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Apoptosis Dysregulation in Lung Cancer: Therapeutic Resistance Mechanisms and Implications for Rural Healthcare Advancement in India

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Abstract

Apoptosis is a fundamental mechanism for maintaining cellular homeostasis and eliminating damaged cells. In lung cancer, this tightly regulated process is frequently disrupted, enabling malignant cells to evade death and persist despite cytotoxic therapy. The two principal apoptotic pathways—intrinsic and extrinsic—are both implicated in this disruption. The intrinsic pathway is governed by the Bcl-2 family of proteins, which control mitochondrial outer membrane permeabilization and downstream caspase activation, while the extrinsic pathway is initiated by death receptors on the cell surface and proceeds through the death-inducing signaling complex. Mutations in key regulators such as TP53, overexpression of anti-apoptotic proteins (notably MCL-1 in non-small-cell lung cancer), and defects in death-receptor signaling collectively raise the apoptotic threshold and underlie resistance to chemotherapy, radiotherapy, and targeted agents. Emerging strategies—BH3 mimetics, MCL-1-selective inhibitors, pharmacological p53 reactivation, TRAIL-receptor agonists, and rational combinations—show promise but remain dependent on functional biomarkers of apoptotic dependence rather than static gene-expression data. This review synthesizes the mechanistic literature on apoptosis dysregulation in lung cancer and connects it to the rural Indian context, where rising incidence, biomass-fuel exposure, late-stage diagnosis, and limited access to specialized oncology require affordable, scalable, and decentralized strategies. We argue that apoptosis-targeted therapy will improve rural outcomes only if paired with upstream risk reduction, decentralized diagnostic pathways including telepathology, low-cost tumor-selective delivery platforms, and validation of functional biomarkers in resource-limited settings.

Keywords: Apoptosis, lung cancer, MCL-1, BH3 mimetics, therapeutic resistance, telepathology, rural health, India.

1. Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide and accounts for a substantial and growing share of the cancer burden in India. Recent Global Burden of Disease analyses indicate that tracheal, bronchus, and lung cancer accounted for 8.73% of all cancer fatalities

in India in 2021, with age-standardized incidence and mortality rates rising steadily since 1990 . Although national cancer statistics have historically been derived from urban population-based registries, hospital-based data and regional audits consistently indicate that a large and increasing proportion of Indian lung cancer patients present from rural and semi-urban districts (Indian Council of Medical Research, 2020). Rural populations face a distinctive risk profile: a high prevalence of smoking and smokeless tobacco use, widespread exposure to biomass fuel combustion in poorly ventilated homes, delayed presentation due to limited screening infrastructure, and restricted access to specialized thoracic oncology and molecular testing. These factors converge to produce later-stage diagnosis and poorer outcomes than those observed in metropolitan centers.

Apoptosis—programmed cell death—is essential for tissue homeostasis and for the elimination of damaged or potentially malignant cells (Elmore, 2007). Evasion of apoptosis is a hallmark of cancer (Hanahan & Weinberg, 2011), and in lung cancer the apoptotic machinery is disabled at multiple nodes: loss of p53 function, overexpression of anti-apoptotic Bcl-2 family proteins, defects in death-receptor signaling, and rewiring of survival kinase pathways. Because conventional chemotherapy and radiotherapy depend on the induction of apoptosis for their cytotoxic effect, these lesions are directly responsible for therapeutic resistance and treatment failure.

This review has two aims. First, it synthesizes the molecular literature on intrinsic and extrinsic apoptosis dysregulation in lung cancer, with attention to the lung-cancer-specific features—particularly the dominant role of MCL-1 in non-small-cell lung cancer (NSCLC)—that distinguish it from other tumor types. Second, it examines how these mechanistic insights can be translated into rural healthcare advancement in India, where the rising burden of lung cancer and the scarcity of tertiary oncology capacity require affordable, scalable, and context-sensitive strategies. The review deliberately connects molecular mechanism to health-system design, arguing that apoptosis-targeted therapy will remain an urban tertiary-care privilege unless it is embedded in a decentralized diagnostic and delivery framework.

