Lysosomes as Oxidative Targets for Cancer Therapy

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Lysosomes are membrane-bound vesicles that contain hydrolases for the degradation and recycling of essential nutrients to maintain homeostasis within cells. Cancer cells have increased lysosomal function to proliferate, metabolize, and adapt to stressful environments. This has made cancer cells susceptible to lysosomal membrane permeabilization (LMP). There are many factors that mediate LMP such as Bcl-2 family member, p53; sphingosine; and oxidative stress which are often altered in cancer. Upon lysosomal disruption, reactive oxygen species (ROS) levels increase leading to lipid peroxidation, mitochondrial dysfunction, autophagy, and reactive iron. Cathepsins are also released causing degradation of macromolecules and cellular structures. This ultimately kills the cancer cell through different types of cell death (apoptosis, autosis, or ferroptosis). In this review, we will explore the contributions lysosomes play in inducing cell death, how this is regulated by ROS in cancer, and how lysosomotropic agents might be utilized to treat cancers.

1. Introduction

Lysosomes are membrane-enclosed vesicles that contain at least 60 hydrolases within an acidic environment. These hydrolases, which include the cathepsin family of proteases, are responsible for degradation, recycling, and disposal of cellular macromolecules [1]. Lysosomes are often termed the garbage disposal of the cell, but as our knowledge and understanding increase, the roles lysosomes play in other cellular functions expand [2]. The lysosomal degradation pathway regulates a variety of cellular functions such as autophagy, endocytosis, and phagocytosis to maintain cellular homeostasis [1]. In addition, this pathway directly or indirectly regulates cell signaling, metabolism, and degradation of protein aggregates and damaged organelles [3–5]. When the degradative pathway is dysregulated, diseases such as cancer can progress. This makes lysosomes a potential target for cancer therapy.

2. Lysosomal Biology

Lysosomes are the most acidic vesicles within the cell. This acidic pH is maintained by the action of a proton pump which hydrolyzes ATP to ADP in order to pump an H+ ion into the lumen of the lysosome [6]. The lysosomal membrane consists of a lipid bilayer and membrane proteins. The most abundant lysosomal membrane proteins are lysosome-associated membrane proteins 1 and 2 (LAMP-1 and LAMP-2). The inner lumen of these proteins is highly glycosylated and protects the lysosomal membrane from the digestive enzymes [7, 8]. These enzymes can digest DNA, RNA, sugars, lipids, and proteins. Among these enzymes is the diverse cathepsin protease family. Cathepsins A and G are serine proteases, meaning that their active site contains a vital serine. Cathepsins B, C, F, H, K, L, O, S, V, X, and W are cysteine proteases. Cathepsins D and E are aspartic proteases. Cysteine cathepsins are the most stable and active at an acidic
shown to be an e
Lysosomal membrane permeabilization (LMP) has been
to increase lysosomal biogenesis [14, 17] and alter cellular
invasion [16]. Despite the ubiquitous nature of lysosomes
of cathepsin B has been associated with increased cancer
microenvironment [4, 14, 15]. Indeed, increased expression
liferation and survive under stress condition in the
radation and recycling macromolecules to maintain cell pro-
nis of lysosomes to maintain homeostasis by the increased deg-
metabolism. Altered sphingolipid metabolism has been found in
many cancers [20–22]. Different cancer cell types overexpress sphingosine kinase (SK) [23–25] and downregulate
acidic sphingomyelinase (ASM) [19]. These changes affect
lysosomal membrane structure and function in cancer cells.

Lysosomes also play an important role in drug resistance
in cancer by sequestering weak-base chemotherapeutic drugs
within the cell. This increases lysosomal biogenesis resulting
in enlargement of the lysosomal compartment in cells [15].
The enlarged compartment allows significant concentration of
chemotherapeutic drugs to be stored in lysosomes and
blocks these drugs from reaching their cellular targets. In
addition, lysosomes provide a mechanism for exocytosis of
drugs from the cancer cells [15]. These mechanisms render
cancer cells drug-resistant, thus highlighting lysosomes as a
target for cancer therapy.

4. Lysosomal Membrane Permeabilization
(Figure 1)
Lysosomal membrane permeabilization (LMP) has been
shown to be an effective therapeutic strategy in many cancer
models [26]. LMP involves either the slight or the complete
permeabilization of the lysosome. This permeabilization
can cause lipid peroxidation and a partial or complete release of
lysosomal contents. Cell death can be mediated by the reactive oxygen species (ROS) and/or lysosomal cathepsins
[3, 4, 26]. In addition, sphingolipids can contribute to LMP
[27]. Sphingosine has been shown to induce LMP when
added to cells [27]. Upon TNFa, radiation, and DNA-
damaging drug treatments, p53 is phosphorylated and translo-
cates to lysosomes where it induces LMP [5]. Various cellular
components can protect the lysosome from permeabilization such as cholesterol [28], lysosomal localization of heat shock
protein 70 [29], and lipid peroxidation scavengers. Tocopherols are endogenous inhibitors of lipid peroxidation.
Among tocopherols is α-tocopherol, otherwise known as vita-
m E [30, 31]. Thus, there are many factors regulating LMP in
cancer cells.

