

Evasion of Cell Death

Mitochondrial apoptosis, oncogenic survival, and therapeutic vulnerabilities



Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning outcomes

- Explain how apoptosis limits survival of damaged or stressed cells.
- Trace mitochondrial signaling from BH3-only proteins to executioner caspases.
- Distinguish p53 loss, BCL2 upregulation, and inhibitor-of-apoptosis activity.
- Apply these mechanisms to follicular lymphoma, CLL, and targeted therapy.

Why evasion of apoptosis matters in cancer

- Tumors often acquire lesions that make cells resistant to regulated apoptotic death.
- This survival advantage operates even when growth signals are abnormal or DNA is damaged.
- The dominant tumor-associated lesions affect the intrinsic, mitochondrial pathway.
- Anticancer therapy may select additional apoptosis-resistant subclones.

Tumor burden reflects survival as well as proliferation.

Population balance: Birth and death

Cell production / proliferation

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Cell elimination / apoptosis



Net cellular accumulation

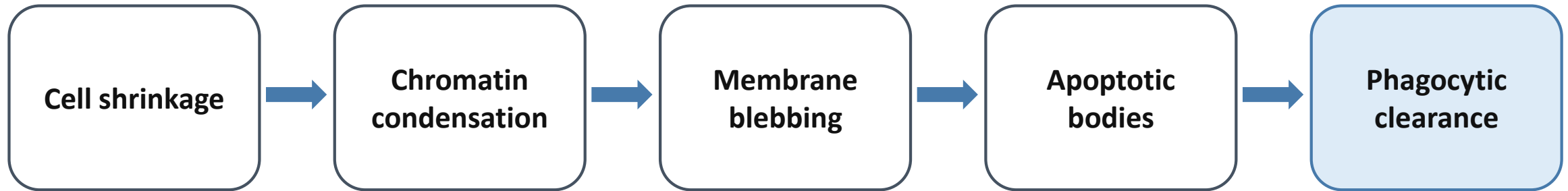
- Net expansion increases when production rises or apoptotic elimination falls.

Apoptosis: Orderly cellular dismantling

- A tightly regulated death program activates enzymes that degrade cellular proteins and DNA.
- The dying cell is partitioned into membrane-bound apoptotic bodies.
- Phagocytes remove fragments efficiently, usually without provoking inflammation.
- Failure to engage this program preserves cells carrying oncogenic damage.

Apoptosis removes individual cells while limiting collateral injury.

Morphologic sequence of apoptosis



Conceptual sequence: No photomicrograph or diagnostic specimen is depicted.

Apoptosis is not synonymous with necrosis

Apoptosis

- Regulated enzyme cascade
- Membranes retained around fragments
- Usually rapid phagocytic clearance
- Little or no associated inflammation

Necrosis

- Cell death with membrane disruption
- Cell contents escape into tissue
- Degradative digestion and debris
- Often elicits local inflammation

A tumor can resist apoptotic signaling yet still contain necrotic regions.

Why apoptosis is usually noninflammatory

- The plasma membrane remains intact during formation of apoptotic bodies.
- Phosphatidylserine becomes exposed on the outer membrane leaflet.
- Macrophages recognize and engulf dying cells: Efferocytosis.
- Rapid engulfment limits release of cellular contents into surrounding tissue.

Morphology reflects an actively regulated clearance process.

Two initiation pathways converge on caspases

Extrinsic / receptor pathway

- Triggered at the cell surface
- Death receptors such as FAS
- Adaptor FADD; Initiator caspase-8
- Can be activated by immune-cell ligands

Intrinsic / mitochondrial pathway

- Triggered by intracellular stress
- Controlled by BCL2-family balance
- Cytochrome c-APAF-1; Caspase-9
- Dominant route dysregulated in many cancers

Both pathways activate executioner caspases.

Extrinsic signaling: A reference pathway



Relevant contrast: Tumors most often evade the mitochondrial rather than receptor arm.