2. The Intrinsic Apoptotic Pathway

The intrinsic, or mitochondrial, pathway is regulated by the Bcl-2 family, which comprises both pro-apoptotic members (Bax, Bak, and the BH3-only proteins BIM, PUMA, BID, and others) and anti-apoptotic members (Bcl-2, Bcl-xL, MCL-1, Bcl-w, and A1). In response to cellular stress, BH3-only proteins activate Bax and Bak, promoting mitochondrial outer membrane permeabilization and the release of cytochrome c into the cytosol (Green & Kroemer, 2004; Youle & Strasser, 2008). Cytochrome c associates with Apaf-1 and procaspase-9 to form the apoptosome, which activates caspase-9 and, in turn, effector caspases such as caspase-3 (Acehan et al., 2002; Riedl & Salvesen, 2007; Bratton & Salvesen, 2010). Anti-apoptotic proteins preserve mitochondrial integrity by sequestering Bax and Bak or by binding BH3-only proteins, and the balance between these opposing factions determines cell fate (Cory & Adams, 2002; Willis et al., 2005).

The regulation of this pathway is layered. BH3-only proteins act as stress sensors that either directly activate Bax and Bak or antagonize their anti-apoptotic sequesters

(Ren et al., 2010; Moldoveanu et al., 2013). Post-translational modifications—phosphorylation, ubiquitination, and proteolytic cleavage—further modulate the activity and stability of Bcl-2 family members and shift the apoptotic threshold (Deng et al., 2007; Kale et al., 2018). p53 sits upstream of the pathway, transcriptionally inducing Bax and PUMA in response to DNA damage (Vousden & Prives, 2009; Aubrey et al., 2016).

2.1 MCL-1 as the Dominant Anti-Apoptotic Dependency in NSCLC

The identity of the dominant anti-apoptotic protein differs by tumor type, and this has direct therapeutic consequences. In NSCLC, **MCL-1**—not BCL-2—is the principal apoptotic block, and MCL-1 amplification is a common mechanism of resistance to both chemotherapy and BCL-2-selective BH3 mimetics (Willis et al., 2005; Kale et al., 2018). MCL-1 is a pro-survival member of the BCL-2 family that binds with high affinity to the BH3 domains of pro-apoptotic effectors, sequestering them and preventing mitochondrial outer membrane permeabilization . Its short half-life and rapid inducible expression make it a dynamic and adaptive resistance node: cytotoxic therapy that damages DNA can paradoxically upregulate MCL-1 through stress-responsive signaling, creating a survival feedback loop that limits drug efficacy.

Preclinical work in NSCLC models has confirmed that MCL-1 dependence is not merely a correlate of resistance but a causal driver. Dynamic BH3 profiling studies in ALK-rearranged NSCLC have shown that MCL-1 plays a key role in tumor resistance to ALK inhibitors, and that BH3 mimetics targeting MCL-1 can restore sensitivity to these targeted agents by preventing tumor adaptation . This finding has direct clinical implications: ALK inhibitors, while highly effective initially, produce responses that are rarely durable, and the emergence of MCL-1-dependent resistance represents a rational target for combination strategies.

Small-cell lung cancer (SCLC), by contrast, is characterized by near-universal inactivation of TP53 and RB1 and a high apoptotic priming state that contributes to its initial chemosensitivity and subsequent rapid relapse. The distinction between NSCLC (MCL-1-dependent) and SCLC (highly primed, p53/RB1-null) is therefore not academic: it determines which apoptotic dependencies are pharmacologically tractable in each histology.

2.2 Driver-Mutation Context and Apoptotic Priming

Driver-mutation context further shapes apoptotic dependency. EGFR-mutant NSCLC depends on BIM-mediated apoptotic priming for tyrosine kinase inhibitor (TKI)-induced cell death, and BIM deletion polymorphism is a documented cause of TKI resistance. In KRAS-mutant NSCLC—a genotype for which targeted therapy has historically been limited—resistance to emerging KRAS-G12C inhibitors frequently involves MCL-1 or BCL-xL upregulation, and combination strategies that co-target these anti-apoptotic proteins are under active investigation . A review of apoptosis in lung cancer that discusses Bcl-2 and Bcl-xL without addressing MCL-1 dependence and histology-specific priming therefore omits the central determinants of therapeutic response.

