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Review Article

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Pharmacological Inhibition of Hsp70 to Degrade c-FLIP: A Novel Indirect Approach for Cancer Therapy: A Narrative Review

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Abstract: The cellular FLICE-inhibitory protein (c-FLIP) is a master regulator of programmed cell death, functioning as a key suppressor of extrinsic apoptosis mediated by death receptor signaling. Its persistent overexpression is a hallmark of numerous cancers, contributing directly to tumorigenesis, therapy resistance, and immune evasion. However, direct pharmacological targeting of c-FLIP has proven exceptionally challenging because of its unstructured protein-interaction domains. This review explores an innovative indirect strategy: inhibiting the molecular chaperone heat shock protein 70 (Hsp70) to promote the proteasomal degradation of c-FLIP. Hsp70 is frequently overexpressed in malignancies and is critically involved in stabilizing oncoproteins, such as c-FLIP, shielding them from ubiquitination and degradation. A synthesis of compelling evidence was presented to demonstrate that diverse Hsp70 inhibitors—including ATP-competitive agents (VER-155008), allosteric inhibitors (PES), and co-chaperone disruptors (MAL3-101)—effectively deplete c-FLIP levels. This depletion robustly re-sensitizes resistant cancer cells to apoptosis, which is induced by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and Fas ligand (FasL). This overcomes conventional chemoresistance and potentially restores immune-mediated cytotoxicity by dismantling a key protective mechanism. This article details the molecular mechanisms of the Hsp70-c-FLIP axis, evaluates the current landscape of Hsp70-targeted therapeutics, and discusses the significant promise and challenges—such as isoform selectivity and drug development hurdles—of exploiting this chaperone-client relationship. The present review concludes that targeting Hsp70 to disrupt c-FLIP stability represents a highly promising and indirect anticancer strategy, warranting extensive further investigation in both preclinical models and clinical settings.

1. Introduction

Avoidance of programmed cell death, which is also known as apoptosis, is a fundamental aspect of oncogenesis. This process underpins tumor formation, disease progression, and resistance to therapeutic interventions[1, 2]. Initiated by death ligands such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and Fas ligand (FasL), the extrinsic pathway, among the various apoptotic pathways, plays a crucial role in immune surveillance. Engagement of death ligands with their corresponding death receptors leads to the assembly of the death-inducing signaling complex (DISC), thereby activating caspase-8 and initiating the apoptotic signaling cascade [3, 4]. A crucial negative regulator in this pathway is the cellular FLICE-inhibitory protein (c-FLIP). This essential anti-apoptotic protein exists in multiple splice variants, including FLIP long (c-FLIPL), FLIP short (c-FLIPS), and

FLIPR. It exerts its function by interacting with the DISC, where it serves as a catalytically inactive decoy. By forming heterodimers with caspase-8 and procaspase-8, c-FLIP inhibits their full activation, leading to prevent the propagation of the apoptotic death signal [4, 5]. The oncogenic significance of c-FLIP is underscored by its frequent overexpression across a range of malignancies, including melanoma, non-small cell lung carcinoma, and pancreatic ductal adenocarcinoma. Its overexpression is strongly correlated with adverse prognostic outcomes, resistance to chemotherapy and radiotherapy, and its role in enabling tumor cells to evade immune surveillance by conferring protection against T-lymphocyte–mediated cytotoxicity [6].

Targeting c-FLIP directly with small-molecule inhibitors presents considerable challenges due to the predominantly unstructured nature of its protein-interaction domains and the complexity of its integration into cellular processes [7, 8]. This has prompted the exploration of indirect targeting strategies that leverage post-translational regulatory mechanisms that affect c-FLIP stability. c-FLIP is a transient protein, whose intracellular levels are tightly regulated through ubiquitin-mediated proteasomal degradation[6].

Recent research emphasizes the role of Heat Shock Protein 70 in stabilizing c-FLIP; this, in turn, aids cancer progression by supporting oncoproteins, reducing proteotoxic stress, and inhibiting apoptosis [9]**.** Emerging evidence robustly supports c-FLIP as a bona fide client protein of heat shock protein 70 (Hsp70). The molecular chaperone interacts with c-FLIP, shielding it from E3 ubiquitin ligases, such as Itch, thereby substantially increasing its half-life and enhancing its anti-apoptotic function [10, 11].

This review will thoroughly examine the scientific rationale for targeting the Hsp70-c-FLIP axis with pharmacological interventions as an innovative, indirect approach to cancer therapy. It will synthesize mechanistic evidence elucidating the role of Hsp70 in stabilizing c-FLIP, assess the current landscape of Hsp70 inhibitors, and discuss the therapeutic promise and associated challenges of leveraging this chaperone-client interaction to restore apoptosis in cancer types resistant to it.

2. Literature Search Methodology

A comprehensive and unbiased synthesis of the current understanding of the Hsp70-c-FLIP axis was achieved through a targeted literature review. The search encompassed primary electronic databases including PubMed/MEDLINE, Scopus, and Web of Science. No restrictions were applied to the start date, and the search was limited to December 2024 to ensure inclusion of the most recent developments.

The search strategy utilized a combination of key terms and Boolean operators. Core terms included: “c-FLIP” OR “CFLAR” OR “CASP8 and Fas-Associated Death Domain (FADD)-like apoptosis regulator,” and “Hsp70” OR “HSPA1A” OR “HSPA8” OR “heat shock protein 70.” These were supplemented with secondary terms related to “inhibitor,” “targeting,” “degradation,” or “chaperone,” as well as “cancer,” “apoptosis,” and “therapy resistance.”