How the extrinsic pathway amplifies death signals

- Ligation of FAS recruits the adaptor FADD via death-domain interactions.
- Recruitment and activation of procaspase-8 initiates the downstream caspase cascade.
- Caspase-8 may cleave BID, linking death-receptor signaling to mitochondrial apoptosis.
- This cross-talk explains why the two pathways are not fully independent.

The intrinsic pathway is cancer's key survival checkpoint

- Intracellular injury normally destabilizes mitochondrial outer-membrane integrity.
- Permeabilization releases death-initiating proteins into the cytosol.
- Cancer cells alter the sensor–inhibitor balance to preserve the membrane.
- The result is persistence despite stresses that would normally be lethal.

Mitochondrial outer-membrane permeabilization is a decisive control point.

DNA damage activates an apoptotic checkpoint

- Mutagenic injury threatens genomic integrity and normally activates p53 responses.
- With sustained or irreparable damage, pro-apoptotic signaling may be induced.
- This removes cells that might otherwise propagate harmful mutations.
- Cancers with impaired p53 responses can retain damaged clones.

DNA damage is both a carcinogenic pressure and an apoptotic trigger.

Growth-factor withdrawal threatens cell survival

- Normal survival depends partly on growth factors and microenvironmental inputs.
- Loss of survival signals reduces anti-apoptotic protection and favors BH3 activity.
- The mitochondrial pathway translates this imbalance into cell death.
- Cancer survival programs can uncouple viability from normal external support.

Hypoxia challenges expanding tumors

- Rapid tumor expansion may outstrip oxygen delivery from the local vasculature.
- Inadequate oxygenation is one of the intrinsic stresses emphasized.
- Persistent hypoxic stress can favor mitochondrial apoptotic signaling.
- Surviving tumor cells have acquired or retained anti-apoptotic adaptations.

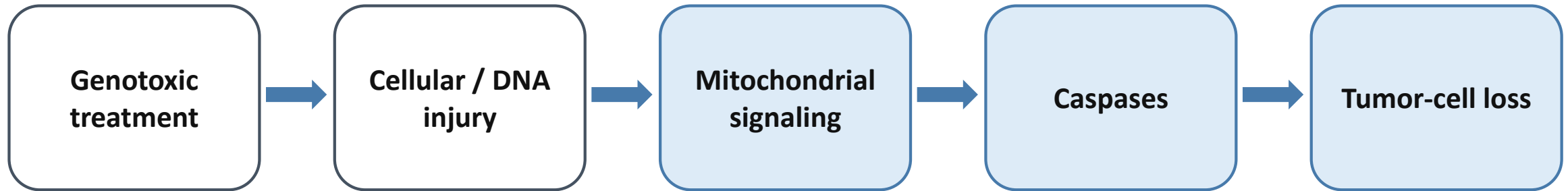
Metabolic imbalance adds apoptotic pressure

- Dysregulated growth raises metabolic and biosynthetic demands.
- Metabolic disturbances can initiate intrinsic-pathway stress responses.
- Apoptotic resistance helps proliferating tumor cells tolerate this strain.
- This is distinct from metabolic reprogramming itself, discussed in the preceding topic.

Misfolded proteins can become a death signal

- Some tumors accumulate increased quantities of misfolded proteins.
- Protein-folding disturbance stresses the endoplasmic reticulum.
- Stress-sensitive BH3-only proteins may be activated or upregulated.
- An apoptosis-resistant tumor can remain viable under the same conditions.

Therapy increases pressure on the apoptotic gate



A defective death pathway can diminish the cytotoxic effect of treatment.

The mitochondrial outer membrane acts as a gate

- An intact outer membrane retains cytochrome c inside mitochondria.
- BAX and BAK mediate stress-dependent membrane permeabilization.
- BCL2-family inhibitors oppose this loss of mitochondrial integrity.
- Once cytochrome c is released, the downstream caspase cascade can begin.

Cancer cells preferentially maintain the anti-apoptotic state.

