Necrobiology of Liver Cancer: Autophagy and Cellular Senescence 179

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Abstract

Autophagy is a process involved in the maintenance of cell and tissue homeostasis, control of protein composition of cells, aging, senescence, and neoplastic transformation. Autophagy induced by oxidative or hypoxic stress, nutrient deprivation, and DNA damage serves to eliminate altered or misfolded proteins, degrade damaged or superfluous organelles, and get rid of pathogens. There are three types of autophagy, i.e., macroautophagy, microautophagy, and chaperone-mediated autophagy. Macroautophagy transports cargo to lysosomes through the autophagosome, a membrane-bound vesicle. This pathway can interact with apoptosis and necroptosis in a complex manner. Autophagy is also connected with inflammasome function, inflammation, and immunogenic cell death. There are several specific autophagic pathways involving organelles, including mitophagy, pexophagy, lipophagy, and nucleophagy. Autophagy is closely connected with the mechanisms that induce and regulate senescence, a process by which normal cells cease to divide, perceived as aging mechanisms and a cancer barrier.

Introduction

Definitions

Autophagy (from Greek, "eating of self") is an important process of ordered self-degradation that plays a role in various pathophysiologic reactions, including nutrient deprivation, hypoxia, oxidative stress, and DNA damage. In particular, autophagy serves to eliminate altered, aggregated, or misfolded proteins that might damage the cell, degrade damaged organelles, and get rid of intracellular pathogens (reviews: Gozuacik and Kimchi 2004; Yang et al. 2005; Williams et al. 2006; Dengjel et al. 2008; Galluzzi et al. 2008; Esclatine et al. 2009; Dalby et al. 2010; Glick et al. 2010; Klionsky et al. 2010; Mehrpour et al. 2010; Dengjel et al. 2012; Liu et al. 2013). Autophagy can also regulate distinct forms of cell death, such as necroptosis (Ryter et al. 2014). There are three defined types of autophagy, i.e., macroautophagy, microautophagy, and chaperone-mediated autophagy (Feng et al. 2014). All types share the capacity to proteolytically degrade cell components in lysosomes.

Macroautophagy: The Autophagosomal Pathway

Macroautophagy transports cargo to the lysosome through a membrane-bound vesicle, the autophagosome which fuses with the lysosome to form the autolysosome. The biogenesis of an autophagosome starts with ER-or trans-Golgi-derived membrane component, the phagophore, which can engulf cytoplasmic proteins and organelles to become a cargo-loaden autophagosome. In microautophagy, cargo is directly delivered to the lysosome through a lysosomal invagination. In chaperone-mediated autophagy, targeted proteins are translocated through the lysosomal membrane in a complex with chaperones/heat shock proteins recognized by a lysosomal membrane receptor, LAMP-2A/lysosomal-associated membrane protein 2A (review: Glick et al. 2010). Formation of the critical phagophore as an initial cargo-seeking structure is tightly regulated by several signaling pathways.

Autophagosome Biogenesis

Autophagosome biogenesis requires deformation and induction of curvatures in the membranes. This bending activity is mediated by the Bax-binding protein, Bif-1 (endophilin B1), a protein which forms complexes with beclin 1. Bif-1 interacts with beclin 1 via UVRAG (Takahashi et al. 2007). Bif-1 accumulates in punctate foci where it colocalizes with light chain 3 protein, Atg5, and Atg9. Specifically, Bif-1-positive crescent-shaped vesicles expand by fusing with Atg9-positive membranes to complete autophagosome formation (Takahashi et al. 2009). Macroautophagy is regulated by endoplasmic reticulum stress, in that the unfolded protein response/UPR associated with ER stress

and reticulophagy can induce autophagy (Deegan et al. 2013).

Autophagy: Induction and the Autophagosomal Proteome

Autophagy is induced by numerous proteins (the autophagosomal proteome; Becker et al. 2012), some of which are oncogenes, including TGF-beta, Atg4c, beclin 1, Bif-1, BH3-only proteins, DAPK1, tuberous sclerosis complexes, death-associated protein kinase 1, LKB1, PTEN, and UVRAG (Maiuri et al. 2009; Morselli et al. 2009; Park et al. 2009a,b; Suzuki et al. 2010). The autophagic process is initiated by mTOR phosphorylation of the serine/threonine kinase ULK1 (autophagy-initiating kinase ULK1/Unc-51-like kinase 1; Dunlop and Tee 2013). ULK1 kinase is, however, also an mTOR-independent node in a complex kinase network (Bach et al. 2011). The Beclin-1 (Atg6) complex is an important initiation factor for the initial step of autophagosome formation and is directly targeted by signaling pathways that involve mTOR (Cao and Klionsky 2007; Pattingre et al. 2008). Beclin-1, which is a key regulator of autophagy, acts as a haploinsufficient tumor suppressor. Beclin 1 has several interaction partners. In the human phosphatidylinositol 3/PI(3)-kinase class III complex, beclin 1 directly interacts with Barkor (Beclin 1-associated autophagy-related key regulator), a protein that is required for autophagosome formation (Sun et al. 2008). A further mediator of the class III PI(3)kinase complex is Bif-1 (endophilin B1), a protein that interacts with beclin 1 through UVRAG. In response to nutrient deprivation, Bif-1 localizes to autophagosomes where it colocalizes with Atg5 and the microtubule-associated protein light chain 3 (Takahashi et al. 2007). Beclin 1 forms two distinct PI(3)-kinase complexes with Atg14 and UVRAG (Itakura et al. 2008). Beclin-1 interacts with the PI-3 kinase, Vps34/vesicular protein sorting 34, forming a complex which is selectively involved in autophagy. PtdIns3P synthesized by Vsp34 are crucial components for autophagy induction and accumulate in membrane extensions of the ER, structures called omegasomes. Proteins that interact with this complex in an autophagy-promoting manner are ubiquitin-like proteins (Atg12, Atg8, and Atg16L; Noda et al. 2008), Bif-1, UVRAG, Atg14L, and Ambra, while autophagy inhibitors include Rubicon and Bcl-2. Bif-1 is directly involved in phagophore biogenesis. Induction of autophagy requires the ULK1 protein kinase complex, which co-localizes with omegasomes (Karanasios et al. 2013).