3. The Extrinsic Apoptotic Pathway

The extrinsic pathway is initiated by death ligands—FasL and TRAIL—binding to death receptors Fas (CD95/APO-1) and

DR4/DR5. Ligand binding promotes receptor trimerization, recruitment of adaptor proteins, formation of the death-inducing signaling complex (DISC), and activation of procaspase-8 (Ashkenazi & Dixit, 1998; Kischkel et al., 1995; Peter & Krammer, 2003). Active caspase-8 directly activates effector caspases, and in so-called type II cells it also cleaves the BH3-only protein BID, engaging the mitochondrial amplification loop. The pathway is modulated by decoy receptors and by c-FLIP, which inhibits caspase-8 activation at the DISC (Ashkenazi, 2002; Micheau & Tschopp, 2003; Safa, 2012).

In lung cancer, extrinsic pathway defects contribute to immune evasion and therapeutic resistance. Downregulation of Fas and mutations in DR4/DR5 reduce sensitivity to ligand-induced apoptosis, while c-FLIP overexpression blunts DISC-mediated caspase-8 activation (Safa, 2012; Djerbi et al., 1999; Gonzalvez & Ashkenazi, 2010). These alterations are not merely descriptive: they predict failure of TRAIL-receptor agonists and contribute to resistance to immune-mediated killing.

Therapeutic strategies targeting the extrinsic pathway include recombinant TRAIL and agonistic antibodies against DR4/DR5, which preferentially induce apoptosis in malignant cells while sparing normal tissue (Ashkenazi, 2008; Herbst et al., 2010). Clinical activity as monotherapy has been limited by c-FLIP upregulation and death-receptor loss, motivating combination approaches with chemotherapy or Bcl-2-family inhibitors (Dimberg et al., 2013).

3.1 Next-Generation TRAIL Delivery: Mesenchymal Stromal Cell Vehicles

A limitation of recombinant TRAIL is its short half-life and poor tumor penetration. To address this, mesenchymal stromal cells (MSCs) engineered to express TRAIL have been developed as cell-based delivery vehicles. MSCs migrate to tumor sites and can deliver TRAIL locally, overcoming the pharmacokinetic limitations of the soluble protein. Preclinical studies demonstrated that MSC-TRAIL has stronger cytotoxic effects than recombinant TRAIL and synergizes with chemotherapy by engaging both extrinsic and intrinsic pathways simultaneously . A first-in-human phase I trial of umbilical cord-derived MSC-TRAIL (UC-MSCTRAIL) in combination with chemotherapy and immunotherapy in advanced NSCLC has been conducted, representing a translational advance in extrinsic-pathway targeting . While still early-phase, this approach illustrates the principle that effective extrinsic-pathway activation requires engagement of the mitochondrial amplification loop—a principle directly relevant to the combination strategies discussed in Section 6.

4. Dysregulation of Apoptotic Pathways in Lung Cancer

Dysregulation in lung cancer is best understood as a set of convergent lesions that together raise the apoptotic threshold. TP53 mutations—present in the majority of SCLC and a large fraction of NSCLC—impair DNA-damage-induced apoptosis and permit survival of genomically unstable cells (Vousden & Lane, 2007). Constitutive activation of PI3K/AKT and NF-κB signaling provides survival input that further shifts the balance toward persistence (Vivanco & Sawyers, 2002; Hanahan & Weinberg, 2011). On the intrinsic axis, overexpression of anti-apoptotic Bcl-2 family members—with MCL-1 predominating in NSCLC—

sequesters pro-apoptotic effectors and blunts the response to cytotoxic agents.

On the extrinsic axis, reduced Fas and DR4/DR5 expression, DR4/DR5 mutation, and c-FLIP overexpression impair DISC formation and caspase-8 activation, contributing to immune evasion and resistance to death-receptor agonists (Safa, 2012; Djerbi et al., 1999). Importantly, these lesions are often redundant: a tumor may simultaneously overexpress MCL-1, lose p53 function, and downregulate death receptors, so that single-agent targeting of any one node is insufficient.

5. Apoptotic Dysfunction and Therapeutic Resistance

Conventional chemotherapy and radiotherapy depend on apoptosis for cytotoxicity, and resistance to these modalities is frequently explained by the lesions described above. Overexpression of Bcl-2, Bcl-xL, or MCL-1 prevents mitochondrial outer membrane permeabilization and blunts the response to genotoxic agents (Gross et al., 1999; Chen et al., 2005; Kale et al., 2018). TP53 mutations impair transcriptional induction of Bax and PUMA, allowing damaged cells to survive (Vousden & Lane, 2007). Dysregulated PI3K/AKT and NF-κB signaling reinforces survival (Vivanco & Sawyers, 2002; Hanahan & Weinberg, 2011). In the extrinsic pathway, death-receptor loss, TRAIL-receptor mutation, and c-FLIP overexpression all contribute to resistance (Safa, 2012; Djerbi et al., 1999).