Three functional groups of BCL2-family proteins

Anti-apoptotic

- BCL2
- BCL-XL
- MCL1
- Prevent cytochrome c release

Effectors

- BAX
- BAK
- Promote mitochondrial permeabilization

BH3-only sensors

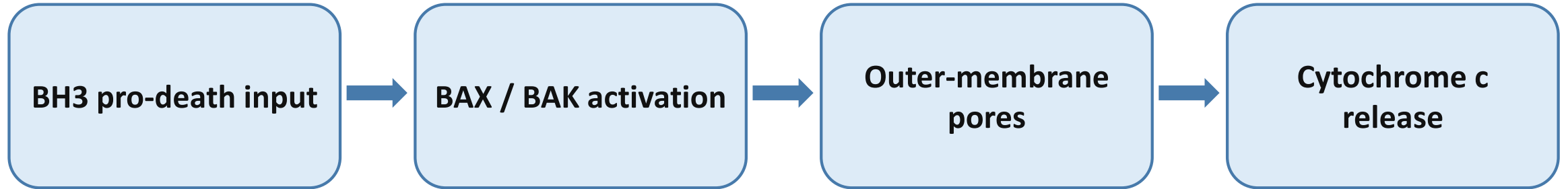
- BIM, BAD, BID
- PUMA, NOXA
- Shift balance toward death

Apoptotic fate depends on functional balance, not one protein in isolation.

BCL2 proteins preserve mitochondrial integrity

- BCL2 and BCL-XL are representative anti-apoptotic family members.
- They restrain BAX/BAK-mediated permeabilization of the outer membrane.
- Their protective action prevents cytochrome c leakage.
- Overexpression moves the threshold for apoptosis upward.

BAX and BAK: The essential effectors



When the mitochondrial gate opens, the execution program becomes accessible.

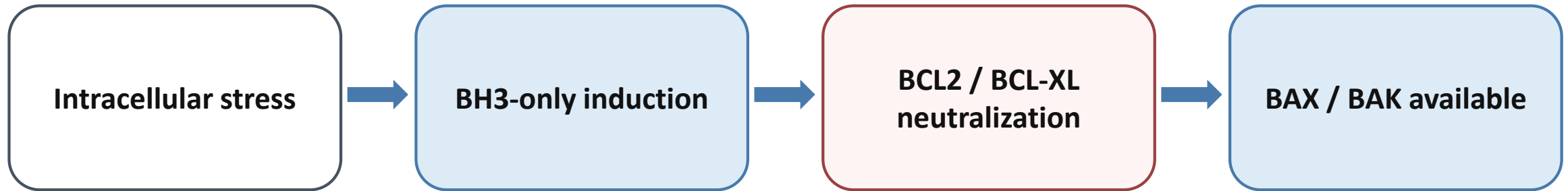
BAX and BAK promote cell death rather than survival

- BAX and BAK are pro-apoptotic family members, distinct from BCL2.
- Upon activation, they oligomerize at the outer mitochondrial membrane.
- This causes membrane permeabilization and efflux of apoptotic mediators.
- BCL2/BCL-XL counteract their effect.

BH3-only proteins report cellular stress

- BIM, BAD, BID, and PUMA are examples specified in the cancer chapter.
- NOXA is additionally listed in the general apoptosis chapter.
- Their activities respond to loss of survival signals or cellular injury.
- They favor activation of mitochondrial apoptosis.

How BH3-only proteins tip the balance



Some BH3-only proteins also contribute directly to effector activation.

