Targeting Lysosomes in Chronic Lymphocytic Leukemia

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Overview

• Introduction
  – Lysosome
  – Lipid Metabolism
  – Lysosome Disruption

• Rationale & Hypothesis

• Results

• Summary

• Future Directions
CLL cells have increased autophagy (drug resistance).

CLL cells have altered lipid metabolism.

CLL cells have special lysosomes for antigen-presentation.

Saftig & Klumperman, Nat Rev Mol Cell Biol, 2009

Calafat et al., J Cell Biol, 1994
CLL cells have altered lipid metabolism

- CLL cells have over-active BCR signaling.
- BCR signaling stimulates transcription of many genes.

- CLL cells have altered transcript and protein levels of many lipid enzymes.

Schwamb et al., Blood, 2012
Altered lipid metabolism can sensitize to lysosome disruption

- Lysosomes are destabilized in transformed cells.

  Petersen *et al.*, Cancer Cell, 2013

- Transformed cells have altered expression of many lipid enzymes.

- Altered lipid enzyme expression destabilizes lysosomes.
Transformation-associated changes in sphingolipid metabolism sensitize cells to lysosomal cell death induced by inhibitors of acid sphingomyelinase.


Lysosomal disruption preferentially targets acute myeloid leukemia cells and progenitors.


Combating apoptosis and multidrug resistant cancers by targeting lysosomes.

Groth-Pedersen L, Jäättelä M.


Stat3 controls lysosomal-mediated cell death in vivo.

Kreuzaler PA, Staniszewska AD, Li W, Omidvar N, Kedjouar B, Turkson J, Poli V, Flavell RA, Clarkson RW, Watson CJ.


Induction of lysosomal membrane permeabilization by compounds that activate p53-independent apoptosis.

Erdal H, Berndtsson M, Castro J, Brunk U, Shoshan MC, Linder S.


Effective tumor cell death by sigma-2 receptor ligand siramesine involves lysosomal leakage and oxidative stress.

Osterfeld MS, Fehrenbacher N, Høyer-Hansen M, Thomsen C, Farkas T, Jäättelä M.
Rationale:
Lysosomes are distinct in CLL.
Lipid metabolism is altered in CLL.
Altered lipid metabolism destabilizes lysosomes and primes for lysosome disruption.

Hypothesis:
Lysosome disruption may be an effective therapeutic strategy in CLL.
Lysotropes agents kill CLL cells and permeabilize lysosomes
Lysosome permeabilization is followed by TFEB translocation

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<th>Relative value of TFEB (normalized to DMSO and loading controls)</th>
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Mitochondrial permeabilization follows lysosome permeabilization
Siramesine induces lipid peroxidation
Siramesine-induced cell death is dependent on lipid reactive oxygen species.
Lipid ROS are required to permeabilize mitochondria, but not lysosomes.
Siramesine-induced cell death is independent on cathepsins and caspases.
Siramesine targets CLL cells selectively.
Summary

• Siramesine and mefloquine induce cell death and lysosome permeabilization
• Lysosome permeabilization occurs prior to mitochondria permeabilization
• Siramesine-induced cell death is dependent on lipid ROS, but independent of cathepsins and caspases
• Siramesine targets CLL cells regardless of p53 status
• Siramesine selectively targets CLL cells
Future Directions

• Source of lipid ROS
• Role of altered lipid metabolic enzymes
• Role of antigen presentation machinery
• Combination therapy
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Thank you!
Boya and Kroemer, Oncogene, 2008
Cancer cells have less ASM. ASM hydrolyzes sphingomyelin producing ceramide. Accumulation of sphingomyelin destabilizes the lysosome. Siramesine disrupts the association of ASM with BMP. Therefore, lower drug concentrations are needed to destabilize lysosomes of cancer cells compared to normal cells.

ASM = acid sphingomyelinase  
BMP = bis(monoacylglycerol)phosphate
Source of ROS yet unidentified