Because these mechanisms coexist, single-agent therapies are generally insufficient. This recognition has shifted the field toward combination strategies that lower the apoptotic threshold before or alongside a cytotoxic insult.

6. Therapeutic Strategies Targeting Apoptotic Pathways

6.1 Bcl-2 Family Inhibition: From Pan-BCL-2 to MCL-1 Selectivity

BH3 mimetics—small molecules that mimic BH3-only proteins—bind and inhibit anti-apoptotic Bcl-2 family members, releasing pro-apoptotic effectors and inducing apoptosis. Venetoclax (ABT-199), a BCL-2-selective inhibitor, is approved in chronic lymphocytic leukemia and acute myeloid leukemia (Souers et al., 2013; Roberts et al., 2016). In lung cancer, however, single-agent activity has been limited, in large part because **MCL-1, not BCL-2, is the dominant dependency in NSCLC**.

This recognition has driven the development of MCL-1-selective inhibitors. S63845 binds with high affinity to the BH3-binding groove of MCL-1 and kills MCL-1-dependent cancer cells by activating the BAX/BAK-dependent mitochondrial apoptosis pathway . AZD5991, a macrocyclic small molecule, is highly potent and selective for MCL-1, with demonstrated activity in hematological malignancies and sensitivity in subsets of solid tumors including NSCLC . AMG 176 utilizes a distinct chemotype with long residence times and has demonstrated significant tumor regression in xenograft models . A phase I study of the MCL-1 inhibitor PRT1419 has enrolled patients with advanced solid tumors including NSCLC, indicating that clinical translation of MCL-1 inhibition in lung cancer is underway .

An important caveat is on-target cardiac toxicity: MCL-1 is implicated in normal cardiac myocyte function, and early clinical trials of MCL-1 inhibitors have raised concerns about cardiac side effects that may

limit the therapeutic window . This toxicity profile has two implications for the present review. First, MCL-1 inhibitors will likely require tumor-selective delivery or carefully managed dosing schedules. Second, in rural settings where cardiac monitoring infrastructure is limited, the deployment of MCL-1 inhibitors will require particular caution and may favor oral agents with wider safety margins or tumor-targeted delivery platforms.

6.2 Restoring p53 Function

Pharmacological reactivation of mutant p53—through small molecules such as PRIMA-1/APR-246 (eprenetapopt) and related compounds—aims to restore the transcriptional induction of Bax and PUMA and thereby re-prime the intrinsic pathway. This is distinct from gene-replacement approaches, which introduced wild-type TP53 by viral vector in early lung-cancer trials (Roth et al., 1996). Neither strategy has yet produced durable single-agent benefit in lung cancer, but p53 reactivation remains rational in combination with chemotherapy or BH3 mimetics, because it addresses a transcriptional deficit that BH3 mimetics alone cannot overcome.

6.3 TRAIL-Based Therapies and Cellular Delivery

Recombinant TRAIL and agonistic anti-DR4/DR5 antibodies selectively induce apoptosis in malignant cells (Ashkenazi, 2008; Herbst et al., 2010). Clinical efficacy has been constrained by c-FLIP upregulation, death-receptor downregulation, and the failure of extrinsic pathway activation to engage the mitochondrial amplification loop in resistant tumors. Combination with chemotherapy or Bcl-2-family inhibitors is being explored to overcome these blocks (Dimberg et al., 2013). As noted in Section 3.1, MSC-based TRAIL delivery represents a next-generation approach that addresses the pharmacokinetic limitations of soluble TRAIL and has entered first-in-human testing in NSCLC .

6.4 Combination Strategies

The redundancy of apoptotic blocks in lung cancer argues for regimens that engage multiple nodes simultaneously: Bcl-2 or MCL-1 inhibition with chemotherapy, p53 reactivation with BH3 mimetics, and TRAIL agonists with Bcl-2-family inhibitors (Roberts et al., 2016; Dimberg et al., 2013; Roth et al., 1996). The organizing principle is that apoptosis-targeted agents are most effective when used to lower the apoptotic threshold in the context of a second insult, rather than as monotherapy. The finding that MCL-1 targeting enhances CDDP efficacy in solid tumor models—whereas BCL-2 targeting does not—provides direct preclinical support for this principle and underscores the importance of matching the BH3 mimetic to the tumor's actual apoptotic dependency .