The initial search results were evaluated for relevance based on their titles and abstracts. Additionally, reference lists of key articles were manually searched to identify additional relevant studies. The selected literature comprised original research articles, authoritative reviews, and seminal studies that explored the molecular mechanisms, preclinical evidence, and therapeutic potential related to the Hsp70-c-FLIP interaction. This approach aimed to establish a solid foundation for the narrative synthesis included in this review.

3. The Central Role of c-FLIP in Apoptosis Evasion and Cancer

3.1. Structure and Isoforms

The CFLAR gene (CASP8 and FADD-like apoptosis regulator), located on chromosome 2q33, encodes several alternatively spliced isoforms. The most prominent variants include c-FLIPL, c-FLIPS, and c-FLIPR [12]. The 55-kDa isoform of c-FLIPL is structurally similar to caspase-8, containing two N-terminal death effector domains (DEDs) that facilitate recruitment to the DISC and a catalytically inactive C-terminal caspase-like domain [13, 14]. In contrast, the shorter isoforms—26-kDa c-FLIPS and 24-kDa c-FLIPR—contain only the two DEDs and lack the caspase-like domain [15].

Although all isoforms can be recruited to the DISC via DED-mediated interactions, their structural differences underlie their distinct functional roles. c-FLIPL can form heterodimers with caspase-8 that maintain limited catalytic activity under particular conditions, potentially initiating non-apoptotic signaling pathways. Conversely, c-FLIPS and c-FLIPR serve solely as inhibitors, effectively preventing caspase-8 activation [16, 17], as shown in table 1.

Table 1: Key isoforms of c-FLIP and their functional roles.

Ref	Isoform	Size (kDa)	Key Structural Features	Primary Function at the DISC	Impact on Cell Fate
[14]	**c-FLIPS**	26	Two Death Effector Domains only.	Acts as a dominant-negative; it competes with procaspase-8 for binding to FADD.	Potently inhibits caspase-8 activation and apoptosis.
[18]	**c-FLIPL**	55	Two Death Effector Domains, caspase-like domain (inactive)	Forms heterodimers with caspase-8; allows limited, non-apoptotic cleavage.	Inhibits full apoptosis; promotes non-apoptotic signaling (nuclear factor kappa B, Mitogen-Activated Protein Kinase).
[19]	**c-FLIPR**	24	Two Death Effector Domains only.	Functions similarly to c-FLIPS; competes for DISC recruitment.	Potently inhibits caspase-8 activation and apoptosis.

3.2. Mechanisms of Apoptosis

The c-FLIP functions as a potent anti-apoptotic agent primarily at the DISC. It acts as a catalytically inactive homolog of caspase-8, consequently competing with procaspase-8 for binding to the adaptor protein FADD. This competitive interaction inhibits the essential dimerization and autocleavage of caspase-8, processes that are critical for the initiation of apoptosis [20]. Structural analyses indicate that the DEDs of c-FLIP exhibit a higher binding affinity for FADD compared to those of caspase-8. This enhanced affinity enables c-FLIP DEDs to effectively occupy binding sites, thereby forming a structural barrier that impedes the initiation of downstream apoptotic signaling [13].

Beyond simple competitive inhibition, c-FLIP isoforms differentially modulate cell fate via intricate allosteric mechanisms. The long isoform (c-FLIPL) forms heterodimers with caspase-8 that exhibit limited proteolytic activity, which is insufficient to induce full apoptosis. However, this complex can activate alternative signaling pathways, such as nuclear factor kappa B, mitogen-activated protein kinase, and extracellular signal–regulated kinase [21]. By converting a death signal into a pro-survival one, this redirected signaling promotes inflammatory responses, enhances cellular growth, and strengthens survival pathways. The short isoforms (c-FLIPS), which lack the caspase-like domain, act as dominant-negative inhibitors, which are entirely blocking caspase-8 activation [22].

The stoichiometric ratio of c-FLIP to caspase-8 at the DISC serves as a critical molecular switch to determine cellular fate. Elevated levels of c-FLIP effectively inhibit apoptosis, whereas intermediate concentrations permit limited caspase-8 activity, which may facilitate non-apoptotic signaling pathways. This precise regulatory mechanism enables cancer cells to resist death receptor-mediated apoptosis while concurrently exploiting these signals to enhance survival and proliferation. Such sophisticated adaptation significantly contributes to therapeutic resistance and tumor progression [23].

3.3. Structural Mechanism of Death Effector Domains-Mediated Inhibition

The principal mechanism by which c-FLIP inhibits apoptosis involves competitive binding at the DISC, which is a process determined by the structural characteristics of its DEDs [13].

The DED constitutes a conserved protein interaction module found in FADD, procaspase-8, and all c-FLIP isoforms. Within the DISC, these domains facilitate homotypic (DED-DED) interactions, thereby mediating the recruitment of procaspase-8 and c-FLIP to FADD [24].

Structural and biophysical analyses reveal that the DEDs of c-FLIP exhibit a higher binding affinity for the DED of FADD compared to those of procaspase-8. This increased affinity enables c-FLIP to effectively compete with procaspase-8 for binding to FADD. By occupying these sites, c-FLIP DEDs establish

a physical barrier at the DISC; this sterically prevents the dimerization and subsequent activation of caspase-8, and in turn inhibits the initiation of the apoptotic cascade [25].