Survival and death reflect competing forces

Survival-favored state

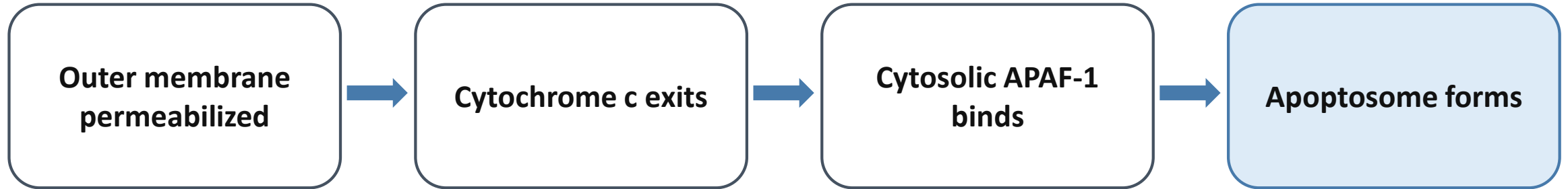
- Abundant BCL2 or BCL-XL
- BAX / BAK restrained
- Mitochondrial membrane intact
- Cytochrome c stays compartmentalized

Apoptosis-favored state

- BH3-only signaling rises
- Anti-apoptotic reserve is overwhelmed
- BAX / BAK oligomerize
- Cytochrome c enters the cytosol

The BCL2-family network acts as a molecular threshold.

Cytochrome c links mitochondria to caspases



Cytochrome c is necessary for respiration inside mitochondria but signals death when released.

APAF-1 assembles the apoptosome

- APAF-1 is the cytosolic adaptor for released cytochrome c.
- Cytochrome c binding favors multimeric apoptosome assembly.
- The apoptosome recruits initiator procaspase-9.
- Caspase-9 activation propagates the apoptotic program.

Caspase-9 initiates the execution cascade



Initiator and executioner caspases have distinct positions in the pathway.

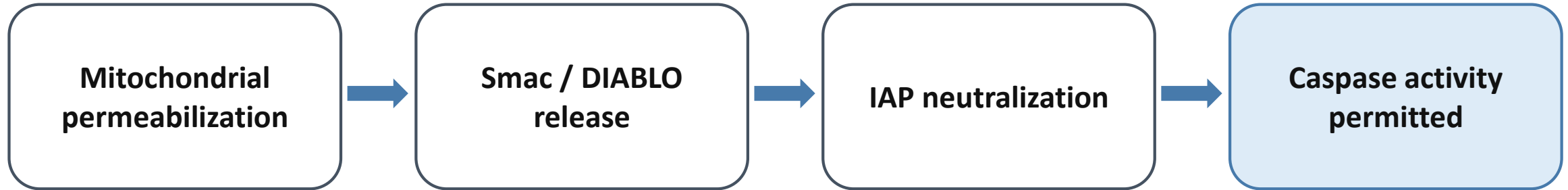
Executioner caspases dismantle the cell

- Executioner caspases cleave many nuclear and cytoplasmic proteins.
- Proteolysis activates a DNase by removing its inhibitor.
- DNA fragmentation, nuclear breakup, and apoptotic-body formation follow.
- Intact fragments are then removed by phagocytes.

Inhibitor of apoptosis proteins provide another brake

- IAPs physiologically suppress inappropriate activation of caspases.
- The cancer chapter specifically highlights inhibition of caspase-9.
- Some cancers increase IAP expression, adding protection against apoptosis.
- This route is less common than p53 loss or BCL2 upregulation.

Mitochondrial proteins can counter IAPs



An additional regulatory layer acts downstream of the BCL2-family gate.

The intrinsic death pathway — integrated



Interference anywhere along this chain can change how a cell responds to injury.

What cancer must overcome to stay alive

- Repeated DNA injury would normally provoke checkpoint or apoptotic responses.
- Hypoxia and metabolic stress intensify during unregulated expansion.
- Chemotherapy and radiation impose additional pro-death pressure.
- Selected tumor clones evade mitochondrial apoptosis through genomic or expression changes.

Apoptotic evasion is a selected phenotype, not merely absence of injury.