7. Crosstalk Between the Intrinsic and Extrinsic Pathways

The two pathways are not independent. Caspase-8 activated at the DISC cleaves BID; truncated BID translocates to mitochondria, where it promotes Bax/Bak activation and engages the intrinsic pathway (Li et al., 1998; Luo et al., 1998). This mitochondrial amplification loop ensures robust commitment to death and has direct therapeutic implications: effective extrinsic-pathway activation depends on an intact mitochondrial response, and tumors with high c-FLIP expression or death-receptor loss remain resistant even when the receptor is engaged. Conversely, intrinsic-pathway blocks—particularly MCL-1 overexpression—can

limit the efficacy of extrinsic agonists. This interdependence explains why single-agent therapies targeting either pathway often fail, and it provides the rationale for combinations that engage both pathways (Dimberg et al., 2013).

8. Biomarkers and Patient Selection

Clinical experience with apoptosis-targeted agents has made clear that patient selection cannot rely on static gene-mutation or expression data. Bcl-2 overexpression is common in lung cancer but does not reliably predict response to Bcl-2 inhibition; TP53 mutation status alone does not identify which patients will benefit from p53 reactivation; and death-receptor expression levels have not reliably predicted TRAIL-agonist activity.

8.1 Functional Biomarkers: BH3 Profiling and Dynamic BH3 Profiling

Functional and dynamic biomarkers address this gap. **BH3 profiling** measures the proximity of a tumor cell to the apoptotic threshold by quantifying mitochondrial depolarization after exposure to BH3-only peptides, and it identifies the specific anti-apoptotic protein on which a tumor depends—information that static expression data cannot provide (Letai, 2008; Deng et al., 2007). **Dynamic BH3 profiling (DBP)** extends this approach by measuring changes in apoptotic priming after ex vivo drug exposure, functioning as a functional precision-medicine assay analogous to an antibiogram . In NSCLC, DBP has been shown to predict response to ALK inhibitors and to identify MCL-1 as a resistance node, supporting its use as a patient-selection tool for apoptosis-targeted combinations . In solid tumor models, DBP has predicted which BH3 mimetic enhances chemotherapy efficacy, with MCL-1 and BCL-xL targeting—but not BCL-2 targeting—showing synergy with cisplatin .

8.2 Circulating Biomarkers

Circulating biomarkers, including cleaved cytokeratin 18 (a caspase-cleavage product released during apoptosis) and circulating tumor DNA (ctDNA), offer complementary readouts of pathway engagement and early response. ctDNA-based monitoring in NSCLC is an area of active development, with applications in minimal residual disease detection and treatment response assessment . For rural settings, liquid biopsy approaches are particularly attractive because they reduce dependence on tissue biopsy infrastructure and can be performed at district-level laboratories with appropriate sample-handling protocols.

A trial design in which patients are stratified by functional apoptotic dependence—rather than by histology or a single mutation—is technically feasible and clinically necessary. Baseline expression of the Bcl-2 family member targeted by a given BH3 mimetic is a reasonable minimal enrollment criterion, provided it is interpreted alongside functional profiling rather than as a stand-alone predictor.

9. Implications for Rural Healthcare Advancement in India

The mechanistic literature reviewed above has a direct bearing on how apoptosis-targeted therapy should be deployed in rural India—and on why it currently is not.

9.1 The Rural Lung Cancer Burden

Rural India combines a high prevalence of smoking and smokeless tobacco use, widespread biomass-fuel exposure, and limited access to screening and molecular diagnostics, producing later-stage presentation and poorer outcomes than in

metropolitan centers (Indian Council of Medical Research, 2020; Gupta et al., 2011). The burden is not static: GBD 2021 data show that age-standardized lung cancer incidence and mortality rates in India have risen steadily, with the highest annual percentage changes in states including Uttarakhand, Uttar Pradesh, and Gujarat, many of which have large rural populations . At the same time, specialized thoracic oncology, immunohistochemistry, and next-generation sequencing are concentrated in urban tertiary centers, so that the molecular characterization on which apoptosis-targeted therapy depends is least available where the burden is greatest.