The Lysosomal Degradation Pathway of Autophagy

At the end of any autophagic process is the lysosomal degradation pathway, an attractor for macroautophagic (autophagosomal), microautophagic, and chaperone-dependent autophagic processes (Shen and Mizushima 2014). Autophagic pathways and endosome/lysosome biogenesis are closely linked. Atg5, an autophagosomal protein, is required for the biogenesis of late endosomes and lysosomes in an autophagy-independent manner (Peng et al. 2014). The small GTPase Rab 11 plays an important role in the "docking" of autophagosomes to late endosomal compartments. Rab11 shifts from recycling endosomes to autophagosomes in response to autophagy induction via removing Hook, a negative regulator of endosome maturation, from mature endosomes (Szatmari et al. 2014).

In order to reach their degradation compartment, autophagosomes are transported along microtubule tracks of the cytoskeleton to fuse with late endosomes or lysosomes. As in other vesicular transport systems, the small GTPase Rab7 is implicated in autophagosomal transport and fusion. Autophagosomal membranes harbor the lipid PtdIns3P and phosphatidylethanolamine-conjugated Agt8/LC3/GABARAP family proteins. The FYVE and coiled-coil domain containing 1 (FYCO1) binds to both LC3, PtdIns3P and Rab7, and functions as an adaptor linking autophagosomes to microtubule plus end-directing molecular motors. FYCO1 is selectively recruited to autophagosomal membranes via a mechanism

involving a conformational change upon LC3-LIR interaction to expose the FYVE domain for PtdIns3P. The autophagy flux through lysosomes is regulated by DNA damage-regulated autophagy modulator 1/DRAM1 (Zhang et al. 2013). In the course of necrosis, dying cells release HMGB1, a mobility group box q1 protein with immunostimulatory functions. HMGB1 also plays important intranuclear, cytosolic, and extracellular roles in the regulation of autophagy, in that HMGB1 is Beclin 1-binding protein active in autophagy (Kang et al. 2011a). Autophagy-associated release of HMGB1 protects cancer cells from many chemotherapeutical agents, in that extracellular HMGB1 protects cancer cells from apoptosis through transcriptional upregulation of Mcl-1 (Zhan et al. 2012). On the other hand, the danger signaling protein HMGB1 induces a distinct form of cell death which in cancer cells depends on the presence of mitochondria. HMGB1 induces a rapid depletion of mitochondrial DNA, severe damage to the mitochondrial proteome, and the formation of giant mitochondria (Gdynia et al. 2010).

Autophagy and Apoptosis

Autophagy interacts with apoptosis in a complex manner (Booth et al. 2013). Beclin 1 fails to stimulate apoptosis (Boya and Kromer 2009). The antiapoptotic proteins Bcl2-2 and Bcl-xL negatively regulate autophagy by directly binding to beclin 1 (Luo and Rubinsztein 2010). This interaction involves a Bcl-2 homology 3/BH3 domain in beclin 1 (Levine et al. 2008) and can be abolished by ubiquitination of beclin 1 (Kang et al. 2011b). A critical negative regulator of Fas-mediated apoptosis, the Fap-1 protein phosphatase, is degraded by autophagy, providing a further link between apoptosis and autophagy (Joshi and Ryan 2013). The autophagosomal membrane serves as a platform for DISC-mediated caspase-8 activation (Young et al. 2012). On the autophagosome, caspase-8 aggregation is promoted by the p62/sequestosome-1, an atypical protein kinase C-interacting protein that is involved in various signaling pathways (Huang et al. 2013; Zotti et al. 2014). In the autophagic process, p62 directly interacts with Bcl-2 and disrupts the association between Bcl-2 and beclin 1 (Zhou et al. 2013). By its function in autophagosomal function, the scaffold protein p62 also links autophagy with oxidative stress pathways active in cancer, as this protein directly interacts with the ubiquitin ligase adaptor Kelch-like ECH-associated protein1/KEAP1, which results in constitutive activation of the transcription factor NF-E2-related factor 2/NRF2, two proteins involved in a stress response pathway and that are frequently mutated in cancer (Nezis and Stenmark 2012). KREAP1 itself is degraded by autophagy which thus regulates KEAP1 and redox homeostasis in the liver (Taguchi et al. 2012).

Autophagy-Mediated Necroptosis

Autophagy is linked to apoptosis and necroapoptosis in a complex manner. In particular, autophagy plays something as a "compensatory" role in the elimination of neoplastic cells having become resistant to apoptosis, acquired apoptosis resistance being a major element in the development of chemoresistance in therapeutic settings. Autophagy can modulate apoptotic pathways through the degradation of proapoptotic factor versus antiapoptotic factors. There is, e.g., a JNK-mediated autophagy pathway that induces the degradation of antiapoptotic cIAPs, thereby promoting autophagy-mediated necroptosis (RIP1- and RIP3-dependent necrosis). This pathway is dependent on JNK-mediated phosphorylation of Bcl-2 and Bcl-xL and dissociation of Bcl-2 or Bcl-xL from the autophagy factor, Beclin-1. In addition, this pathway involves formation of the ripoptosome that contributes to necroptosis (He et al. 2014).

Autophagy in Hepatocellular Carcinoma

Autophagy plays an important role in pathways of tumor cell elimination, but this mode of tumor suppression predominantly works in early cancer. In established or advanced tumors, autophagy acts as a cytoprotection mechanism to promote cancer

cell survival (Chen and Karantza-Wadsworth 2009; Chen and Debnath 2010; Dalby et al. 2010; Reyjal et al. 2014). Autophagy has a tumor promoter role by suppressing the p53 response, maintaining mitochondrial function, and promoting metabolic homeostasis (Guo et al. 2013). Autophagy also exerts an influence on cancer cells through its effects on stromal cells and immune cells, mainly tumor-associated macrophages/TAMs, acting against tumor cells. Autophagy in cancer-associated fibroblasts promotes tumor cell survival, mediated by induction of hypoxia-induced factor 1alpha (Martinez-Outschoom et al. 2010). Targeting of nuclear factor-kappaB by autophagy is involved in the polarization and activation of HCC-associated TAMs (Chang et al. 2013). Autophagy is a key factor in innate immunity and regulates the production of macrophages at different developmental stages of these cells (Chen et al. 2014).