Cancer cells are sensitive to LMP by a variety of mech-
nisms. Cell lines transformed with oncogenic Src and Ras
display altered lysosomal localization and decrease in
LAMP-1 and LAMP-2 [18]. Decreases in the LAMP proteins
prime cells for LMP. Other cancer cells increase lysosomal
biogenesis [14, 17], increase lysosomal size, and alter heat shock protein 70 (HSP-70) localization creating destabilized lysosomes [29]. Cancer cells have altered sphingolipid
metabolism which increases the amount of sphingosine and
renders lysosomes sensitive to LMP [22, 27, 32]. Finally,
many cancer cells have altered metabolism that increases
ROS leading to destabilization of lysosomes leading to LMP
[3, 23]. Thus, cancer cells might be sensitive to lysosomemediated cell death.

5. Lysosome-Mediated Cell Death (LCD)
Since their discovery as the suicide bags of the cell, lysos-
omes have been explored as therapeutic targets in cancer.
Due to these numerous alterations to this pathway, LMP is
an effective way to kill many different cancer cell types.
These include breast cancer [19, 30, 33], ovarian cancer
[19], cervical cancer [19], colon cancer [18, 34, 35], pros-
tate cancer [19], lung cancer [35–37], bone cancer [19],
skin cancer [35], and AML [14]. Cancer cells are suscepti-
bles to lysosome-mediated cell death through increased
ROS and lipid peroxidation leading to mitochondrial dys-
function and plasma membrane permeabilization [38].
Furthermore, the release of cathepsins caused cleavage and
degradation of proteins leading to cell death [3].
The relations of lysosome-mediated cell death with other
forms of cell death will be discussed below.

6. Lysosomes and Apoptosis
Apoptosis is a form of program cell death involving mito-
chondrial dysfunction and activation of cysteine proteases
called caspases. It leads to DNA condensation and mem-
brane blebbing and eventually to the formation of apoptotic
bodies that are phagocytosed by the surrounding cells. Mito-
chondrial dysfunction is triggered by the translocation of the
Bcl-2 family member Bax to the mitochondria where it inter-
acts with Bak and other BH3-only Bcl-2 family members
such as BID to form a pore allowing cytochrome c to be
released and loss of membrane potential to occur. This leads
to an increase in ROS and activation of caspase 9 and caspase
3 leading to cell death [39].
Lysosomes could play important roles in regulating apo-
potis upstream of mitochondrial function and after caspase
activation. Following oxidative stress, it was shown that low concentrations of hydrogen peroxide cause LMP before mitochondrial dysfunction and caspase activation [40]. Blocking cathepsin D activation also prevented the release of mitochondrial cytochrome c and caspase activation [41]. Moreover, ultraviolet radiation induces LMP under conditions of oxidative stress before mitochondrial release of cytochrome c [42]. Bax interacts with other BH3-only Bcl-2 family members such as BIM and BID at lysosomes contributing to LMP independent of its mitochondrial functions. BID is also a target of cathepsins allowing its translocation to the mitochondria to interact with Bax and Bak [42]. Similar to mitochondrial regulation, antiapoptotic Bcl-2 family members can prevent LMP [26]. This suggests that lysosomal disruption can lead to mitochondrial dysfunction.

Lysosomal disruption can also occur after mitochondrial dysfunction. Following loss of membrane potential, ROS production is increased. ROS destabilizes lysosomal membranes through lipid peroxidation leading to rupture [14, 27]. Activation of caspase 8 by death receptors or activation of caspase 9 has been associated with LMP [36, 43]. Overall lysosomes can play a role in either initiating or executing apoptosis.

