver damage and the development of immune tolerance [139]. Recently, HSCs have been shown to be involved in the entosis of antifibrotic natural killer cells in HBV cirrhotic patients as a potentially novel mechanism of fibrosis enhancement [140].

2. CROSS-REGULATION OF DIFFERENT PCD PATHWAYS

Analysis of the involvement of various forms of PCD in liver diseases shows that separate forms of PCD can participate simultaneously with others in any one pathology and, besides, certain forms of PCD, having common markers with other forms of PCD, participate in formation of various nosological types of diseases. Since different forms of PCD, having different mechanisms, nevertheless cross-regulate each other, it gives the grounds to assume that at least some forms of PCD (ferroptosis, necroptosis, pyroptosis, partanatosis) are intermediate stages of formation of basic forms of PCD, such as apoptosis and mPT-driven necrosis. The best-known mechanisms of cross-regulation of the interaction between different PCD forms in liver diseases are presented in Table 2.

It has also been shown that CypD, an indispensable participant in mPT-driven necrosis, reverses the inhibitory effect of cIAP on RIPK1 to promote necrosome formation to facilitate the necrotic cell death pathway [141]. Activated RIPK3 and MLKL activate NLRP3 inflammasomes [142], and this mechanism promotes a direct link between cell necrosis and inflammation in addition to the existing mechanism of inflammasome activation by DAMP. Caspase-8, an effector of the extrinsic pathway of apoptosis similar to caspase-1, is also capable of activating NLRP3 inflammasome to trigger pro-IL-1β to stimulate inflammatory processes [143].

Apparently, cross-regulation of PCD in the liver is designed to effectively ensure cell death of different phenotypes with different levels of damage. In addition, cross-regulation seems to be designed to promote the formation of the main form of PCD that will dominate in cells at the final stages of the pathological process –

Table 2

Cross-regulation of metabolic pathways in different forms of PCD [6]*

PCD pathway	Effector	Mechanism of Action	Regulated PCD pathway
Apoptosis	CASP8	Inactivates RIPK3	Inactivates Necroptosis
		Inactivates CypD	Inhibits mPT-driven necrosis
		Activates NLRC4 inflammasome	Induces pyroptosis
	CASP3	Activates GSDM-E – regulated pyroptosis	Regulates pyroptosis
	CASP3/ CASP-7	Inactivates GSDMD	Inactivates pyroptosis
mPT-driven necrosis	CypD	Reverses the inhibitory effect of cIAP on RIPK1	Regulates necroptosis
Necroptosis	RIPK1	Inhibits CASP8	Inhibits CASP8-dependent apoptosis
		Stimulates anti-apoptotic activation of NF-kB	Regulates apoptosis
	RIPK1/ RIPK3	Activates PARP-1	Stimulates partanatosis

* for Table 2 legend, see Table 1 legend and the list below. cIAP, cellular inhibitor of apoptosis proteins; GSDME, Gasdermin E; NLRC-4, NOD-like receptor family CARD domain-containing protein 4; NF-kB, Nuclear factor kappa-light-chain-enhancer of activated B cells.

inflammation, fibrosis, cell transformation or even cell recovery with induction of autophagy and regulation of early reversible apoptosis mechanisms. The possibility of reorienting PCD processes towards restorative and regenerative processes in damaged cells is supported by numerous studies on the positive role of optimally selected schemes of postconditioning of ischemically damaged organs used to attenuate ischemic (necrotic) and reperfusion (apoptotic) injury. Postconditioning limits cell necrosis, and the severity of the anti-necrotic effect depends on ischemia time and postconditioning protocol used [144]. Postconditioning also inhibits development of cell apoptosis and enhances autophagy processes in cells. Such restorative processes can be stimulated in the liver not only when optimal postconditioning schemes of an ischemically damaged organ are used, but also when adequate medication and cellular therapy for disorders caused by PCD are applied.

3. WAYS TO REGULATE PCD PROCESSES IN LIVER DISEASES

The analysis of mechanisms of involvement of various forms of PCD in liver diseases allows to outline several ways for their inhibition.