Similar to normal cells, Beclin-1 plays an important role in autophagy regulation in HCCs. Beclin-1 levels are lower in HCCs than in nonneoplastic liver, suggesting a downregulation of autophagy in HCCs (Shi et al. 2009; Kotsafti et al. 2012). Autophagy in HCCs is stimulated by TGF-beta, associated with accumulation of autophagosomes in HCC cells, conversion of microtubule-associated protein light chain 3 and enhanced degradation rate of long-lived proteins. The induction of autophagy by TGF-beta occurs significantly earlier than the induction of apoptosis (Kiyono et al. 2009). The finding that p62 protein is increased in HCCs suggests that HCCs are autophagy defective (Bao et al. 2014). In HCCs, the autophagy-related marker LCs (light chain 3) predicts prognosis, in that LC3 expression is related with longer time to recurrence and overall survival (Lee et al. 2013). Autophagy enhances HCC progression by activation mitochondrial beta-oxidation, in that autophagy promotes hypoxia-inducible factor-1alpha-mediated proliferation through the maintenance of intracellular ATP linked to an activated mitochondrial beta-oxidation (Toshima et al. 2014). Autophagy is activated in metastatic colonization of HCC, but not in invasion, migration, and detachment of HCC cells (Peng et al. 2013). In HCC cells, inhibition of the Hedgehog signaling pathway induces autophagy via upregulation of the proapoptotic protein, Bnip3 (Wang et al. 2013). HCC cells exposed to endoplasmic reticulum stress revealed a significant accumulation of autophagosomes and increased conversion of LC3-I to LC3-II as well as an increased autophagic flux (Ma et al. 2013). microRNA-375 inhibits autophagy in HCC cells and reduces the viability of these neoplastic ells under hypoxic conditions (Chang et al. 2012).

Autophagy: Connections with Immunity and Inflammation, and Immunogenic Cell Death/ICD

Introduction

Autophagic pathways are closely linked with certain mechanisms that operate in immunity (Yuk and Jo 2013). Nod-like receptors (NLRs), proteins that are cytoplasmic sensors for microbial molecules (cytoplasmic pattern recognition receptors), interact with autophagy-associated proteins (Carneiro and Travassos 2013). This interaction has a broad range of effects, as the various species of NLRs have different functions. NRLRC5 and CIITA regulate antigen presentation, NLRP1, NLRP3, NLRC1, and NLRC4 act in pathogen/damage sensing, and NLRC3, NLRP6, NLRP12, and NLRX1 suppress or modulate inflammatory responses (Lupfer and Kanneganti 2013).

Inflammasomes

NLRs are components of the inflammasome, large multiprotein platforms and guardians of cell and tissue integrity, sensors of metabolic stress, and critical regulators of immune reactions (Lamkanfi and Dixit 2009; Jin and Flavell 2010; Schroder and Tschopp 2010; Gross et al. 2011; Leemans et al. 2011; Haasken and Sutterwala 2013; Tsuchiya and Hara 2014). The central role of inflammasomes in immunity is underlined by the fact that mutations in NLRP3 activity cause severe autoinflammatory disease (Lawlor and Vince 2014). Inflammasome

assembly depends on several NLR family members such as NALPs (pyrin domain-containing NLRs), NAIP, and IPAF.

Inflammasomes as Mediators of Cell Death

Apart from danger signals derived from infectious agents and cancer cells, the NLRP3 inflammasome is activated by reactive oxygen species released from dysfunctional mitochondria (Tschopp 2011), a further link to cell death pathways. Inflammasomes and their activated inflammatory caspases (caspase-1 and caspase-5) are critical mediators of immunity and inflammatory reaction directed against microorganisms and cells expressing neoantigens, including cancer cells (Martinon and Tschopp 2007; Wen et al. 2013). The canonical pathway in inflammasomes involves activation of caspase-1, which in turn results in the release of interleukins 1beta and -18 in response to danger signals. The noncanonical inflammasome pathway is mediated by caspase-11 and leads to release of interleukins 1beta, -18 and -1alpha, and promotes pyroptosis (Vigano and Mortellaro 2013).

Inflammasomes contain proteins that participate in immune mechanisms linked to cell death, including the adapter molecules ASC, IPAF, and cryopyrin/Nalp3 which regulate the inflammatory caspases, caspase-1, and caspase-5. In inflammasomes, activation of caspase-1 results in cleavage and activation of proinflammatory cytokines (Mariathasan 2007; Martinon et al. 2007). In HCCs, caspase-1 activated by hypoxia induces the release of IL-1beta and IL-18 which in turn promote invasion and metastasis (Yan et al. 2012). On the other hand, inflammasomes mediate pyroptotic and apoptotic cell death, in that active caspase-1 mediates pyroptosis through an unknown mechanism, and activated inflammasomes can recruit procaspase-8, thus initiating apoptosis (Aachoui et al. 2013).

It is expected that damage-sensing NLRs play a role in cancer cells undergoing injury, including liver cancer cells, and pave the track for autophagic cell elimination. Autophagy produces a link between tumor cell death and immunity (immunogenic tumor cell death, ICD) in that damage-associated molecular patterns/DAMPs enhance autophagy (Hou et al. 2013). DAMPs mediate immunogenic features of this form of cell death in their function as pattern recognition receptors that are in part emitted actively by cells undergoing ICD (Krysko et al. 2013). Proteins of the NLRP3 inflammasome, which orchestrates mechanisms of innate immunity and adaptive immune responses, are expressed in HCC cells as a function of tumor progression (Wei et al. 2014) and interact with proteins of the autophagic pathways. Reactive oxygen species escaping from injured mitochondria induce lysosomal damage in an NLRP3-dependent manner (Heid et al. 2013) and may thus modify lysosome-dependent autophagy. As mentioned above, the noncanonical inflammasome pathway related to caspase-11 activation promotes pyroptosis (Vigano and Mortellaro 2013).

Resistance to Apoptosis and Autophagy

Resistance to apoptosis is a key feature of many malignant neoplasms and is a phenomenon involved in cancer progression and treatment failure. Failure of apoptotic cell death can be circumvented by autophagy-related mechanisms that lead to elimination of cancer cells. Injured or stressed cells can release damage-associated molecular patterns/DAMps. Release of DAMP molecules contributes to autophagy induction and hence to cell decay. Autophagy in turn regulates DAMP release and degradation (Hou et al. 2013).