Major tumor-associated escape routes

Loss of p53 signaling

- TP53 mutation
- MDM2 overexpression
- Reduced PUMA induction

BCL2-family shift

- BCL2 upregulation
- BAX / BAK function opposed
- Mitochondria remain intact

Downstream blockade

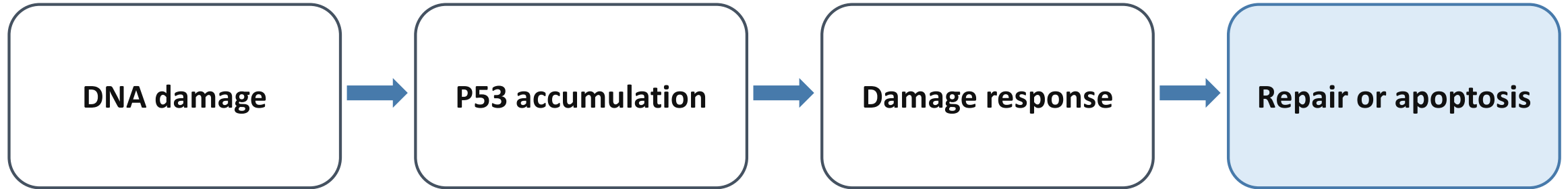
- Increased IAP activity
- Caspase activation inhibited
- Less common escape route

Multiple lesions converge on the same phenotype: Resistance to apoptotic death.

P53 is a stress-responsive tumor suppressor

- TP53 encodes p53, which coordinates cell-cycle arrest, repair, senescence, and apoptosis.
- DNA injury can stabilize p53 and activate transcriptional responses.
- Repairable damage may be followed by recovery and cell-cycle re-entry.
- Persistent severe injury can direct the cell toward apoptosis or senescence.

Functional p53: From DNA damage to cell fate



P53 couples detection of injury to a biologically appropriate response.

PUMA links p53 activity to mitochondria

- PUMA is a BH3-only, pro-apoptotic BCL2-family member.
- DNA damage can induce PUMA as part of the p53 response.
- PUMA shifts mitochondrial regulation toward BAX / BAK action.
- This creates an executable death signal downstream of genomic injury.

The p53–PUMA mitochondrial axis



Loss of p53 function interrupts a major stress-to-apoptosis link.

TP53 loss uncouples damage from apoptosis

DNA injury is present, but p53-dependent transcription is impaired



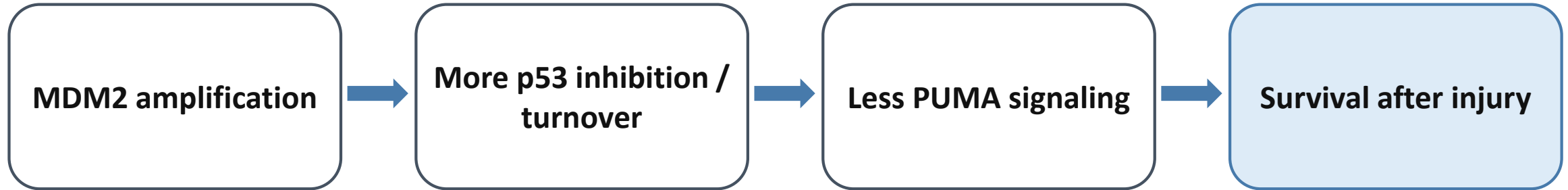
PUMA is not adequately induced; Damaged cells can survive

The defect affects signaling from stress, not necessarily the stress itself.

TP53 mutation is a prevalent resistance mechanism

- Loss of TP53 function as a major route to apoptotic evasion.
- It is common in cancers at diagnosis and more frequent in some relapsed tumors.
- A plausible selection advantage is resistance to genotoxic therapy.
- This interpretation is mechanistic; Do not infer resistance from mutation alone in every clinical setting.

MDM2 can suppress otherwise intact p53



Functionally disabling p53 does not always require a TP53 mutation.

Two routes to deficient p53 signaling

TP53-mutant tumor

- Defective p53 gene or protein
- P53-dependent apoptotic response compromised
- Restoring a defective gene is difficult
- May resist DNA-damaging therapy

MDM2-amplified tumor

- TP53 may remain genetically intact
- Excess MDM2 limits p53 abundance
- Blocking MDM2 could restore p53 activity
- Therapeutic approach described as under study

Distinguish genetic loss from negative regulation of functional p53.

