Selinexor for Endometrial (and Ovarian) Cancer

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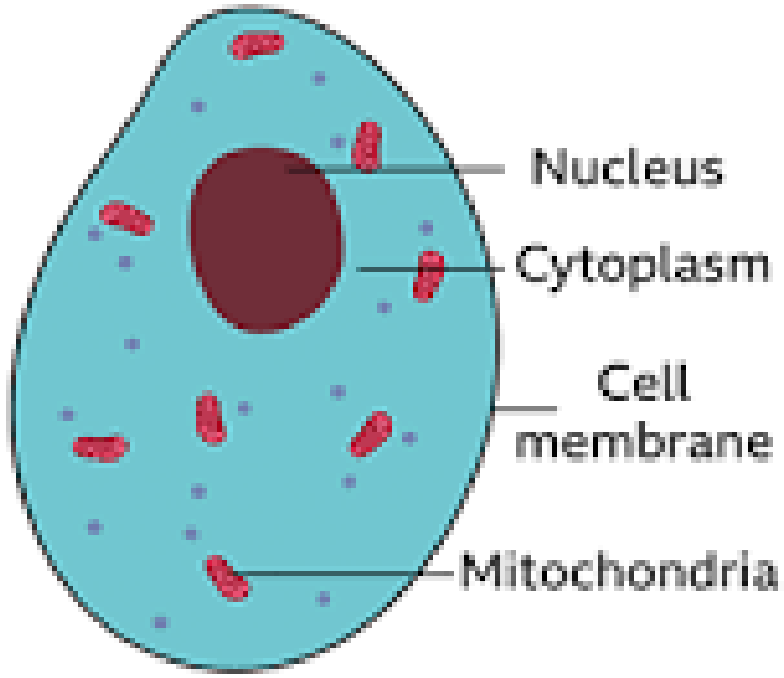
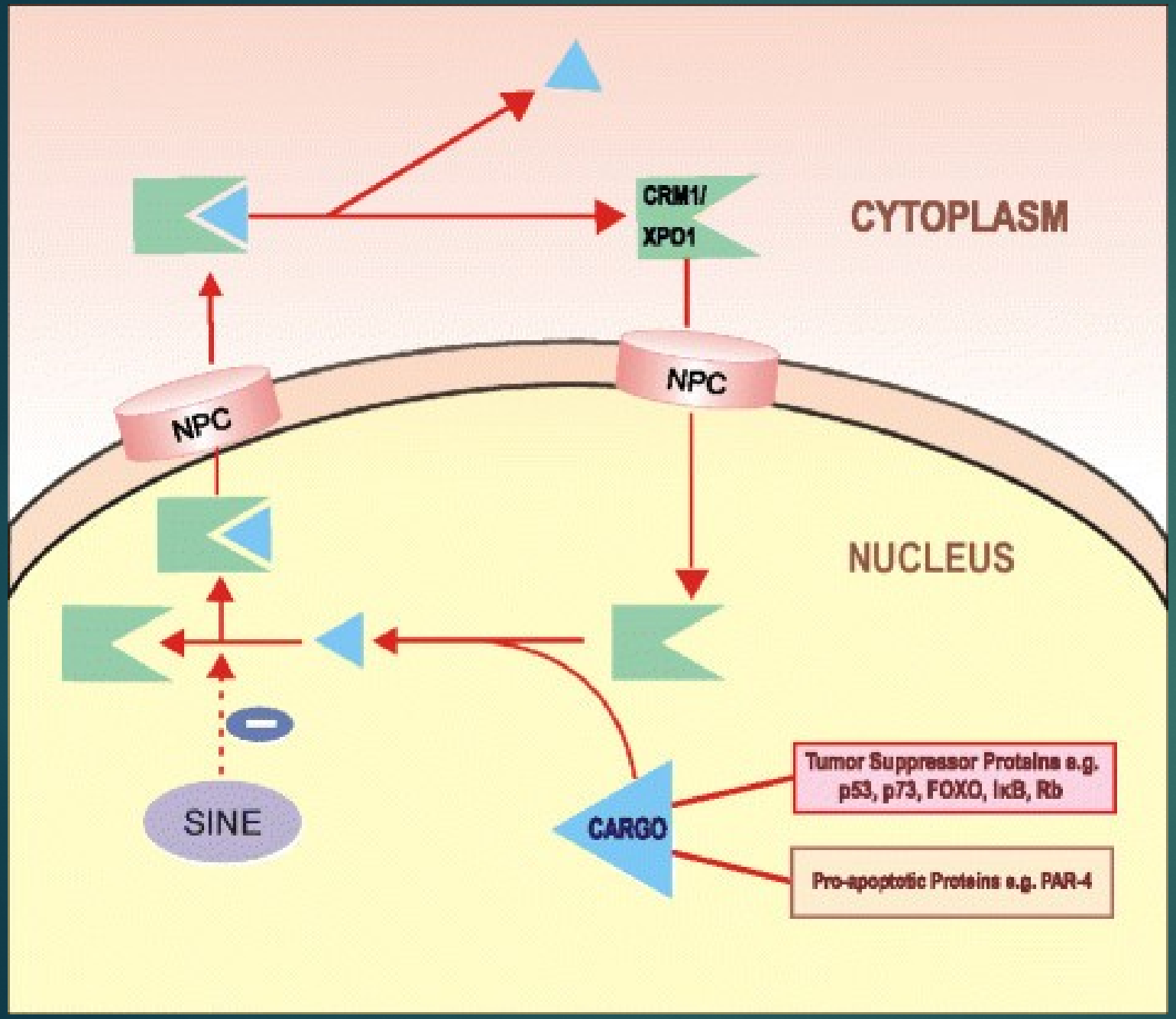