Organellophagy

There are numerous complex autophagic mechanisms that can elicit degradation and controlled elimination of damaged or superfluous organelles and cell nuclei. These processes are summarized under the term organellophagy (Table 1).

Table 1 Types of organellophagy

Type of phagy	Target of phagy
Mitophagy	Mitochondria
Pexophagy	Peroxisomes
Reticulophagy	Endoplasmic reticulum
Ribophagy	Ribosomes
Lipophagy	Lipid droplets (lipid organelles)
Ciliophagy	Cilia and associated structures
Nucleophagy	Nucleus
Nucleolophagy	Nucleolus

Mitophagy

Mitophagy as a Central Feature of Autophagy

In the setting of autophagic processes, mitophagy is a particularly important phenomenon. Mitophagy is the selective autophagic degradation of damaged and/or superfluous mitochondria and is regarded as an essential process for mitochondrial quality and quality control (reviews: Mijaljica et al. 2010a; Novak and Dikic 2011; Rambold and Lippincott-Schwartz 2011; Wang and Klionsky 2011; Hirota et al. 2012; May et al. 2012; Novak 2012; Okamoto and Kondo-Okamoto 2012). Mitochondria with their relatively small genome, their successive cycles of fission and fusion, and their exposition to oxidative stress are prone to damage, requiring a potent mechanism to eliminate "dangerously altered" mitochondria. There is evidence that mitophagy is an instrument not only to sense damaged mitochondria and eliminate them but that also the overall oxygen radical burden is sensed and the signal transmitted in a systematic or episodal removal of mitochondria (review: Gottlieb and Carreira 2010).

Mitophagy is an important mechanism to protect cells from the deleterious effects of damaged mitochondria, in particular apoptosis. Mitophagy can also mitigate an additional catastrophic event. Severe mitochondrial stress can cause the pathologic opening of the mitochondrial permeability transition pore(MPTP), followed by transient but massive release of calcium and radical oxygen species/ROS. This release reaction can trigger other mitochondria to undergo the same crisis, finally resulting in the activation of calcium-dependent proteases such as calpain, lipases (cPLA2), and ROS-activated iPLA2, steps that cause necrosis (reviews: Gottlieb and Carreira 2010). Mitophagy is the major instrument of the cell to regulate mitochondrial number and mass, and there is a regulatory cross talk between mitochondrial function and dysfunction, and mitochondrial abundance (Michel et al. 2011), suggesting the presence of a mitochondrial abundance sensor. Mitophagy belongs to the group of autophagic processes, which also comprise pexophagy, ER-phagy, ribophagy, golgiphagy, and nucleophagy. Autophagy, as discussed in a separate chapter, serves removing of altered proteins and dysfunctional organelles.

Mechanisms of Mitophagy

Injury of mitochondrial DNA, e.g., mtDNA mutations, can result in mitophagy (Gilkerson et al. 2012; de Vries et al. 2012). Mutations in the gene for ATPase type 13A2 (ATP13A2), involved in autosomal-recessive Parkinsonism (Kufor-Rakeb syndrome) are associated with a higher frequency of mtDNA lesions, increased oxygen consumption rates, fragmentation of the mitochondrial network, and mitophagy (Grünewald et al. 2012). Oxygen damage via reactive oxygen species (ROS) as potential mitochondrial damaging agents can normally be neutralized within the mitochondria through enzymatic activity. In case this system is overcharged, mitochondrial damage and mitophagy can occur (Lee et al. 2012). Elimination of mitochondria being overcharged with oxidized proteins via mitophagy is a mechanism suppressing cell damage by mitochondrial oxidative products (Kurihara et al. 2012). But also hypoxia causes mitochondrial injury leading to mitophagy.

PINK1-and Parkin-Mediated Mitophagy

The Parkinson disease-related proteins PINK1 (PTEN-induced kinase 1, a mitochondrially

localized serine/threonine kinase) and Parkin (PARK2, a cytosolically localized E3 ubiquitin ligase) are guardians of mitochondrial fidelity and are essential for targeting mitochondria for mitophagy (Matsuda and Tanaka 2010; Huang et al. 2011; Kane and Youle 2011; Springer and Kahle 2011; Youle and Narendra 2011; Jin and Youle 2012). The mitochondrial turnover of PINK1 and Parkin is tightly controlled. The mitochondrial intramembrane protease PARL cleaves human PINK1 within its conserved membrane anchor. Mature PINK1 is then free to be released into the cytosol or the mitochondrial intermembrane space. In PINK1-dependent mitophagy and following uncoupling of the outer mitochondrial membrane potential, the canonical import of PINK1 and PARL-catalyzed processing is blocked, leading to the accumulation of the PINK1 precursor. Accumulation of PINK1 precursor and its targeting to the outer mitochondrial membrane triggers mitophagy (Meissner et al. 2011). Generally, loss of PINK1 function causes oxidative stress via production of ROS and mitochondrial damage (Cui et al. 2011). Endogenous PINK1 forms a 700 kDa complex with the translocase of the outer membrane (TOM) on depolarized mitochondria. Association of PINK1 with TOM complex allows rapid reimport of PINk1 to rescue depolarized mitochondria from mitophagy (Lazarou et al. 2012). In Parkin-dependent mitophagy, PINK1, which is located in the mitochondrial outer membrane, recruits Parkin from the cytosol to the mitochondria as a first step leading autophagous destruction of the organelle. Complexes containing upstream Atg proteins (autophagy-related proteins), including ULK1 (the mammalian homologue of Agt1), Atg12, Atg14, DFCP1, WIPI-1, and Atg16L1, can associate with depolarized mitochondria. Atg9A and ULK1 structures are also recruited to damaged mitochondria as well as to the autophagosome formation site in the earliest steps of mitophagy, while the autophagosomal LC3 (MT-associated protein 1 light chain 3) family of proteins is involved in later stages of mitophagy (Itakura et al. 2012). LC3 interacts with microtubule-associated protein 1S/MAP1S bridging autophagic components with the microtubular system (Xie et al. 2011). In human endothelial cells, targeted mitochondrial damage upregulated the autophagy factors LC3B, Atg5, and Atg12, and this upregulation resulted in an improved mitochondrial membrane potential, enhanced ATP production, and an antiapoptotic effect (Mai et al. 2012). One of the effectors of the mitophagic cascade, Ulk1, is phosphorylated by AMP-activated protein kinase connecting energy sensing to mitophagy (Egan et al. 2011) and is regulated by the Hsp90-Cdc37 chaperone complex (Joo et al. 2011).