Applied mechanism: Surviving DNA damage

Clinical / molecular observation

- A malignant clone sustains substantial DNA injury after cytotoxic treatment.
- Molecular analysis identifies inactivating TP53 abnormalities.
- The clone persists despite cellular damage.

Why may the clone survive?

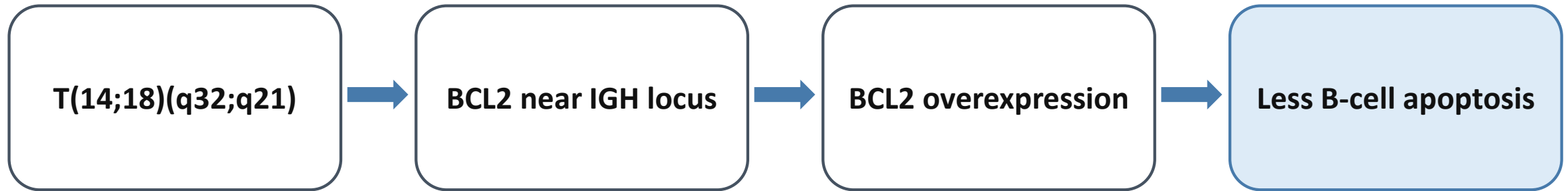
- P53-dependent induction of PUMA is impaired.
- The intrinsic pathway is less efficiently activated.
- This provides a plausible resistance mechanism—not a patient-specific prediction.

BCL2 overexpression raises the apoptotic threshold

- Abundant anti-apoptotic BCL2 restrains mitochondrial permeabilization.
- Cells require stronger BH3-only input to activate BAX / BAK.
- Pro-death injury can therefore coexist with continued viability.
- The growth advantage can arise primarily from reduced cell loss.

BCL2 acts on the mitochondrial gate rather than initiating proliferation.

Follicular lymphoma: Translocation to survival



The hallmark biological advantage is survival of transformed B lymphocytes.

T(14;18) alters BCL2 expression

- The translocation involves the immunoglobulin heavy-chain locus and BCL2.
- The transcriptionally active IGH regulatory environment increases BCL2 expression.
- Excess BCL2 protects lymphocytes from intrinsic apoptotic cues.
- The lesion promotes survival rather than directly acting as a growth-factor receptor.

Why follicular lymphoma can be indolent

- A tumor mass reflects the net balance of proliferation and cell death.
- In BCL2-overexpressing follicular lymphoma, reduced apoptosis is particularly important.
- Accumulation may therefore be gradual rather than driven by explosive proliferation.
- This survival-dominant mechanism with typically indolent behavior.

Slow growth does not imply absence of malignant survival signaling.

Two distinct routes to larger tumor mass

Proliferation-dominant expansion

- More cells enter and complete the cell cycle
- Division rate rises
- Net cell numbers can increase rapidly
- Not the primary mechanism emphasized for BCL2 in follicular lymphoma

Survival-dominant accumulation

- Cells are eliminated less efficiently
- Ordinary divisions yield greater net gain
- Tumor persists despite stresses
- Central to the follicular lymphoma illustration

Apoptosis resistance is an independent driver of tumor accumulation.

CLL illustrates post-transcriptional survival control

- Increased BCL2 expression in chronic lymphocytic leukemia.
- Loss of microRNAs that normally restrain BCL2 levels is a proposed mechanism.
- Reduced microRNA-mediated repression permits additional BCL2 production.
- This differs from the IGH–BCL2 translocation mechanism in follicular lymphoma.

Follicular lymphoma versus CLL: BCL2 control

Follicular lymphoma

- Canonical example: T(14;18)(q32;q21)
- IGH-associated transcriptional drive
- Survival advantage for transformed B cells
- Clinically often indolent

Chronic lymphocytic leukemia

- BCL2 upregulation is emphasized
- Loss of restraining microRNAs is implicated
- Post-transcriptional regulation is altered
- BCL2-directed therapy is a relevant concept

Different molecular defects converge on BCL2-dependent survival.