7. Lysosome and Autophagy

Lysosomes fuse with autophagosomes forming an autolysosome to degrade extracellular or intracellular material [44]. Autophagy plays important roles in cancer cell adaptation to stress where it protects cancer cells from death during development and where its induction is limited to further progression of the disease [45]. Lysosomes function in autophagy regulation in three main areas: (i) lysosomal restoration, (ii) lysophagy, and (iii) autolysosomal degradation. Under normal conditions, lysosomal biogenesis occurs through biosynthesis and endocytic pathways to maintain homeostasis. Under stress conditions, the number of lysosomes decreased due to their role in degrading macromolecules for recycling or removing damaged organelles. Lysosomal levels are restored through a process called autophagic lysosomal reformation (ALR) [46]. This process can be prevented by autophagy inhibitors such as rapamycin and cathepsin inhibitors [46]. The second way autophagy regulates lysosomes is when lysosomes themselves become damaged such as through LMP. The damaged lysosomes are engulfed by autophagosomes which then fuse with functional lysosomes to remove them from the cells [47]. The levels of lysosomes are then restored by lysosomal biogenesis.
Table 1: The use of lysosomotropic agents as therapeutics in cancer.

| Lysosomotropic Agent | Model | Effective doses | Reference |
|----------------------|-------|-----------------|-----------|
| Siramesine           | In vitro | Mast cells (primary) | 2–20 μM | [18, 19, 30] |
|                      |        | Osteosarcoma cell line: U2OS | 1–10 μM |
|                      |        | Ovarian carcinoma cell line: SKOV3 | 8–10 μM |
|                      |        | Prostate cancer cell lines: PC3 and Du145-P | 5–10 μM |
|                      | In vivo | Mcf-7 in SCID mice | 30–100 mg/kg/d |
|                      |        | PC3-MDR in SCID mice | 30 mg/kg |
| Desipramine          | In vitro | Breast cancer lines: Mcf-7 and Mcf-10A | 25 μM |
|                      |        | Cervix carcinoma cell line: HeLa | 25–50 μM |
|                      |        | Colorectal cancer cell lines: Hkh2 and HCT116 | 8 μM |
|                      |        | Fibroblast cell line: NIH3&3-SrcY527F | 8–25 μM | [19] |
|                      |        | Osteosarcoma cell line: U2OS | 25–50 μM |
|                      |        | Ovarian carcinoma cell line: SKOV3 | 40–60 μM |
|                      | In vivo | PC3 and Du145-P | 40–80 μM |
|                      |        | Mcf-7 in SCID mice | 30 mg/kg, 2x/wk |
| Nortriptyline        | In vitro | Breast cancer line: Mcf-7 | 25–50 μM |
|                      |        | Cervix carcinoma cell line: HeLa | 25–50 μM |
|                      |        | Colorectal cancer cell lines: Hkh2 and HCT116 | 8 μM |
|                      |        | Fibroblast cell line: NIH3&3-SrcY527F | 10–25 μM | [19] |
|                      |        | Osteosarcoma cell line: U2OS | 25–50 μM |
|                      |        | Ovarian carcinoma cell line: SKOV3 | 40–60 μM |
|                      | In vivo | Prostate cancer cell lines: PC3 and Du145-P | 40–50 μM |
| Amlodipine           | In vitro | Breast cancer line: Mcf-7 | 25–50 μM |
|                      |        | Fibroblast cell line: NIH3&3-SrcY527F | 10–30 μM | [19] |
|                      |        | Ovarian carcinoma cell line: SKOV3 | 37.5–50 μM |
|                      | In vivo | Prostate cancer cell lines: PC3 and Du145-P | 40–50 μM |
| Terfenadine          | In vitro | Breast cancer line: Mcf-7 | 25–50 μM |
|                      |        | Colorectal cancer cell lines: Hkh2 and HCT116 | 8 μM |
|                      |        | Fibroblast cell line: NIH3&3-SrcY527F | 2.5–5 μM | [19] |
|                      |        | Ovarian carcinoma cell line: SKOV3 | 6–8 μM |
|                      | In vivo | Prostate cancer cell lines: PC3 and Du145-P | 1–10 μM |
|                      |        | Mcf-7 in SCID mice | 10 mg/kg, 2x/wk |
| Mefloquine           | In vitro | AML cells (primary) | 5–15 μM |
|                      |        | AML cell lines: HL60, KG1A OCI-AML2, and TEX | 1–10 μM |
|                      |        | APL cell line: NB4 | 5–7 μM |
|                      |        | CML cell line: K562 | 6–10 μM |
|                      |        | Dendritic cells (primary) | 25–50 μM |
|                      |        | Erythroleukemic cell line: OCI-M2 | 7–9 μM | [14] |
|                      |        | Gastric cancer cell lines: AGS, Hs746T, MKN45, MKN74, NCI-N87, SNU1, SNU16, TCC1, YCC10, and YCC11 | 0.5–5 μM |
|                      |        | Lymphosarcoma cell line: MDAY-D2 | 3–5 μM |
|                      |        | Macrophage/monocyte cell lines: THP-1 and U937 | 5–18 μM |
|                      |        | Oral cancer cell line: KVP20C | 5 μM |
that accumulate in lysosomes. This occurs through di-
agents are weak-base lipophilic or cationic amphiphilic drugs 
collectively called lysosomotropic agents. Lysosomotropic 
LMP can be induced by numerous di-
9. Lysosomotropic Agents