Parkin itself as an ubiquitin E3 ligase ubiquitinates intracellular proteins and via this mechanism induces clearance of cellular molecular debris and of organelles, including mitophagy, whereby ubiquitinylated outer mitochondrial membrane proteins, including mitofusins 1 and 2, are targeted for proteasomal degradation (Gegg et al. 2010; Chan and Chan 2011; Karbowski and Youle 2011; Khandelwal et al. 2011). In the pathway of mitophagy, Parkin binds to Ambra1 (activating molecule in beclin 1-regulated autophagy), a protein that promotes autophagy (Van Humbeeck et al. 2011). PINK1 and Parkin also exert important effects on mitochondrial motility. PINk1 phosphorylates Miro, a component of the primary motor/adaptor complex that anchors kinesin to the mitochondrial surface. The phosphorylation of Miro activates proteasomal degradation of Miro in a Parkin-dependent manner. By thus stopping mitochondria in their tracks, the PINK1/Parkin pathway may quarantine damaged mitochondria prior to their mitophagic clearance (Wang et al. 2011).

Execution of Mitophagic Pathways

Bnip3 (Nip3-like protein X; NIX), an atypical BH3-only protein causing mitochondrial dysfunction and cell death, can under certain circumstances also protect against cell death by inducing mitophagy. Bnip3 activation is a pro-mitophagic signal, and this pathway involves impairment of mitochondrial oxidative phosphorylation and is independent of apoptosis (Thomas et al. 2011). This response requires homodimerization of Bnip3, and clearance of

mitochondria is mediated in part via binding of Bnip3 to the microtubule-associated protein 1 light chain 3 (LC3) on the autophagosome (Hanna et al. 2012). On the other hand, Bnip3 mediated mitophagy is inhibited by activation of the p53-TIGAR axis (Hoshino et al. 2012).

Mdivi (mitochondrial division inhibitor) attenuates mitochondrial division in cells by selectively inhibiting the mitochondrial division dynamin-related protein (Cassidy-Stone et al. 2008). Dynamin-related protein 1 (Drp1) docks at mitochondria, regulating their positioning and activity (Baixauli et al. 2011). Mdivi is also a mitophagy inhibitor that operates via inhibition of Drp1 (Park et al. 2011; Givvimani et al. 2012). FUNDC1, a mitochondrial outer membrane protein, is a receptor for hypoxia-induced mitophagy. Hypoxia leads to dephosphorylation of FUNDC1 and enhances its interaction with LC3 for selective mitophagy (Liu et al. 2012). Following mitophagy, organelle remnants can enter a lysosomal degradation pathway, whereby a distinct system of mitochondria-derived vesicles (MDVs) generates the contact with lysosomes to deliver degradable cargo (Soubannier et al. 2012). BECN1s, a short splice variant of BECN1, function in mitophagy (Cheng et al. 2015).

Other Factors Regulating Mitophagy

The ATM gene mutated in ataxia telangiectasia plays a role in mitochondrial homeostasis. Atm-deficient thymocytes in mice show an altered mitochondrial homeostasis, suggesting that ATM plays a role in regulating mitophagy (Valentin-Vega and Kastan 2012). Melatonin, a highly efficient antioxidant, is involved in the control of mitophagy (Coto-Montes et al. 2012). Mitophagy is also mediated by the C2-domain containing protein, SMURF1 (Orvedahl et al. 2011).

Sequelae of Inhibited Mitophagy

It has been shown that inhibition or blockade of mitophagy leads to the accumulation of damaged, ROS-generating mitochondria, which in turn activate the NLRP3 inflammasome, a pathway positively regulated by reactive oxygen species/ROS. The NLR3P inflammasome acts as a sensor of damaged mitochondria, explaining the frequent association of mitochondrial damage and inflammatory diseases (Zhou et al. 2011).

Mitophagy in Carcinogenic and Hepatocarcinogenic pathways

HBV infection, a major driving force for hepatocarcinogenesis, disrupts mitochondrial dynamics in that it induces mitochondrial fission and mitophagy, two processes that attenuate apoptosis, while perturbation of mitophagy by silencing of Parkin enhances apoptotic signaling (Kim et al. 2013). This is a mechanism that can promote liver cell expansion in the setting of carcinogenic pathways. Generally, mitochondrial dynamics regulated by large GTPase family proteins is functionally linked with apoptosis (Otera and Mihara 2012). Autophagy triggered by oncogenic K-Ras mediates functional loss of mitochondria and mitophagy during cell transformation and early tumorigenesis, and mitophagy in this situation is a process that overcomes the cellular energy deficit triggered by insufficient glucose availability (Kim et al. 2011).

Pexophagy

Pexophagy is defined as the process of specific autophagic degradation and elimination of peroxisomes, organelles which are present in hundreds to thousands in mammalian cells (review: Till et al. 2012). As peroxisomes hold an important position in the metabolome of cells, their number and function is tightly controlled by environmental and genetic conditions. Metabolic situations requiring increasing levels of peroxisome functions lead to peroxisome proliferation and to an augmentation of peroxisomal biomass. Following such metabolic situations with a downregulation of peroxisomal function, superfluous peroxisomes are degraded by autophagy to again reach the baseline level of peroxisome numbers and mass.

In peroxisome autophagy, both macro- and microautophagy are involved (macropexophagy and micropexophagy). In the course of macropexophagy, peroxisomes are individually sequestered by membranes, resulting in pexophagosomes that fuse with degradation vacuoles. In micropexophagy, clusters of peroxisomes are enclosed within vacuolar membrane protrusions, or are integrated into a specific membrane complex, the micropexophagy-specific membrane apparatus/MIPA (Sakai et al. 2006).