Nucleus
Cytoplasm
Cell
membrane
Mitochondria

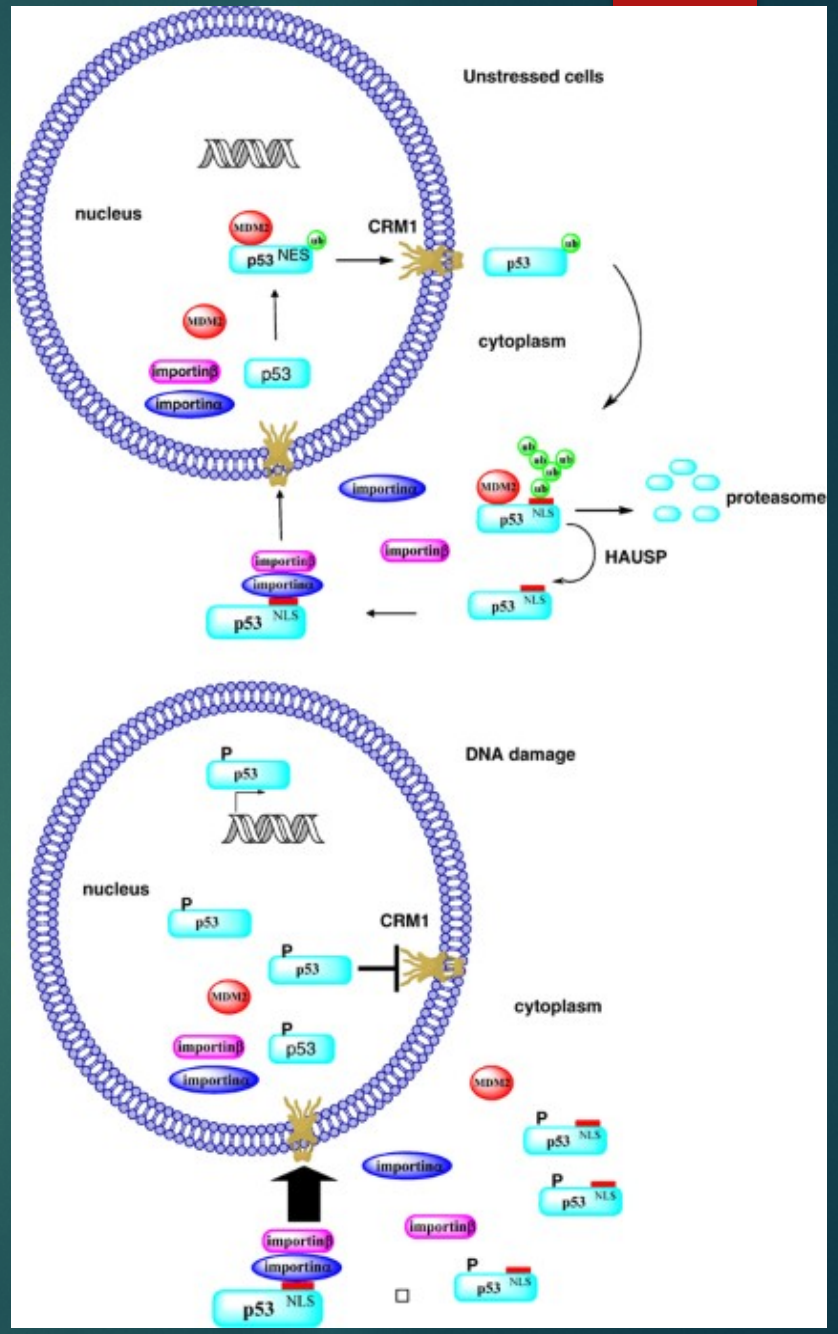
XPO-1 Pathway

- Chromosome region maintenance 1 (CRM1), better known as exportin 1 (XPO1), is the protein transporter responsible for the nucleus-cytoplasm shuttling of most of the tumor suppressor proteins
  - Allows the cell to direct its proliferation or apoptosis pathways
  - Plays a role in mitosis
- XPO1 is also upregulated in many malignancies and associated with a poor prognosis
  - Its inhibition has been a target of therapy
  - The selective inhibitors of nuclear transport (SINE) compounds were developed as a novel class of anti-cancer agents.

Selective Inhibitor of Nuclear Transport (SINE)

- Among the list of XPO1-mediated proteins
  - p53, p27, BCR-ABL, p21, PI3K/AKT, APC, and Rb, all of which are significant targets in oncogenesis
- Selinexor is the most well known SINE
  - Currently undergoing study in about 60 clinical trials
  - lymphoma, sarcomas, lung, breast, leukemia, multiple myeloma, gastric, pancreatic, esophageal, prostate, melanoma, colorectal, and gynecologic cancers
  - Oral agent
  - Commonly used in Multiple Myeloma after first line treatment
  - Used in relapsed/refractory Diffuse Large B-Cell Lymphoma


CRM1/
XPO1
CYTOPLASM
NPC
NPC
NUCLEUS
SINE
CARGO
Tumor Suppressor Proteins e.g.
p53, p73, FOXO, IκB, Rb
Pro-apoptotic Proteins e.g. PAR-4


Unstressed cells
nucleus
MDM2
p53 NES
CRM1
p53
cytoplasm
importinβ
importinα
p53
proteasome
HAUSP
p53 NLS
DNA damage
P
p53
nucleus
CRM1
cytoplasm
MDM2
p53 NLS

Side Effects

- Nausea/vomiting
- Low platelets, anemia
- Low WBCs
- Dizziness, hallucinations
- Weight loss/decreased appetite
- New/worsening cataracts

Phase I study of Selinexor with carbo/taxol in advanced OC or EC