3.4. Role in Therapy Resistance and Immune Evasion

The anti-apoptotic function of c-FLIP plays a pivotal role in two prominent clinical challenges in oncology: therapy resistance and immune escape. Elevated levels of c-FLIP inhibit the activation of caspase-8 at the DISC, thereby conferring significant resistance to death receptor-targeted therapies, such as recombinant TRAIL and TRAIL receptor agonists [26]. This resistance similarly extends to various conventional chemotherapeutic agents, such as 5-fluorouracil and cisplatin, as well as to radiotherapy. These treatments often rely on the extrinsic pathway to augment their cytotoxic effects through secondary autocrine and paracrine signaling by death ligands [7, 27].

Furthermore, c-FLIP functions as a critical mediator in tumor immune evasion. Cytotoxic T lymphocytes and natural killer cells predominantly induce apoptosis in target cells through the granzyme B/perforin pathway, engaging death receptors such as Fas (CD95) on the target cell [28]. High levels of c-FLIP expression in cancer cells effectively inhibit FasL-mediated apoptosis, thereby conferring resistance to this essential mechanism of both the adaptive and innate immune responses [29]. This protective shield allows tumor cells to persist within an immunologically hostile microenvironment, facilitating immune evasion and disease progression. As a result, overexpression of c-FLIP is frequently associated with poor prognosis and therapeutic failure in diverse cancers [5].

4. Hsp70: The Oncogenic Chaperone

4.1. Structure and Function in Proteostasis

Hsp70 is a highly conserved, adenosine triphosphate (ATP)-dependent molecular chaperone that is a crucial component of the cellular proteostasis network. Its primary function is to facilitate proper folding of nascent polypeptide chains, prevent aggregation of misfolded proteins, and direct client proteins toward degradation or refolding pathways. The operational cycle of Hsp70 is regulated allosterically between its two principal domains: an N-terminal nucleotide-binding domain (NBD). This binds and hydrolyzes ATP and a C-terminal substrate-binding domain, which interacts with hydrophobic peptide segments of client proteins [30].

In the ATP-bound conformation, Hsp70 exhibits low substrate affinity coupled with rapid exchange rates. The hydrolysis of ATP, significantly facilitated by J-domain co-chaperones, such as Hsp40, induces a conformational transition to the adenosine diphosphate-bound state. This state is characterized by a high affinity for substrate proteins, consequently "trapping" the clients effectively [30]. Client release is triggered by nucleotide exchange factors, such as Bcl-2-associated athanogene family proteins. These proteins promote adenosine diphosphate dissociation and facilitate ATP rebinding, allowing the cycle to continue. This regulation, which is mediated by co-chaperones, enables Hsp70 to perform various functions, including protein folding, protein transport across organelle membranes, and protein aggregation. This process helps maintain the health of the cell's proteins under normal and stressful conditions [31, 32].

4.2. Hsp70's Function in Protein Stabilization

The oncogenic function of Hsp70 primarily arises from its capacity to stabilize a diverse array of client proteins that are essential for tumor progression and therapeutic resistance. Hsp70 interacts with short, degenerate hydrophobic peptide segments that are exposed on inherently unstable proteins or under stress conditions [30]. This interaction is not solely protective; it also disrupts the cell's quality-control mechanisms. Hsp70 effectively binds to and hides these hydrophobic degrons (i.e. short sequences that serve as recognition sites for E3 ubiquitin ligases), thereby preventing the ubiquitin ligase machinery from tagging the client protein for proteasome-mediated degradation [9, 33].

This chaperone-mediated stabilization extends the half-life of numerous oncoproteins, including mutant p53, Akt, Raf-1, and, notably, c-FLIP, which is a central focus of this review. The persistent activity of these stabilized clients facilitates uncontrolled cellular proliferation, inhibits apoptotic processes, and

enhances metastatic potential. Under the stressful tumor microenvironment—characterized by hypoxia, nutrient scarcity, and proteotoxic stress—the overexpression of Hsp70 emerges as a crucial adaptive mechanism, allowing cancer cells to maintain a functional proteome and endure conditions that would otherwise disrupt proteostasis [34, 35], as shown in figure 1.

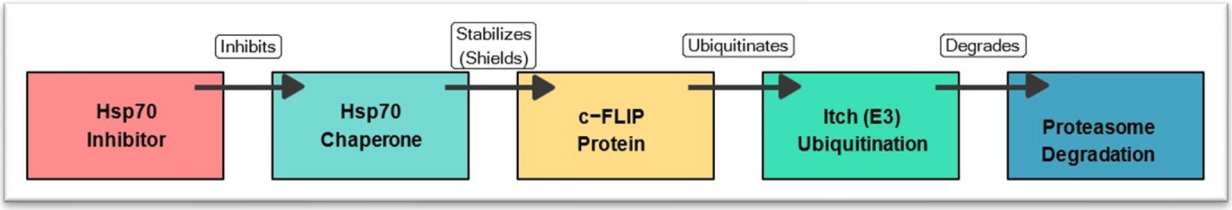

Figure 1: Hsp70–c-FLIP Stabilization and Inhibition Mechanism. The molecular mechanism by which Hsp70 stabilizes c-FLIP and the effects of its pharmacological disruption are examined. Under physiological conditions, Hsp70 interacts with hydrophobic degrons on c-FLIP, shielding it from recognition by the E3 ubiquitin ligase Itch. This interaction prevents ubiquitination and subsequent proteasomal degradation of c-FLIP. Pharmacological agents such as VER-155008, 2-Phenylethynesulfonamide, or MAL3-101 inhibit Hsp70 activity, thereby disrupting this protective binding. Consequently, c-FLIP degrons are exposed, leading to Itch-mediated polyubiquitination and proteasome-mediated degradation. This process reactivates caspase-8 and enhances cellular sensitivity to extrinsic apoptotic stimuli.

