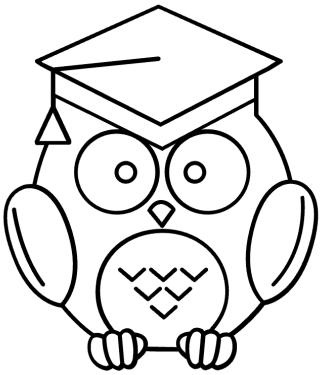

TLDR

Targeting the Inhibitors of Apoptosis Proteins (IAPs) to Combat Drug Resistance in Cancers

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The Big Idea:

Around 90% of cancer-related deaths are a result from drug resistance, often due to cancer cells evading programmed cell death through Inhibitor of Apoptosis Proteins (IAPs); thus, targeting IAPs is emerging as a promising strategy to overcome resistance and restore natural cell death.

Key terms and concepts:

Inhibitor of Apoptosis Proteins (IAP):
A family of proteins found in your cells that help regulate when and how cells die. Their job is to keep a healthy balance between cell survival and cell death.

Apoptosis:
A natural process where a cell undergoes programmed cell death (kind of like a suicidal mechanism) when it is no longer needed or becomes damaged to keep you healthy.

Drug resistance:
When cancer cells don’t respond to a drug that is usually able to weaken/kill them.

Caspases:
A family of enzymes within your cells that help trigger and carry out apoptosis.

SMAC:
A protein found in mitochondria that is released into the cell's cytosol to antagonize/block IAPs. Allowing caspases to execute cell death.

Pro-Apoptotic Mitochondrial Proteins:
"Death-promoting" proteins that live in the mitochondria and help destroy unhealthy cells when needed.

Apoptogenic factors:
Molecules/stimuli that tell a cell it is time to die (apoptosis).

Ubiquitination:
The process of attaching a small protein called ubiquitin to an unwanted protein so the cell knows it should be broken down.

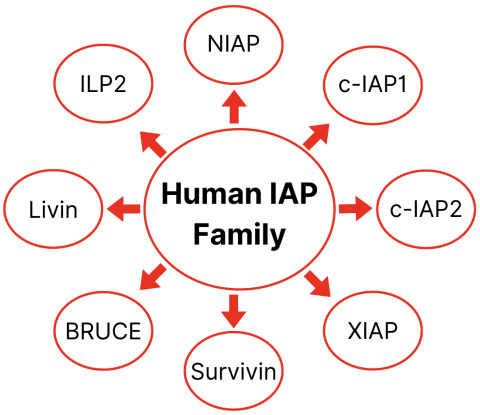
Small molecule inhibitors:
An umbrella term to define drug compounds that are designed to block the activity of specific proteins (like IAPs in this review) to stop harmful cell processes.

Proteolysis Targeting Chimeras (PROTACs):
Artificial molecules designed to break down specific proteins.

Biomarkers:
Measurable signs in the body used to guide diagnosis or treatment.

Key findings:

- Overexpressed IAPs allow cancers to avoid apoptosis and develop drug resistance.
- There are eight members in the human IAP family.



- Each member (except for NAIP and ILP2) is associated with causing drug resistance in particular treatment methods for specific cancers.
- Scientists don't completely understand how all eight of these proteins behave in cancer, but they do have a decent understanding of the following:

IAP	Notes
X-Linked IAP (XIAP)	• Attaches to and stops caspases -3, -7, and -9 (specific types of caspase enzymes), which are key players in starting and continuing programmed cell death. • Interferes with cell death by delaying the release of important molecules (cytochrome-c, Apaf-1, SMAC) from the mitochondria • Work with other molecules to further control cell death.

Cellular IAP 1/2 (c-IAP1/2)	• Controls key signalling pathways that turn on NF-κB, a protein that activates survival genes. • Stops death-triggering complexes (called complex IIb) which would usually lead to apoptosis.
Survivin	• Stops caspase-9 from initiating the cascade of apoptosis • Prevents SMAC from entering the cytosol from the mitochondria on a cellular level. Without SMAC in the cytosol, the IAPs keep working, and apoptosis is stopped.
Baculovirus IAP Repeat containing ubiquitin-conjugating enzyme (BRUCE)	• Binds to and prevents pro-apoptotic mitochondrial proteins (SMAC/DIABLO and HtrA2/Omi) from neutralizing XIAP, the IAP that suppresses caspases • Keeps the mitochondria intact, preventing the release of apoptogenic factors. • Tags cell-death proteins like caspase-9 for destruction in ubiquitination, helping cells avoid apoptosis and survive longer • Interferes with the way cells respond to extracellular signals to trigger apoptosis, helping the cell survive when it normally wouldn't

- Simply, the way IAPs contribute to drug resistance can be simply expressed through the following figure:

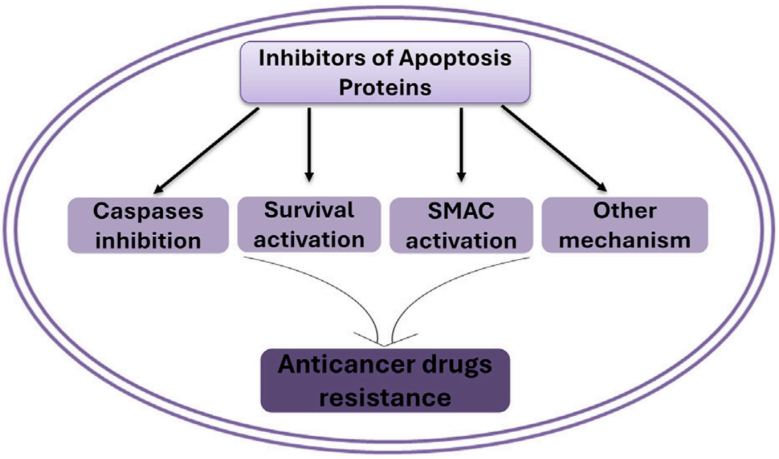


FIGURE 1
IAPs induces drug resistance via multiple mechanisms.

- Small molecule inhibitors are used as a strategy target and bind to IAPS, and in slightly different ways with the help of other cancer therapies, induce apoptosis.

- Targeting IAP's is a feasible approach towards overcoming drug resistance in cancers; drastically improving patient clinical outcomes.

Future Directions:

- **Development in highly-specific medicines** that precisely target IAPS. A novel approach involves leveraging PROTACs to degrade IAPs, rather than blocking them like traditional inhibitors.

- Exploration of more effective combinations between IAP-targeted treatments with other cancer therapies. Potentially, **reforming the healthcare system** by individualising patient to patient treatment strategies.

- Identification of biomarkers to help **predict how patients will respond** to IAP-targeted treatments by looking for signs of IAP activity within tumors.

- **More clinical trials** to test for safety, effectiveness, ideal dosages, and long-term effects of IAP-targeted treatments before they can be widely used.

References:

Ye, Q., Zhuang, X.-Z., Li, J., & Zhou, X. (2025). Targeting the inhibitors of apoptosis proteins (IAPs) to combat drug resistance in cancers. Frontiers in Pharmacology, 16. https://doi.org/10.3389/fphar.2025.1562167

Ye, Q., Zhuang, X.-Z., Li, J., & Zhou, X. (2025a). *Figure 1. IAPs induces drug resistance via multiple mechanisms*. Targeting the Inhibitors of Apoptosis Proteins (IAPs) to Combat Drug Resistance in Cancers. Frontiers in Pharmacology. Retrieved April 22, 2025, from https://doi.org/10.3389/fphar.2025.1562167.