Anti-apoptotic signaling is not the same as mitogenic signaling

- A mitogenic lesion promotes cell-cycle entry and division.
- An anti-apoptotic lesion prevents elimination of stressed or aged cells.
- Both may increase tumor-cell abundance but act through different mechanisms.
- A tumor commonly combines proliferative drive with survival adaptation.

BCL2-family changes can limit treatment response

- Many cytotoxic therapies induce DNA injury and related apoptotic stress.
- An intact apoptotic apparatus converts injury into executioner caspase activation.
- Excess BCL2 opposes mitochondrial permeabilization upstream of caspases.
- Cancer-cell killing can be reduced even when treatment-induced injury occurs.

IAP overexpression is an additional escape route

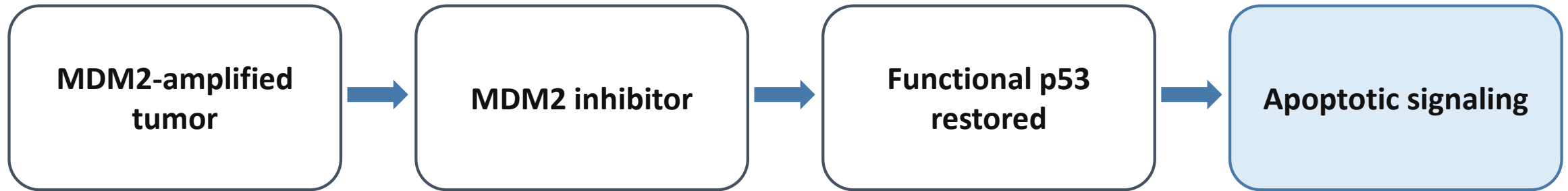
- Cancers can increase expression of inhibitors of apoptosis proteins.
- IAP activity blocks steps in the caspase-dependent killing program.
- This is less frequent than p53 or BCL2 abnormalities.
- It is mechanistically distinct from directly maintaining mitochondrial membrane integrity.

Compare the molecular points of resistance

Lesion	Immediate effect	Downstream consequence
TP53 loss	Less p53-driven PUMA induction	Insufficient pro-death signaling
MDM2 excess	p53 activity suppressed	Reduced stress response
BCL2 excess	BAX / BAK restrained	Cytochrome c remains in mitochondria
IAP excess	Caspase activity suppressed	Execution program obstructed

Different upstream lesions converge on failure of cellular execution.

Target concept: Relieve MDM2 suppression

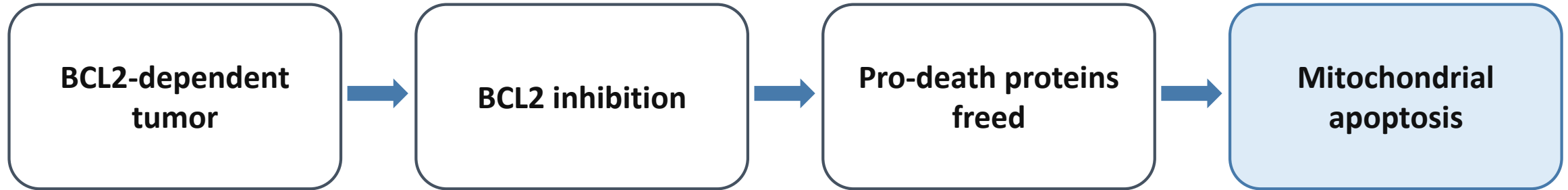


MDM2 inhibition as a clinical-trial strategy, not a universal standard.

Why restoring p53 is therapeutically challenging

- Loss-of-function TP53 mutations damage the molecular effector itself.
- Reversing a defective tumor suppressor gene is technically difficult.
- In contrast, pharmacologic MDM2 inhibition may release an otherwise intact p53 protein.
- The distinction determines the mechanistic plausibility of the intervention.