4.3. The Role of Hsp70 in Modulating Immunity and Cancer Surveillance

Beyond its function in stabilizing intracellular proteins, Hsp70 plays a pivotal role in modulating the immune system, influencing both tumor detection and immune escape. Having been released by stressed or apoptotic cancer cells, extracellular Hsp70 functions as a damage-associated molecular pattern, thereby initiating innate immune responses by binding to pattern recognition receptors, such as Toll-like receptors, on antigen-presenting cells [36]. This interaction promotes antigen-presenting cell maturation and the cross-presentation of tumor-associated antigens, leading to the stimulation of adaptive anti-tumor immunity. Conversely, cancer cells exploit Hsp70 to create an immunosuppressive tumor microenvironment. Tumor-derived Hsp70 can induce the expansion of regulatory T cells and myeloid-derived suppressor cells, which suppress cytotoxic T lymphocyte and natural killer cell activity [37, 38].

Intracellularly, Hsp70 stabilizes client proteins, such as c-FLIP; thus, they directly contribute to cancer cells' resistance to immune-mediated cytotoxicity via the Fas and TRAIL death receptor pathways. This dual functionality—serving as an extracellular immune adjuvant and reinforcing intracellular tumor-cell defenses—underscores the complexity of Hsp70's role in cancer immunology. Therapeutic targeting of Hsp70 could offer a dual advantage: destabilizing oncogenic proteins and resensitizing tumor cells to immune-mediated destruction by disrupting critical survival mechanisms [39, 40].

5. The Hsp70-c-FLIP Axis: A Mechanistic Link

5.1. Evidence of Interaction and Stabilization

The hypothesis that c-FLIP functions as a bona fide client protein of Hsp70 is robustly supported by converging biochemical, genetic, and pharmacological evidence. Initial co-immunoprecipitation assays conducted across diverse cancer cell lines—including Hodgkin's lymphoma and pancreatic adenocarcinoma—have consistently demonstrated a direct physical interaction between Hsp70 and c-FLIP [41]. Crucially, this interaction is not merely incidental; it is functionally significant and becomes markedly enhanced under conditions of cellular stress, such as heat shock or exposure to chemotherapeutic agents, which strongly induce Hsp70 overexpression. This indicates a dynamic and stress-responsive relationship between the chaperone and its client [42-44].

The most compelling evidence supporting Hsp70-mediated stabilization of c-FLIP derives from loss-of-function experiments. Specifically, targeted genetic knockdown of Hsp70 using small interfering RNA (siRNA) or short hairpin RNA (shRNA) results in a rapid and pronounced reduction in c-FLIP protein levels. In contrast, c-FLIP mRNA expression remains unchanged, subsequently confirming that Hsp70 exerts its regulatory effect post-translationally by augmenting c-FLIP stability rather than affecting its transcription [45]. This finding is corroborated by pharmacological inhibition with compounds, such as VER-155008 and PES, which mimic the siRNA phenotype by dose-dependently

reducing c-FLIP protein levels. Mechanistically, this reduction is mitigated by pretreatment with proteasome inhibitors, such as MG-132, consequently establishing a direct link between Hsp70 inhibition and enhanced ubiquitin-proteasome system-mediated degradation of c-FLIP [34, 46].

The ubiquitin-proteasome system is the primary mechanism for targeted protein degradation in the cell. This process involves the covalent linkage of ubiquitin chains to lysine residues on substrate proteins, such as c-FLIP, mediated by E3 ubiquitin ligases, including Itch. Polyubiquitin chains serve as signals for recognition by the 26S proteasome, a large proteolytic complex responsible for protein degradation. This highly regulated pathway maintains the rapid turnover of c-FLIP, thereby modulating its anti-apoptotic activity [47].

5.2. Proposed Molecular Mechanism

The precise molecular mechanisms underlying Hsp70-mediated stabilization of c-FLIP remain under investigation. However, a compelling model has been proposed based on current evidence. According to this model, Hsp70 directly interacts with specific, likely hydrophobic, regions of the c-FLIP protein. This interaction appears to be active, as it protects c-FLIP from its primary cellular regulator, which is the ubiquitin-proteasome system. Notably, the E3 ubiquitin ligase Itch (also known as AIP4) has been definitively identified as a critical enzyme that mediates the polyubiquitination of c-FLIP, targeting it for proteasomal degradation [34, 48].

The interaction between Hsp70 and c-FLIP is postulated to form a steric hindrance; this, in turn, obstructs the degron motifs on c-FLIP that Itch typically recognizes. This obstruction impedes the efficient transfer of ubiquitin molecules, consequently preventing the proteasomal degradation of c-FLIP [30]. Alternatively, or concurrently, the Hsp70-c-FLIP complex may adopt a conformation that renders the ubiquitination sites on c-FLIP inaccessible to the Itch catalytic domain. Pharmacological inhibition or genetic depletion of Hsp70 disrupts this chaperone shielding mechanism. Consequently, the degrons on c-FLIP are exposed, and this facilitates rapid recognition and polyubiquitination by Itch, which is followed by immediate engagement with the 26S proteasome [41]. Following Hsp70 inhibition, this model systematically elucidates the rapid depletion of c-FLIP protein, and this helps to notice the absence of alterations in its mRNA expression levels. Furthermore, it underscores the Hsp70-c-FLIP-Itch axis as a promising therapeutic target for inducing pro-apoptotic protein activity, as shown in figure 2.