Ability to cross-regulate PCD pathways, preserved in dying liver cells at various diseases, indicates the feasibility of controlled correction of emerging disorders, first of all, primarily with the help of agents whose action is directed on inhibition of effector mechanisms of PCD. Among such remedies, new drugs are known and are undergoing clinical trials: emricane (IDN-6556), a pan-caspase inhibitor for patients with nonalcoholic steatohepatitis with fibrosis F1–F3 or liver cirrhosis; Selonsertib (GS-4997), inhibitor of Apoptosis signal-regulating kinase 1 (ASK-1) for patients with nonalcoholic steatohepatitis and progressive liver cirrhosis; drugs: GSK-2982772 and GSK-2983559, RIPK1 inhibitors for treatment of various chronic inflammatory diseases [6], as well as ferrostatin [125] and Artesunate, ferroptosis regulator with antifibrogenic effect [145]; Montelukast, inhibitor of TNF-α/JNK signaling pathway [146]; DAPT, inhibitor of Notch signaling pathway [147], and others.

With sluggish restorative (regenerative) processes, as well as in the early reversible stages of apoptosis, when the liver cells still retain the ability to autoregulate and independently survive, adaptogens may be effective for the correction of liver failure and restoration of liver cells structure. These include autophagy inducers and regulators of cell apoptosis, promoting activation of metabolic pathways – AMPK and NF-kB and inhibition – mTORC-1-dependent metabolic pathways. It is also advisable to use metabolic inducers with antioxidant and anti-inflammatory activity [148–154] since oxidative stress and inflammation are constant companions of almost all forms of PCD.

Besides drug therapy for chronic (non-oncological) liver diseases, for inhibition of PCD processes and activation of repair processes in damaged liver cells, it is reasonable to develop methods of cellular regeneration therapy, which are based on the use of apoptotically altered donor liver cells and donor bone marrow [155]. These cells produce numerous paracrine factors that act as targeted carriers of the regenerative signal complex – regulators of regenerative processes. So, isolated cultured donor hepatocytes have already found application in the clinic. They are used as the basic element in auxiliary liver support systems, in the perfusion circuit of which the patient's blood (or plasma) continuously comes in contact with isolated donor hepatocytes cultivated in it and is enriched with paracrine factors released by apoptotic donor cells [156]. Isolated donor hepatocytes began to be used also as part of cell-engineered constructs implanted directly into the damaged patient's liver. The ratio of cellular elements (hepatocytes/mesenchymal stem cells) in the implanted cell-engineered constructs was optimized to increase the efficiency of their use [157, 158]. Induction of repair processes in the damaged liver is also performed by application of total RNA from bone marrow cells, which is a nonspecific factor of regulation of repair processes and acts as a carrier of a complex of multiple regenerative signals to the damaged liver cells [159].

CONCLUSION

Analysis of the role of programmed cell death in liver diseases allows us to conclude as follows:

1. Among the known forms of PCD, autophagy, apoptosis and mPT-driven necrosis should be considered the main forms; other forms of PCD (ferroptosis, necroptosis, pyroptosis, partanatosis, entosis) remain insufficiently studied and, apparently, should be considered as intermediate stages of the main forms of PCD (apoptosis and mPT-driven necrosis).
2. Cross-regulation of different forms of PCD in the liver is intended to increase the efficiency of formation of cell death of different phenotypes with different levels of damage, as well as to ensure development of one of the dominant consequences of PCD such as inflammation, fibrosis, cellular transformation or reparative regeneration.
3. Preservation of cross-regulation in different forms of PCD in the liver indicates the possibility of controlled correction of the resulting disorders with the help of drugs and cell technologies. Among the drugs, the promising ones are those that inhibit effector-mediated PCD pathways and have an adaptive effect on liver cells by induction of autophagy, early reversible apoptosis and enhancement of antioxidant and anti-inflammatory activity. Application of cell technologies is based on the use of apoptotic donor

liver and bone marrow cells that produce paracrine regulatory factors, which inhibit PCD and specifically induce reparative regeneration in liver cells.

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