In mammalian cells, the following main pathways of peroxisome elimination are recognized: the Lon protease system (Lon is a chaperone-like ATP-dependent protease involved in the degradation of misfolded and unassembled peroxisomal proteins); 15-lipoxygenase-mediated autolysis; and pexophagy. Pexophagy (in a process resembling macropexophagy in yeast) accounts for 70–80 % of peroxisome clearance in mammalian liver (Yokota and Dariush Fahimi 2009). In a hypothetical model of mammalian cell pexophagy, processed and lapidated LC3 (LC3-II) is integrated into the expanding phagophore membrane. LC3 may also mediate the association of the phagophore membrane with cytoskeletal microtubules through the Rab7 effector FYCO1 getting into contact with kinesin. Targeting of the LC3-labeled phagophore membrane to the peroxisome involves p62-mediated detection of ubiquitin motifs on peroxisomal membrane proteins, or by direct binding of LC3 to a distinct peroxisomal protein, Pex14 (review: Till et al. 2012).

Reticulophagy (ER-phagy) and Ribophagy

The homeostasis of the endoplasmic reticulum (ER), in particular its remodeling, is mediated by a distinct reaction called the unfolded protein response (UPR). In the course of a cell's life, numerous components of the cell body, including organelles, undergo a cycle of production and degradation. In cells, activation of UPR induces a distinct type of macroautophagy characterized by the elimination of ER elements, a process called ER-phagy, in analogy to pexophagy or mitophagy (Bernales et al. 2007; Cebollero et al. 2012). Reticulophagy is a specific form of starvation-induced autophagy. ER-phagosomes use membranes derived from ER itself, suggesting that ER can serve as a membrane source for autophagosome biogenesis. ER stress is characterized by a marked expansion of membrane compartments that contain unfolded proteins which may interfere with cell functions and induced cell injury. ER-phagy may serve to eliminate ER compartments with their damaging cargo. ER-phagy might, however, also prepare and deliver modified signaling lipoproteins in cancer cells, signal substances that can become cargo of exosomes.

In the setting of autophagy, the autophagic process can also selectively engulf sub-organellar structures, including ribosomes, a process termed ribophagy (Cebollero et al. 2012). Ribosomes are detectable within autophagosomes of normal mammalian cells and tumor cells, and ribosomal degradation via ribophagy displays distinct dynamics (Kristensen et al. 2008).

Lipophagy

Lipophagy, the process of elimination and degradation of cellular lipid droplets plays an important role in the reversion of hepatic steatosis, and probably also in lipid droplet turnover in steatotic hepatocytes, HCCs, and other lipid-rich liver tumors (Weidberg et al. 2009; Beller et al. 2010; Noguchi et al. 2011; Singh and Cuervo 2012; Christian et al. 2013). Lipophagy is a form of organellophagy because lipid "droplets" are now known to be complex organelles. Lipid droplets are heterogeneous and dynamic organelles with a complex and specific proteome, regulated assembly and maintenance, and controlled turnover (Digel et al. 2010; Hashemi and Goodman 2015). Lipophagy is one pathway to regulate lipid stores in several cell types (Liu and Czaja 2013; Carmona-Gutierrez et al. 2015). Except adipocytes and hepatocytes with macrovesicular steatosis, lipid droplets are small and mobile and interact with other organelles, including lysosomes,

processes mediated by Ras proteins (in particular Rab18), regulators of membrane traffic and caveolin, a membrane protein that provides a functional link between cell surface and lipid droplets (Martin et al. 2005; Murphy et al. 2009). During lipophagy in HCC cells, the small GTPase Rab7 is markedly activated, resulting in trafficking of multivesicular bodies and lysosomes to the cell surface to form a lipophagic synapse (Schroeder et al. 2015). Lipid droplets have been identified as a substrate for macroautophagy, whereby lipid droplets are sequestered in autophagosomes followed by fusion with lysosomes, where droplet constituents are degraded by lysosomal enzymes (Singh et al. 2009; Dong and Czaja 2011; Settembre and Ballabio 2014). In lipophagy, the large GTPase DNM2/dynamin 2 is involved by facilitating the scission of nascent lysosomes from autolysosomal tubules during autophagy (Schulze et al. 2013; Schulze and McNiven 2014). Lysosomes engaged in lipophagic processes can undergo signal exchange with the nucleus, where nutrient-sensing receptors are present to coordinate autophagy (Settembre et al. 2013; Lee et al. 2014).

Ciliophagy

Autophagy possibly regulates the biogenesis and turnover of cilia and associated cytoskeletal structures by a mechanism called ciliophagy. In addition, autophagy is involved in a pathway near the basal body that regulates cilium assembly (Pampliega et al. 2013, reviews: Pierce and Nachury 2013; Wrighton 2013). LC3, a protein of the autophagosomal membrane, interacts with a protein of the centriolar satellite, OFD1 (oral-facial-digital syndrome 1), and removes this protein from the satellite (Tang et al. 2013, 2014). Autophagy can also result in cilium shortening by a mechanism involving histone deacetylase 6 (Cloonan et al. 2014). Such mechanisms affect the sensing capability of cells, as the cilium is a major factor controlling cell polarity and shape, and is a sensor for cell position within a population. Ciliophagy may, therefore, play an important role in cancer.

Nucleophagy

Introduction

In normal and neoplastic cells, processes are active that act to repair nuclear damage through both repair of maintained nuclei and the coordinated removal of damaged nonfunctional nuclear components. Parts of the nucleus or the entire nucleus can be specifically degraded by an autophagic process termed nucleophagy. Degradation of entire nuclei was observed in murine seminal vesicle epithelial cells (Kovacs et al. 2000). In human liver cells, sequestration of mitotic phase chromosomes in autophagosomes was found (Sit et al. 1996). Senescent keratinocytes die through massive degradation of their nuclei (Gosselin et al. 2009). Dying senescent keratinocytes acquired a particular intracellular organization, whereby a cytokeratin network emerged and partitioned the cell into a cortical domain devoid of organelles and a central core domain containing a high number of autophagic vacuoles, mitochondria, and the nucleus. In muscle cell nuclei of patients with laminopathies caused by mutations of the genes encoding A-type lamins and emerin, perinuclear vacuoles are seen, that are sometimes larger than the nucleus. These vacuoles are autophagosomes/autolysosomes containing debris and myelin figures caused by the degradation of damaged or partially extruded nuclei. In the area of nuclear membrane interfacing with autophagosomes, accumulation of nuclear envelope proteins takes place, suggesting that nuclear autophagy/nucleophagy could contribute to the rapid repair of the nuclear membrane (Park et al. 2009a).