Ferroptotic cell death is a type of cell death that is distinct 
from apoptosis and autophagy [50, 51]. It is characterized 
by iron-dependent accumulation of ROS. Several proteins 
responsible for the regulation of iron such as ferritin and 
transferrin and the cysteine antiporter receptor have implied 
the regulation of ferroptosis [52, 53]. One of the major 
storage sites for iron is lysosomes. In the presence of 
hydrogen peroxide, free iron undergoes a Fenton reaction 
creating reactive iron and increasing ROS [38]. The lysoso-
mal disruptor siramesine induces a rapid rise in the 
lysosomal pH followed by lysosomal leakage mediated in 
part by inhibiting sphingomyelinase (ASM) [19]. This 
destabilization of lysosomal membranes leads to increased 
reactive iron and increased ROS causing cell death [30]. 
We found that the combination with a dual tyrosine 
kine inhibitor of ErbB1 and ErbB2 tyrosine kinase 
receptors called lapatinib with siramesine could induce 
ferroptosis through blocking iron transport allowing the 
iron released by lysosomal disruption to accumulate and 
crease ROS [54]. The role lysosomes play in regulating 
ferroptosis through increased active iron and ROS requires 
future investigations.

9. Lysosomotropic Agents

LMP can be induced by numerous different stimuli that are 
collectively called lysosomotropic agents. Lysosomotropic 
agents are weak-base lipophilic or cationic amphiphilic drugs 
that accumulate in lysosomes. This occurs through diffusion 
across the lysosomal membrane where the agents become 
protonated and become trapped in the lysosome [26]. This 
causes damage to the lysosomal membranes leading to 
LMP. Lysosomotropic agents include metal nanoparticles 
[55], kinase inhibitor ML-9 [56], and numerous different 
types of pharmaceuticals. Pharmaceutical lysosomotropic 
agents include the antidepressants siramesine, nortriptyline, 
desipramine, imipramine, and clomipramine [19]. These 
have shown effectiveness in breast cancer, colon cancer, and 
CLL cells. Antimalarials mefloquine and chloroquine have 
shown effectiveness in breast cancer, lymphoma, and leukemia 
cells [14, 57]. Chloroquine has been investigated in 
clinical trials with only partial activity in lymphoma 
reported. There is, however, no evidence in these trials 
that chloroquine is acting through LMP. Antiallergy drugs 
terfenadine and loratadine [19] were effective at inducing 
cell death in breast and lung cancer cells. The treatments 
of stilbenoid antioxidant pterostilbene [35, 60] and anti-
psychotics chlorpromazine, thioridazine, and aripiprazole 
[19] showed effectiveness in breast cancer, colon cancer, and 
ALL cells. Antimalarials mefloquine and chloroquine have 
shown effectiveness in breast cancer, colon cancer, and leukemia 
cells [14, 57–59]. Chloroquine has been investigated in 
clinical trials with only partial activity in lymphoma 
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of stilbenoid antioxidant pterostilbene [35, 60] and anti-
psychotics chlorpromazine, thioridazine, and aripiprazole 
[19] showed efficacy in breast and leukemia cells. The use 
of these agents is summarized in Table 1. Many of these 
agents are FDA-approved or have been extensively studied 
in clinical trials but, with the exception of chloroquine, 
not in cancer patients [61]. This provides the foundation 
for many of these lysosomotropic agents to be clinically 
investigated for their efficacy in a variety of cancers in 
the near future.

10. Conclusion

Lysosomes play a dynamic role in cells and are altered in 
cancer. The initiation of LMP in cancer cells is a novel 
mechanism to engage the different cell death mechanisms 
selective for cancer. LMP is induced by lysosomotropic 
agents through increased ROS, lipid peroxidation, and 
activation of cathepsins. Many of these lysosomotropic agents 
are FDA-approved and could be moved rapidly to the clinic. 
Targeting lysosomes to induce oxidative stress will be
dependent on the context of other therapies and drug resistance mechanisms found in cancer cells. Further investigation is needed to understand the regulation of lysosome-mediated cell death and the use of lysosomotropic agents in combination with other standard chemotherapy drugs or novel targeted anticancer drugs. Nevertheless, targeting lysosomes provides hope that effective treatment against drug-resistant cancers could be developed.

**Conflicts of Interest**

There is no conflict of interest in publishing this manuscript.

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