6. Therapeutic Targeting: Hsp70 Inhibitors to Deplete c-FLIP

6.1. Classes of Hsp70 Inhibitors

The development of Hsp70 inhibitors has led to the emergence of several distinct pharmacological classes, with each targeting specific components of the Hsp70 chaperone cycle. However, none of these inhibitors has yet received clinical approval as summarized below.

6.1.1. ATP-Competitive Inhibitors

This class targets the conserved NBD explicitly to interfere with the essential ATPase cycle. VER-155008, a prototypical adenosine analogue, exhibits high-affinity binding to the ATP pocket, subsequently inhibiting ATP hydrolysis. This action stabilizes Hsp70 in a low-substrate-affinity state, consequently preventing client protein binding, promoting their release, and facilitating subsequent degradation. Recent developments have introduced compounds, such as JG-98, which also target the NBD. These newer compounds demonstrate enhanced potency and represent a next-generation class of ATP-competitive inhibitors [49, 50].

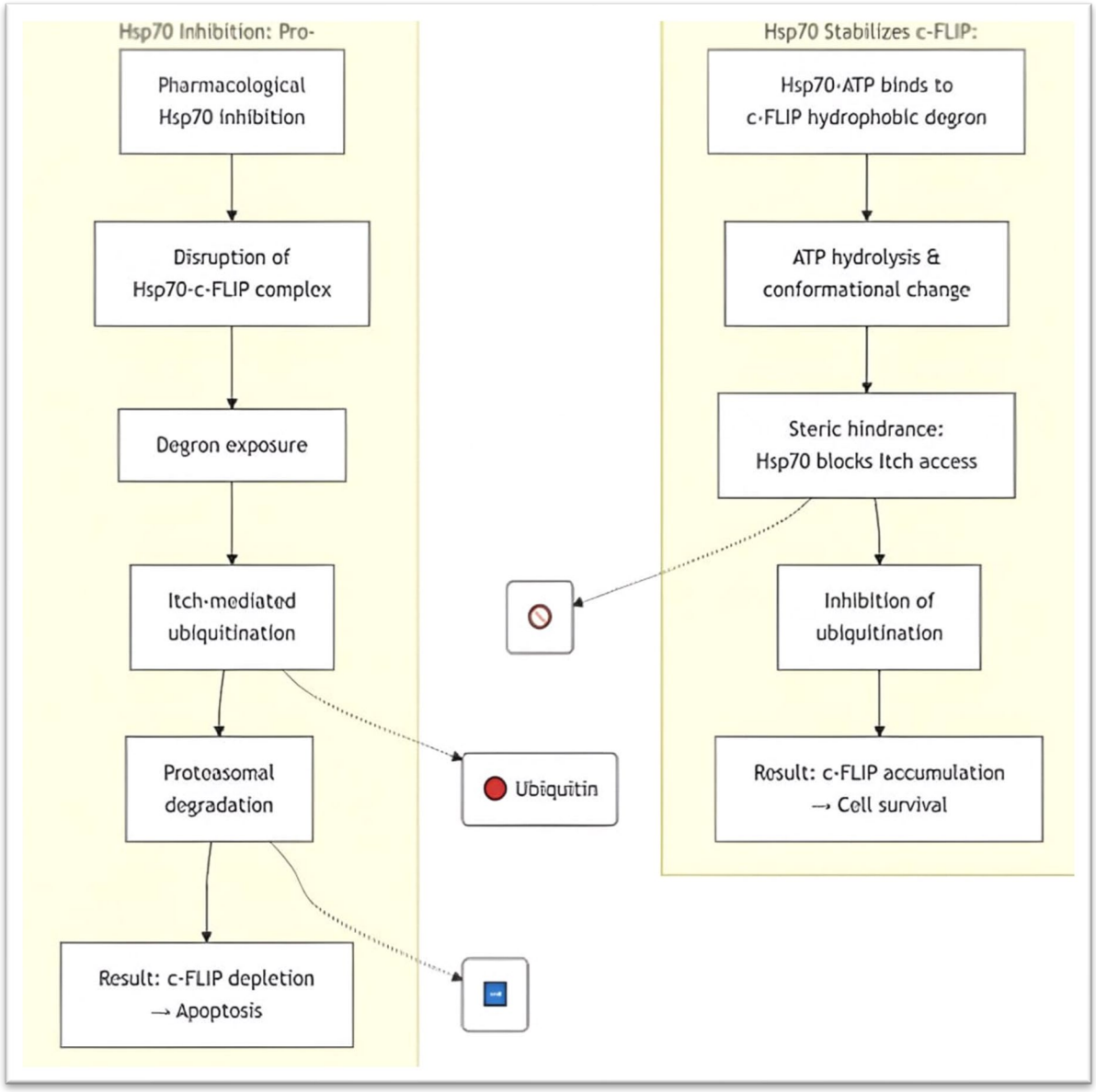

Figure 2: Proposed molecular mechanism of Hsp70-mediated c-FLIP stabilization and its pharmacological disruption. Under normal conditions, Hsp70 binds to hydrophobic degrons on c-FLIP, shielding it from recognition by the E3 ubiquitin ligase Itch. This chaperone-client interaction prevents c-FLIP ubiquitination and subsequent proteasomal degradation, thereby stabilizing c-FLIP and promoting its anti-apoptotic function. Pharmacological inhibition of Hsp70 (e.g., by VER-155008, PES, or MAL3-101) disrupts this protective interaction, leading to exposure of c-FLIP degrons, Itch-mediated polyubiquitination, and proteasomal degradation of c-FLIP. The resulting depletion of c-FLIP restores caspase-8 activation at the DISC, thereby re-sensitizing cancer cells to extrinsic apoptotic stimuli.