Mechanisms of Nucleophagy

In yeast cells, where nucleophagy has been studied in great detail, piecemeal microautophagy of the nucleus or nucleophagy (micronucleophagy) requires a direct interaction of the nuclear membrane with that of the fungal lytic compartment, the vacuole. During yeast micronucleophagy, the nuclear membrane as a dynamic structure

undergoes marked reorganization (Park et al. 2009a; Mijaljica et al. 2010b; Mijaljica and Devenish 2013). In Saccharomyces, starvation stress is followed by nuclear damage, with formation of nucleus-vacuole junctions through interactions between Vas8 in the vacuole membrane and Nvj in the perinuclear ER. Vesicles containing part of the nucleus emanate from these junction sites and finally pinch off into invaginations of the vacuole (Kvam and Goldfarb 2007; Dawaliby and Mayer 2010). This process has been termed piecemeal microautophagy of the nucleus, or PMN, a process that requires a number of ATG genes and the Ygr223c gene known to be involved in macroautophagy in yeast (Kvam and Goldfarb 2007; Krick et al. 2008, 2009; Nair et al. 2010). Micronucleophagy is a mechanism to protect against chromosomal instability (Boya and Codogno 2012).

Nucleophagy in Cancer Cells

Micronuclei, which arise as a result of deficient bipolar chromosome sequestration in cells with cell cycle perturbations, can be removed by autophagy/nucleophagy, detectable by ultrastructural analysis, and the presence of autophagy-associated factors (Rello-Varona et al. 2012). Micronuclei as such are discussed in a separate chapter.

Phagy by Multicellular Components: Angiophagy and Cancerophagy

In angiophagy, endothelial lamellipodia surround thrombotic/embolic material within hours of occlusion. This important mechanism markedly reduces hemodynamic washout and tissue plasminogen activator-mediated fibrinolysis. Within days, the thromboembolic material is completely engulfed by endothelium and extravasated into perivascular space, causing reconstitution of blood flow (Grutzendler et al. 2014). We anticipate that angiophagy in cancer tissue plays a role in the delivery of growth factors and angiogenic factors stored in thrombotic material to cancer tissue. Also circulating signal substances, microRNAs and exosomes may be transported by angiophagic endothelial pockets into the extravascular space of tumor tissue.

Senescence

Cellular senescence denotes a growth-arrest program by which cells prevent uncontrolled cell proliferation and thus limit the lifespan of cell populations. Initiating events of cellular senescence mainly comprise genomic damage, telomere shortening, epigenomic damage, deregulated mitogenic and proliferation-associated signals, and the activation of tumor suppressors (reviews: Sharpless and DePinho 2005; Shay and Wright 2005; d'Adda di Fagagna 2008; Chandeck and Mooi 2010; Campisi 2013; Ivanov et al. 2013; Abdelmohsen and Gorospe 2015; Mar et al. 2015). In cancerogenic pathways, senescence mechanisms are canceled, an effect counteracted by elements of a senescence-messaging secretome that limits the expansion of early neoplastic cells (Schmitt 2003; Dimri 2005; Hornsby 2007; Prieur and Peeper 2008; Kuilman and Pepper 2009; Collado and Serrano 2010; Serrano 2010; Byun et al. 2015; Roos et al. 2016). Normal cells chiefly senescence via the mechanism of replicative senescence. In this process, progressive loss of telomeres associated with DNA double-strand breaks is followed by a DNA damage response (DDR). Part of cancer cells circumvent this senescence reaction by persistent telomerase activity (Xu et al. 2015), whereas other cancer cells are subject to telomere dysfunction and are thus vulnerable to senescence mechanisms. Sensing of intrinsic DNA damage and the subsequent induction of cellular senescence have been implicated as an important barrier against malignant transformation and the development of cancers. On the other hand, senescence is, through the inflammasome platform (see above), associated with inflammation, which in turn promotes cancerogenesis (reviews: Pribluda et al. 2013; Lasry and Ben-Neriah 2015).

Senescence is closely connected with autophagy. Oncogene hyperactivation induces

autophagy to establish a permanent proliferative arrest (Galluzzi et al. 2016). Autophagy affects nuclear and nuclear lamina structure and via these mechanisms exerts an influence on cellular senescence. Loss and elimination of lamin B1, an important component of the nuclear lamina, is a typical feature of senescence (Freund et al. 2012; Dou et al. 2015), and this depletion in senescent cells triggers a large-scale change in gene expression and chromatin landscape (Shah et al. 2013). In senescence, the autophagy-lysosomal pathway causes processing of chromatin contributing to the stability of cellular senescence (Adams 2007; Funayama and Ishikawa 2007; Corpet and Stucki 2014; Ivanov et al. 2013). Autophagy also maintains stemness by preventing senescence (Garcia-Prat et al. 2016).

Neosis: A Pathway to Circumvent Senescence

Neosis is defined as a novel form of cell division which represents a mode of escape of cells from senescence and involved in neoplastic transformation and cancer progression. The process is one of those that are studied to explain several paradoxes concerning current concepts of cancerogenesis (review: Baker and Kramer 2007). Neosis is characterized by polyploidy giant cells which, before they die, give rise to several cells with viable genomes via nuclear budding and asymmetric cytokinesis. It is a parasexual somatic reductive cell division characterized by DNA damage-induced senescence/mitotic crisis and polyploidization; generation of aneuploid daughter cells through nuclear budding; asymmetric cytokinesis and cellularization conferring extended, but limited mitotic life span to the offspring; and is repeated several times to transiently display stem cell properties and eventually neoplastic properties. The most important event of neosis seems to be the generation of mitotically viable daughter genomes after epigenetic modulation from the nonviable polyploidy genome of the so-called neosis mother cell/NMC (Sundaram et al. 2004; Rajaraman et al. 2005, 2006; reviews: Erenpreisa and Cragg 2007; Wheatley 2010). Neosis is a process whereby p53 function-deficient tumor cells undergo self-renewal after genotoxic damage via senescing endopolyploid tumor cells/ETCs. ETCs show autophagic degradation and exhibit extrusion of DNA, and during these conditions, self-renewal transcription factors are activated. ETCs restoring after failed multipolar mitosis undergo subnuclei differentiation, and surviving subnuclei sequester nascent cytoplasm to form subcells. These preformed paradiploid subcells then become released from their linking chromosome bridges through autophagy and begin cell division (neotic ETCs; Erenpreisa et al. 2011). Neosis is thought to play a significant role in carcinogenesis pathways and the development of chemoresistance (Navolanic et al. 2004). Neosis may also operate in syncytia formed in the setting of the formation of unstable syncytia generated by cell fusion between tumor cells and normal cells (Parris 2005). In case acquired genotoxic DNA damage cannot be compensated, it is known that progression through mitosis following DNA damage initiates a p53-and caspase-independent cell death response (Varmark et al. 2009).