- **Patients and methods: D**ose-escalation study of selinexor + CP.
- **Results:** Twenty-three patients were treated (5 serous OC; 18 EC)
- The most common SEs were thrombocytopenia (100%), leukopenia (91%), and hyperglycemia (87%).
  - Twelve patients achieved a PR and 1 achieved a CR.
- **Conclusions:** Selinexor + CP was safe and tolerated in OC and EC.

Phase 2 study of Selinexor in patients with recurrent gynecologic malignancies

- 114 patients with OC, EC or CC
  - DCR was 30%, which included confirmed PRs in 8%, 9%, and 4% of patients with OC, EC, and CC respectively.
- **Results:** Median PFS and OS for patients with OC, EC and CC were 2.6, 2.8 and 1.4 months, and 7.3, 7.0, and 5.0 months, respectively.
- Common AEs were thrombocytopenia (17%), fatigue (14%), anemia (10%), nausea (9%) and hyponatremia (9%).
- **Conclusions:** Selinexor demonstrated single-agent activity and disease control in patients with heavily pre-treated OC and EC.

Phase 3 SIENDO Trial

- Prospective, multicenter, double-blind, placebo-controlled study of Selinexor vs. placebo as maintenance therapy in 263 patients with advanced or recurrent EC after one line of CT chemotherapy with partial or complete remission.
- **Results:** Median PFS of 5.7 months (SEL) vs. 3.8 months (PLB).
- Subgroup analysis
  - *TP53*wt showed a PFS of 13.7 mo with SEL vs. 3.7 mo with PLB
  - MSS disease had a PFS of 6.9 mo with SEL vs. 5.4 with PLB
  - Patients with no specific mutation showed a substantial difference in PFS for SEL vs. PLB: median NR and 3.71 months
- **Conclusions:** SEL showed improved PFS over PLB in patients with TP53wt, MSS, and the NSMP EC - comprising approximately 50% of patients with advanced/recurrent EC.

Thank you! (and References)

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