6.1.2. Allosteric Inhibitors

These compounds bind to alternative sites, inducing conformational changes that impair their function. 2-Phenylethynesulfonamide (also known as Pifithrin-μ) is a well-characterized inhibitor that interacts with a cryptic cleft within the substrate-binding domain; this, in turn, allosterically locks it in a closed conformation. This mechanism not only prevents client protein binding but also appears to destabilize oncogenic clients more effectively than housekeeping proteins [51, 52].

6.1.3. Chemical Modulators Targeting Co-Chaperone Interactions

This innovative compound targets the functional epitopes involved in the interaction between Hsp70 and its essential co-chaperones. For instance, MAL3-101 specifically binds to the interface between Hsp70 and the J-domain of Hsp40. Disruption of this critical interaction inhibits Hsp40-mediated

ATP hydrolysis, leading to effectively arresting the chaperone cycle and resulting in the destabilization of client proteins [53]. This approach offers a potential pathway to achieve greater selectivity (Table 2).

Table 2: Classes of Hsp70 inhibitors and their mechanisms.

Ref	Class	Mechanism of Action	Representative Compound(s)	Key Advantages	Key Challenges
[54]	**ATP-competitive**	Binds to the nucleotide-binding domain, blocking ATP hydrolysis and trapping Hsp70 in a low-affinity state.	VER-155008, JG-98	Targets a well-defined, conserved active site.	Often lack isoform selectivity; can have poor drug-like properties.
[55]	**Allosteric**	Binds to a cryptic cleft in the substrate-binding domain, locking it in a closed conformation.	2-Phenylethynesulfonamide (Pifithrin-μ)	May preferentially destabilize oncogenic clients over housekeeping proteins.	Off-target effects; potential toxicity.
[56]	**Co-chaperone Disruptors**	Inhibits the interaction between Hsp70 and its co-chaperones (e.g., Hsp40), halting the chaperone cycle.	MAL3-101	Potential for greater selectivity by targeting protein-protein interfaces.	The complexity of the chaperone network may lead to the development of compensatory mechanisms.
[57]	**Repurposed Drugs**	Off-target or newly discovered interactions that inhibit Hsp70 function or expression.	Mebendazole, Oridonin	Known safety profiles; can accelerate clinical translation.	Mechanism may not be fully elucidated; potency may be lower.

6.2. Preclinical Evidence of Efficacy

Preclinical investigations employing Hsp70 inhibitors have yielded substantial and diverse evidence corroborating their efficacy in targeting the Hsp70-c-FLIP axis. Administration of compounds, such as VER-155008 and 2-Phenylethynesulfonamide across a range of cancer cell lines—including breast (MDA-MB-231), lung (A549), and leukemia (Jurkat)—consistently induces a rapid, dose-dependent diminution in c-FLIP protein levels, subsequently affirming the primary mechanism of action [45]. This pharmacological intervention effectively reverses the fundamental blockade of apoptosis. Cancer cells that exhibit inherent resistance to death receptor agonists, such as recombinant TRAIL or FasL, exhibit substantial, synergistic induction of apoptosis when concurrently treated with an Hsp70 inhibitor, indicating significant re-sensitization of the extrinsic apoptotic pathway [49].

Beyond merely targeting death receptors, Hsp70 inhibition demonstrates a broad capacity to overcome multidrug resistance. Empirical studies suggest that Hsp70 inhibition depletes c-FLIP; thus, it resensitizes various cancer models to standard chemotherapeutic agents, including 5-fluorouracil, cisplatin, and doxorubicin. This effect is primarily mediated by preventing c-FLIP-driven suppression of caspase-8 activation, a critical downstream event in chemotherapy-induced apoptosis [58]. Furthermore, this strategy demonstrates significant promise in immuno45-oncology. By disrupting the c-FLIP-mediated protective mechanism that shields tumor cells from Fas-induced cytolysis, Hsp70 inhibitors may enhance the cytotoxicity of T lymphocytes and natural killer cells. This suggests the potential for synergistic effects when combined with adoptive cell transfer or immune checkpoint blockade therapies [59, 60], as shown in table 3 and figure 3.

Table 3: Preclinical evidence for Hsp70 inhibition in cancer models.