Target concept: Directly inhibit BCL2



The source reports potent activity in selected BCL2-overexpressing cancers, including CLL.

Clinical significance of BCL2-targeted drugs

- Pharmacologic blockade can counteract an acquired survival dependency.
- Selected cancers with excess BCL2 are particularly responsive.
- Chronic lymphocytic leukemia as a prominent example.
- Therapeutic implications here are mechanistic; Dosing and eligibility are not addressed.

Two intervention strategies act at different levels

MDM2-directed strategy

- Removes inhibition of p53
- Requires potentially functional p53 signaling
- Attempts to re-create upstream stress response
- Robbins: Agents being tested in trials

BCL2-directed strategy

- Removes mitochondrial anti-apoptotic brake
- Targets survival dependency downstream of p53
- Enables BAX / BAK-mediated permeabilization
- Robbins: Clinical activity in selected cancers

Drug target selection should follow the actual molecular defect.

Selection occurs before and after treatment

- Spontaneous DNA damage, metabolic stress, and hypoxia favor apoptosis resistance.
- Treatment adds strong stress, especially for the intrinsic pathway.
- Cells with defective p53 signaling or excess BCL2 may preferentially survive.
- Relapsed disease can therefore be enriched for anti-apoptotic phenotypes.

Mechanistic case: Follicular lymphoma

Clinical / molecular observation

- A B-cell neoplasm exhibits t(14;18)(q32;q21).
- BCL2 expression is abnormally increased.
- Tumor-cell accumulation is relatively slow.

What is the primary advantage?

- IGH-associated dysregulation elevates BCL2.
- Intrinsic apoptosis is suppressed.
- Reduced cell loss can explain indolent growth.

Mechanistic case: Relapse after genotoxic therapy

Clinical / molecular observation

- A tumor recurs after a DNA-damaging treatment regimen.
- Molecular profiling now identifies TP53 loss of function.
- The tumor persists despite treatment-induced damage.

Which death signal is reduced?

- P53–PUMA signaling may be impaired.
- The apoptotic threshold is increased.
- Selection is plausible; Causal attribution needs more than a single genomic observation.

Mechanistic case: BCL2 dysregulation in CLL

Clinical / molecular observation

- A chronic B-cell malignancy is associated with increased BCL2.
- Regulatory microRNAs that ordinarily repress BCL2 are reduced.
- Cellular survival is enhanced.

Where is control lost?

- Loss of microRNA repression permits BCL2 elevation.
- BAX / BAK activation is opposed.
- This is a different regulatory mechanism from t(14;18).

Integrated resistance map: Points of intervention



Failures can arise upstream of mitochondria, at the membrane, or downstream.

Check understanding: Identify the blocked step

- If MDM2 is amplified, ask whether the p53 response can still be induced.
- If BCL2 is overexpressed, identify the inhibited mitochondrial effectors.
- If IAPs are increased, identify the caspase-stage restriction.
- If PUMA induction fails, trace the defect back to p53 signaling.

Correct four common misconceptions

Incorrect claim	Mechanistic correction
"BCL2 is a mitogen."	BCL2 chiefly protects cells from mitochondrial apoptosis.
"TP53 mutation is the only way to lose p53."	MDM2 overexpression can suppress p53 without TP53 mutation.
"Cytochrome c is always a death signal."	Its release into the cytosol enables apoptosis; within mitochondria it supports respiration.
"All apoptosis uses caspase-9."	Intrinsic uses caspase-9; extrinsic begins through caspase-8/10.

Mechanistic synthesis

- Intrinsic stress normally activates BH3-only proteins and BAX / BAK.
- Outer-membrane permeabilization releases cytochrome c and recruits APAF-1.
- Caspase-9 then activates executioner caspases.
- Cancer cells commonly evade death through p53 loss or excessive BCL2.
- Molecular escape pathways also create selectively targetable vulnerabilities.