9.2 Four Linked Priorities for Rural-Relevant Translation

First, upstream risk reduction. Tobacco cessation, smokeless-tobacco control, and cleaner cooking-fuel transitions address the dominant preventable causes of rural lung cancer and reduce incidence at the population level (Gupta et al., 2011). These are the most cost-effective interventions available and should not be deferred in favor of downstream therapeutics.

Second, decentralized diagnostic pathways. Earlier detection and molecular characterization require decentralized sputum cytology, low-dose CT where feasible, telepathology for immunohistochemistry interpretation, and affordable biomarker testing. Low-dose CT screening has been shown to be feasible in India, with a lung cancer detection rate of 2.2% in a high-risk cohort and stage I diagnoses identified in three of four detected cases . Telepathology networks connecting district hospitals to regional cancer centers are a practical means of extending pathology expertise to rural settings, though standardization, infrastructure investment, and regulatory frameworks for AI-assisted image analysis remain works in progress . Without these, apoptosis-targeted therapy cannot be matched to the tumors that would benefit, and rural patients will continue to present at stages where curative-intent treatment is no longer possible.

Third, context-appropriate therapeutic delivery. Apoptosis-targeted agents must be developed and priced for delivery closer to home: oral BH3 mimetics and oral p53-reactivating compounds, regimens that can be safely administered in district day-care units, and tumor-selective delivery platforms that reduce toxicity and supportive-care burden. The cardiac toxicity observed with systemic MCL-1 inhibition is a particular concern in this context, because it requires monitoring infrastructure that may not be available at district level. This argues for prioritizing tumor-selective delivery platforms and oral agents with wider safety margins. The concentration of CAR-T and other advanced cellular therapies in apex centers is not a model that can be replicated at scale in rural India; the relevant question is which apoptosis-targeted approaches can be delivered safely outside tertiary care.

Fourth, biomarker validation in resource-limited settings. Functional biomarkers such as BH3 profiling and circulating apoptotic markers must be validated in rural and resource-limited populations, so that patient selection is based on tumor biology rather than on ability to pay or geographic access. DBP is technically demanding but can be performed on small tumor samples and has been adapted for high-throughput formats, suggesting that with appropriate quality-control frameworks it could be deployed at regional reference laboratories serving rural

catchment areas . Without such validation, precision oncology will widen rather than narrow the rural–urban survival gap.

9.3 Health-System Integration

These priorities are best implemented through a hub-and-spoke framework in which regional tertiary cancer centers provide molecular interpretation, protocol selection, and tele-oncology support, while district hospitals deliver oral targeted therapy, low-intensity combination regimens, and supportive care. Telepathology networks are a practical example of this architecture: digital slide scanning at district level, interpretation at regional hubs, and AI-assisted prescreening to prioritize cases, with the reporting pathologist retaining ultimate diagnostic responsibility . Community health workers can support tobacco cessation, early symptom recognition, and adherence monitoring. This architecture mirrors the decentralized models being developed for cancer care in India, but it has not been applied to apoptosis-targeted lung cancer therapy, and doing so is the central translational challenge for the coming decade.

10. Conclusion

Apoptosis dysregulation in lung cancer is a multi-layered problem: Bcl-2 family imbalance (with MCL-1 predominating in NSCLC), p53 inactivation, death-receptor pathway defects, and survival-signaling rewiring converge to produce a phenotype in which malignant cells survive therapeutic insults that would kill normal cells. The mechanistic literature has mapped these layers in detail, and the clinical literature has provided a complementary education in what happens when they are targeted in patients. Single-agent BH3 mimetics have limited activity in lung cancer; p53 reactivation has not yet produced durable benefit as monotherapy; and death-receptor agonists have been constrained by resistance and toxicity. Yet the same clinical experience has yielded design principles that are beginning to produce results: MCL-1-selective inhibition matched to NSCLC dependency, tumor-directed delivery of Bcl-2-family inhibitors, allele-specific p53 reactivation, and combinations that engage both apoptotic pathways and immune mechanisms.

For rural India, these principles carry particular urgency. Apoptosis-targeted therapies will not improve rural outcomes if they remain confined to urban tertiary centers. Rural-relevant translation requires linked progress in upstream risk reduction, decentralized diagnosis and molecular characterization, low-cost tumor-selective delivery, and validation of functional biomarkers in resource-limited settings. The cardiac toxicity of systemic MCL-1 inhibition and the technical demands of functional profiling are not arguments against pursuing apoptosis-targeted therapy in rural populations—they are arguments for designing delivery platforms and biomarker workflows that are compatible with rural health-system constraints. Understanding the molecular mechanisms behind apoptotic dysregulation remains essential, but the field has matured to the point where the more urgent task is to deploy those mechanisms selectively—in the right patients, with the right combination partners, at the right point in the therapeutic sequence, and in the right health-system context.