Ref	Hsp70 Inhibitor	Cancer Model(s) Tested	Observed Effect on c-FLIP	Functional Outcome
[61]	**VER-155008**	Breast (MDA-MB-231), Lung (A549)	Dose-dependent depletion	Re-sensitization to TRAIL-induced apoptosis
[62]	**2-Phenylethynesulfonamide (Pifithrin-μ)**	Leukemia (Jurkat), Pancreatic	Rapid reduction in protein levels	Overcoming resistance to FasL and chemotherapy
[63]	**MAL3-101**	Multiple Myeloma	Increased ubiquitination and degradation	Synergistic cell death with proteasome inhibitors
[64]	**si/shRNA (Genetic)**	Various (Pan-cancer)	Knockdown reduces c-FLIP protein (not mRNA)	Validation of axis; enhanced apoptosis
[65]	**Mebendazole**	Acute Myeloid Leukemia	Client protein degradation via HSP inhibition	Anti-leukemic effects in preclinical models

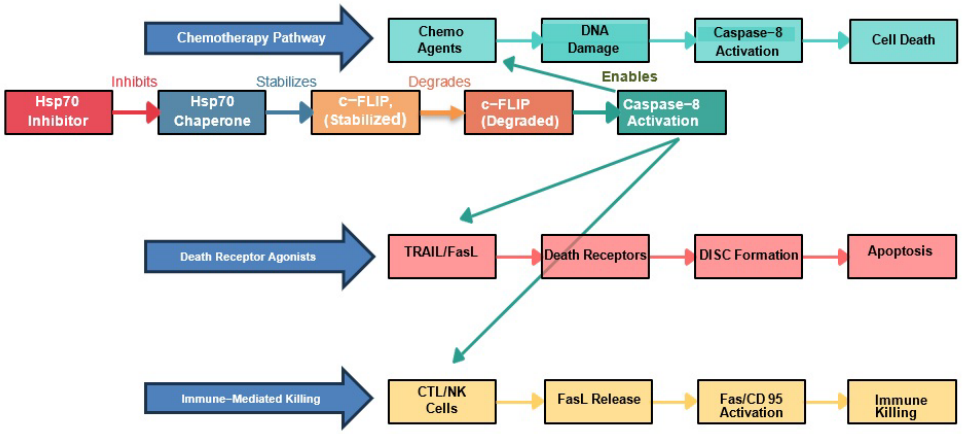

Figure 3: Hsp70 inhibition re-sensitizes resistant cancer cells to multiple therapeutic modalities. (Schematic representation of the multimodal therapeutic re-sensitization achieved through Hsp70 inhibition and subsequent c-FLIP depletion). The central axis depicts the core mechanism: pharmacological inhibition of Hsp70 disrupts its chaperone function, leading to proteasomal degradation of c-FLIP and restoration of caspase-8 activation at the DISC. This restored apoptotic signaling re-enables three key therapeutic pathways that are otherwise suppressed in resistant cancers: (1) Death Receptor Agonists (TRAIL/FasL Pathway): Re-sensitization to extrinsic apoptosis triggered by death ligands; (2) Conventional Chemotherapy: Overcoming chemoresistance by enabling caspase-8-mediated apoptotic responses to DNA-damaging agents; and (3) Immune-Mediated Cytotoxicity: Enhancing the killing efficacy of cytotoxic T lymphocytes and natural killer cells by removing the c-FLIP blockade of Fas/CD95 death receptor signaling. This integrative model highlights the broad potential of targeting the Hsp70–c-FLIP axis to overcome multidrug and multimodal therapy resistance.

6.3. Chaperone-Mediated Modulation of Immune Cell Function

Molecular chaperones (i.e. Hsp70 and Hsp90) play a pivotal role in modulating the function of T lymphocytes and natural killer cells. In cytotoxic T lymphocytes, these chaperones are instrumental in ensuring proper folding and assembly of essential signaling proteins, including those that constitute the T-cell receptor complex, leading to underpinning of effective antigen recognition and cellular activation [66]. In natural killer cells, chaperone proteins play a crucial role in maintaining the stability of cytotoxic granules and the perforin/granzyme apparatus, which are essential for the destruction of target cells. Conversely, tumor cells can release extracellular chaperones that directly inhibit cytotoxic T lymphocyte and natural killer cell functions by engaging inhibitory receptors, thereby facilitating immune escape [36].

6.4. Novel Strategies and Future Directions

Beyond monotherapy, the future of Hsp70 inhibition will largely depend on the development of strategic combination approaches. These approaches described below.

6.4.1. Synthetic Lethality with Proteasome Inhibitors

While proteasome inhibitors, such as bortezomib, facilitate the degradation of c-FLIP, they concurrently elicit a substantial upregulation of Hsp70 as a cellular survival mechanism. The concomitant use of an Hsp70 inhibitor can mitigate this resistance, consequently producing a synthetic lethal interaction that induces pronounced proteotoxic stress and activates subsequent cellular responses [67].

6.4.2. Nanoparticle Delivery

To address the pharmacokinetic shortcomings of existing inhibitors, novel delivery systems are currently under development. Encapsulation of Hsp70 inhibitors within nanoparticles or antibody-drug conjugates targeting tumor-specific antigens can enhance tumor-specific delivery, diminish systemic exposure, and minimize off-target effects [68].

6.4.3. Targeting Specific Isoforms

While sparing the constitutive Hsc70 (also known as heat shock protein family A member 8) and the endoplasmic reticulum-specific isoform (BiP, HSPA5- Immunoglobulin Heavy Chain Binding Protein), developing inhibitors that specifically target the stress-induced Hsp72 (heat shock protein family A member 1A) represents a crucial area of research aimed at improving selectivity and safety profiles [69].

6.5. Repurposing Existing Drugs to Target Hsp70

Beyond the development of novel compounds, the strategic repurposing of food and drug administration-approved drugs offers a promising, expedient approach to targeting the Hsp70-c-FLIP axis in clinical settings. This strategy leverages established pharmacokinetic and safety profiles; thus, it potentially accelerates translation to clinical application. Several currently utilized drugs have been identified as indirect or off-target inhibitors of Hsp70 function or expression. For instance, the anthelmintic agent Mebendazole has been shown to bind to the substrate-binding domain of Hsp70; this, in turn, disrupts its chaperone activity and promoting the proteasomal degradation of client oncoproteins, including those essential for oncogenic processes [70]. Another noteworthy example is Oridonin, a naturally occurring diterpenoid with well-documented anti-cancer properties. It directly interacts with Hsp70, inhibiting its ATPase activity and facilitating the degradation of its client proteins [71].