Netosis/ETosis: Netting Neutrophils and NETotic Cell Functions That Can Trap Cancer Cells?

In the extracellular space, neutrophils can generate DNA-containing fibrils forming a network, termed neutrophil extracellular traps (NETs; Brinkmann et al. 2010; Remijsen et al. 2011b). This process is termed NETosis or, more recently, ETosis, meaning death with release of extracellular traps/ETs (Guimaraes-Costa et al. 2012). NETs can trap microorganisms (bacteria, fungi), unicellular parasites, and host cells (macrophages, eosinophils, mast cells) followed by their phagocytosis-independent killing while minimizing injury to host cells. NETs can release modified antigens and DNA and play an important role in the regulation of innate immunity and modulation of autoimmunity, specifically in systemic lupus erythematodes (Carmona-Rivera and Kaplan 2014). NET is considered to be the missing link

between cell death and autoimmune disorders (Bouts et al. 2012; Darrah and Andrade 2013; Mesa and Vasquez 2013). Ultrastructurally, NET manifests as fibrillar lattice whereby individual NET fibers consist of DNA filaments and associated globular protein domains, together forming threads with a diameter of 50 nm. These threads can associate to form much thicker and longer elements. In the course of NETosis, neutrophil nuclei lose their shape, and the euchromatin and heterochromatin homogenize, followed by disintegration of the nuclear membrane and granule membranes, so that the NET components can mix (Fuchs et al. 2007). The pathogenesis of NET formation involves a classical step in neutrophil shape change, i.e., activation of protein kinase C by its physiological activator, diacyl glycerols or by phorbol esters, or interleukin-8, causing granule release of release of chromatin to form a compound extracellular network. NET formation also requires both autophagy and superoxide generation (Remijsen et al. 2011a). The mTOR pathway has a pivotal role in NET formation via regulation of autophagy (Itakura and McCarty 2013). NETs contain bacteriocidic proteins bound to DNA (histones, neutrophil elastase), proteins from azurophilic granules (myeloperoxidase, cathepsin G), specific neutrophil granules (lactoferrin), tertiary granules (gelatinase), and DNA that can be delivered to extracellular compartments. The release of these molecules from NETs requires reactive oxygen species/ROS, which trigger the dissociation of neutrophil elastase from a membrane-associated complex into the cytosol, where it activates its proteolytic activity in a myeloperoxidase-dependent manner. Activated neutrophil elastase in the cytosol binds and degrades actin to arrest actin dynamics (Metzler et al. 2014). Aggregated NETs promote the resolution of neutrophil-mediated inflammation by degrading cytokines and chemokines and disrupting neutrophil recruitment and activation (Schauer et al. 2014). The fate of NETs is not yet clarified. However, the extracellular DNA in NETs can associate with proteins, taken up by cells, and stimulate intracellular DNA sensors, including Toll-like receptor 9, to activate DAMPs/pattern recognition molecules (Pisetsky 2012). This is a major pathway linking nuclear components with chromatin-induced immunity (Brinkmann and Zychlinsky 2012).

A special form of NET is intravascular NET, also occurring in the liver and specifically in liver sinusoids and tumor vessels. Intravascular NET is closely associated by thrombosis, and both NET and pathologic thrombosis are regulated by peptidylarginine deiminase 4, an enzyme that mediates chromatin decondensation (Martinod and Wagner 2014). Extracellular histones released from NETs can themselves induce thrombosis and can trigger innate immunity by activating Toll-like receptors and the NLRP3 inflammasome (Allam et al. 2014). Intravascular NET formation is a controlled process in which platelets that have sensed circulating microbes via their TLR4 attach to neutrophils and activate them to generate NETs. This pathway is rapid and does not lead to neutrophil cell death. NETosis associated thrombosis plays a significant role in cancer growth and spread (Demers and Wagner 2014), as it influences homing of cancer cells in thrombotic niches and facilitates spread along platelet- and coagulation factor-containing tracks. NETs can also promote the differentiation and function of fibroblasts (Chrysanthopoulou et al. 2014) and may therefore participate in the generation of a cancer stromal niche.

Roles of Apoptosis and Non-apoptotic Cell Death in Cell Competition: Losers and Winners in Cancerogenesis

In a novel concept of the cellular interactome, termed cell competition, there are winner cells that identify and eliminate viable cells from an expanding cell population without engulfment. According to this concept of "cell war," the demise of loser cells caused by winner cells involves apoptosis of suboptimal or superfluous cells. Killed loser cells are subsequently eliminated by the phagocyte system (Tamori and Deng 2011; Lolo et al. 2012, 2013; Vivarelli et al. 2012). Cell competition may be involved in cellular cooperation in early tumor progression (Krepkin and Costa 2011). The mechanism of cell competition seems to play a role in the

generation of so-called cancerization fields, involving a competition between wild-type cells and mutated preneoplastic or neoplastic cells (Rhiner and Moreno 2009). In the cancerization field, a battle is thought to take place between less well-adapted cells (the losers) and best-adapted cells (winners). For this Darwinian-type model of cancerogenesis, a mechanism of cell-to-cell communication during cell competition has been proposed and termed, the "flower code," due to the involvement of the Drosophila cell membrane protein Flower/Fw conserved in multicellular animals and required to label cells as "winners" or "losers" (Rhiner et al. 2010; Casas-Tinto et al. 2011).

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