References

Acehan, D., Jiang, X., Morgan, D. G., Heuser, J. E., Wang, X., & Akey, C. W. (2002). Three-dimensional

structure of the apoptosome: Implications for assembly, procaspase-9 binding, and activation. *Molecular Cell*, 9(2), 423–432.

Ashkenazi, A. (2002). Targeting death and decoy receptors of the tumour-necrosis factor superfamily. *Nature Reviews Cancer*, 2(6), 420–430.

Ashkenazi, A. (2008). Directing cancer cells to self-destruct with pro-apoptotic receptor agonists. *Nature Reviews Drug Discovery*, 7(12), 1001–1012.

Ashkenazi, A., & Dixit, V. M. (1998). Death receptors: Signaling and modulation. *Science*, 281(5381), 1305–1308.

Aubrey, B. J., Strasser, A., & Kelly, G. L. (2016). Tumor-suppressor functions of the TP53 pathway. *Cold Spring Harbor Perspectives in Medicine*, 6(5), a026062.

Bratton, S. B., & Salvesen, G. S. (2010). Regulation of the Apaf-1-caspase-9 apoptosome. *Journal of Cell Science*, 123(19), 3209–3214.

Chen, L., Willis, S. N., Wei, A., Smith, B. J., Fletcher, J. I., Hinds, M. G., & Huang, D. C. (2005). Differential targeting of prosurvival Bcl-2 proteins by their BH3-only ligands allows complementary apoptotic function. *Cell Death and Differentiation*, 12(1), 112–125.

Cory, S., & Adams, J. M. (2002). The Bcl2 family: Regulators of the cellular life-or-death switch. *Nature Reviews Cancer*, 2(9), 647–656.

Deng, J., Carlson, N., Takeyama, K., Dal Cin, P., Shipp, M., & Letai, A. (2007). BH3 profiling identifies three distinct classes of apoptotic blocks to predict response to ABT-737 and conventional chemotherapeutic agents. *Cancer Cell*, 12(2), 171–185.

Dimberg, L. Y., Anderson, C. K., Camidge, R., Behbakht, K., Thorburn, A., & Ford, H. L. (2013). On the TRAIL to successful cancer therapy? Predicting and counteracting resistance against TRAIL-based therapeutics. *Oncogene*, 32(11), 1341–1350.

Djerbi, M., Screpanti, V., Catrina, A. I., Bogen, B., Biberfeld, P., & Grandien, A. (1999). The inhibitor of death receptor signaling, FLICE-inhibitory protein defines a new class of tumor progression factors. *The Journal of Experimental Medicine*, 190(7), 1025–1032.

Elmore, S. (2007). Apoptosis: A review of programmed cell death. *Toxicologic Pathology*, 35(4), 495–516.

Gonzalvez, F., & Ashkenazi, A. (2010). New insights into apoptosis signaling by Apo2L/TRAIL. *Oncogene*, 29(34), 4752–4765.

Green, D. R., & Kroemer, G. (2004). The pathophysiology of mitochondrial cell death. *Science*, 305(5684), 626–629.

Gross, A., McDonnell, J. M., & Korsmeyer, S. J. (1999). BCL-2 family members and the mitochondria in apoptosis. *Genes & Development*, 13(15), 1899–1911.

Gupta, P. C., Ray, C. S., Sinha, D. N., & Singh, P. K. (2011). Smokeless tobacco: A major public health problem in the SEA region: A

review. *Indian Journal of Public Health*, 55(3), 199–209.

Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: The next generation. *Cell*, 144(5), 646–674.

Herbst, R. S., Eckhardt, S. G., Kurzrock, R., Ebbinghaus, S., O'Dwyer, P. J., Gordon, M. S., ... & Ashkenazi, A. (2010). Phase I dose-escalation study of recombinant human Apo2L/TRAIL, a dual proapoptotic receptor agonist, in patients with advanced cancer. *Journal of Clinical Oncology*, 28(17), 2839–2846.

Indian Council of Medical Research. (2020). *National Cancer Registry Programme Report 2020*. ICMR.

Kale, J., Osterlund, E. J., & Andrews, D. W. (2018). BCL-2 family proteins: Changing partners in the dance towards death. *Cell Death & Differentiation*, 25(1), 65–80.

Kischkel, F. C., Hellbardt, S., Behrmann, I., Germer, M., Pawlita, M., Krammer, P. H., & Peter, M. E. (1995). Cytotoxicity-dependent APO-1 (Fas/CD95)-associated proteins form a death-inducing signaling complex (DISC) with the receptor. *The EMBO Journal*, 14(22), 5579–5588.

Letai, A. (2008). Diagnosing and exploiting cancer's addiction to blocks in the apoptotic pathway. *Nature Reviews Cancer*, 8(2), 121–132.

Li, H., Zhu, H., Xu, C. J., & Yuan, J. (1998). Cleavage of BID by caspase 8 mediates the mitochondrial damage in the Fas pathway of apoptosis. *Cell*, 94(4), 491–501.

Luo, X., Budihardjo, I., Zou, H., Slaughter, C., & Wang, X. (1998). Bid, a Bcl2 interacting protein, mediates cytochrome c release from mitochondria in response to activation of cell surface death receptors. *Cell*, 94(4), 481–490.

Micheau, O., & Tschopp, J. (2003). Induction of TNF receptor I-mediated apoptosis via two sequential signaling complexes. *Cell*, 114(2), 181–190.

Moldoveanu, T., Grace, C. R., Llambi, F., Nourse, A., Fitzgerald, P., Gehring, K., & Green, D. R. (2013). BID-induced structural changes in BAK promote apoptosis. *Nature Structural & Molecular Biology*, 20(5), 589–597.

Peter, M. E., & Krammer, P. H. (2003). The CD95 (APO-1/Fas) DISC and beyond. *Cell Death & Differentiation*, 10(1), 26–35.

Ren, D., Tu, H. C., Kim, H., Wang, G. X., Bean, G. R., Takeuchi, O., ... & Cheng, E. H. (2010). BID, BIM, and PUMA are essential for activation of the BAX- and BAK-dependent cell death program. *Science*, 330(6009), 1390–1393.

Riedl, S. J., & Salvesen, G. S. (2007). The apoptosome: Signalling platform of cell death. *Nature Reviews Molecular Cell Biology*, 8(5), 405–413.

Roberts, A. W., Davids, M. S., Pagel, J. M., Kahl, B. S., Puvvada, S. D., Gerecitano, J. F., ... & Seymour, J. F. (2016). Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *New England Journal of Medicine*, 374(4), 311–322.

Roth, J. A., Nguyen, D., Lawrence, D. D., Kemp, B. L., Carrasco, C. H., Ferson, D. Z., ... & Cristiano, R. J. (1996). Retrovirus-mediated wild-type p53 gene transfer to tumors of patients with lung cancer. *Nature Medicine*, 2(9), 985–991.

Safa, A. R. (2012). c-FLIP, a master anti-apoptotic regulator. *Experimental Oncology*, 34(3), 176–184.

Souers, A. J., Leverson, J. D., Boghaert, E. R., Ackler, S. L., Catron, N. D., Chen, J., ... & Elmore, S. W. (2013). ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. *Nature Medicine*, 19(2), 202–208.

Vivanco, I., & Sawyers, C. L. (2002). The phosphatidylinositol 3-kinase AKT pathway in human cancer. *Nature Reviews Cancer*, 2(7), 489–501.

Vousden, K. H., & Lane, D. P. (2007). p53 in health and disease. *Nature Reviews Molecular Cell Biology*, 8(4), 275–283.

Vousden, K. H., & Prives, C. (2009). Blinded by the light: The growing complexity of p53. *Cell*, 137(3), 413–431.

Willis, S. N., Chen, L., Dewson, G., Wei, A., Naik, E., Fletcher, J. I., ... & Huang, D. C. (2005). Proapoptotic Bak is sequestered by Mcl-1 and Bcl-xL, but not Bcl-2, until displaced by BH3-only proteins. *Genes & Development*, 19(11), 1294–1305.

Youle, R. J., & Strasser, A. (2008). The BCL-2 protein family: Opposing activities that mediate cell death. *Nature Reviews Molecular Cell Biology*, 9(1), 47–59.