7. Challenges and Future Perspectives

Despite encouraging preclinical results, significant challenges remain as follow:

7.1. Selectivity and Toxicity

Hsp70 comprises several isoforms, including cytosolic Hsc70 and Hsp70, mitochondrial mtHsp70, and endoplasmic reticulum BiP, each serving vital roles in cellular homeostasis. While preserving its fundamental proteostatic activities, the development of inhibitors that selectively target the oncogenic functions of Hsp70 is crucial for mitigating potential off-target toxicities.

7.2. Drug Development

The potency, pharmacokinetic profiles, and pharmacodynamic properties of existing Hsp70 inhibitors necessitate further optimization to enhance their suitability for clinical application.

7.3. Biomarker Identification

Not all types of cancer depend equally on the Hsp70-c-FLIP axis. The identification of biomarkers, such as the concurrent high expression of Hsp70 and c-FLIP, will be essential for stratifying patients in future clinical trials.

7.4. Combination Strategies

The highest potential is likely found in rational combinations, such as Hsp70 inhibitors paired with TRAIL receptor agonists, conventional chemotherapy, or immune checkpoint inhibitors.

8. Conclusions

The ongoing effort to develop effective cancer therapies continues to face a significant obstacle: overcoming adaptive resistance mechanisms. As discussed in this review, the anti-apoptotic protein c-FLIP plays a vital role in therapeutic resistance, yet direct pharmacological targeting of c-FLIP remains challenging. Consequently, a novel indirect approach has been devised: targeting the molecular chaperone Heat Shock Protein 70 (Hsp70) to promote c-FLIP degradation.

Robust preclinical data demonstrate that inhibition of Hsp70, through agents such as VER-155008, 2-Phenylethynesulfonamide, and MAL3-101, effectively reduces c-FLIP protein levels via the ubiquitin-proteasome pathway. This reduction sensitizes resistant cancer cells to extrinsic apoptosis induced by death receptor agonists (e.g. TRAIL and FasL), overcomes traditional chemoresistance, and potentially restores immune-mediated cytotoxicity by alleviating c-FLIP's blockade of Fas signaling. Consequently, pharmacological targeting of Hsp70 to destabilize c-FLIP emerges as a promising indirect anticancer strategy. Progress in this area depends on developing more specific Hsp70 inhibitors, discovering predictive biomarkers for patient selection and combining this strategy with existing chemotherapy, immunotherapy, or targeted therapies. Further research is essential to translate these preclinical findings into clinical improvements for patients with cancer.

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References

[1] B. A. Carneiro and W. S. El-Deiry, "Targeting apoptosis in cancer therapy," *Nature Reviews Clinical Oncology,* vol. 17, no. 7, pp. 395-417, 2020. doi: 10.1038/s41571-020-0341-y.

[2] W. S. Hashim, A. H. Jumaa, N. T. Alsaadi, and A. G. Arean, "Physiological study comprising the sequelae of magnetic radiation on human," *Indian Journal of Forensic Medicine & Toxicology,* vol. 14, no. 2, pp. 421-425, 2020. doi: 10.37506/ijfmt.v14i2.2828.

[3] D. de Miguel, J. Lemke, A. Anel, H. Walczak, and L. Martinez-Lostao, "Onto better TRAILs for cancer treatment," *Cell Death & Differentiation,* vol. 23, no. 5, pp. 733-747, 2016. doi: 10.1038/cdd.2015.174.

[4] A. H. Jumaa, A. S. Jarad, and W. S. H. Al Uboody, "The effect of esomeprazole on cell line human cervical cancer," *Medico-Legal Update,* vol. 20, no. 1, pp. 646-652, 2020. doi: 10.37506/mlu.v20i1.437.

[5] A. R. Safa, "Roles of c-FLIP in apoptosis, necroptosis, and autophagy," *Journal of Carcinogenesis & mutagenesis,* p. 003, 2013. doi: 10.4172/2157-2518.S6-003.

[6] A. R. Safa and K. E. Pollok, "Targeting the anti-apoptotic protein c-FLIP for cancer therapy," *Cancers,* vol. 3, no. 2, pp. 1639-1671, 2011. doi: 10.3390/cancers3021639.

[7] S. Shirley and O. Micheau, "Targeting c-FLIP in cancer," *Cancer Letters,* vol. 332, no. 2, pp. 141-150, 2013. doi: 10.1016/j.canlet.2010.10.009.

[8] A. H. Jumaa, W. S. H. Al Uboody, and A. M. Hady, "Esomeprazole and Amygdalin combination cytotoxic effect on human cervical cancer cell line (Hela cancer cell line)," *Journal of Pharmaceutical Sciences and Research,* vol. 10, no. 9, pp. 2236-2241, 2018. [Online]. Available: https://www.pharmainfo.in/jpsr/Documents/Volumes/vol10Issue09/jpsr10091825.pdf. [Accessed January 9, 2026].

[9] J. Wu, T. Liu, Z. Rios, Q. Mei, X. Lin, and S. Cao, "Heat shock proteins and cancer," *Trends in Pharmacological Sciences,* vol. 38, no. 3, pp. 226-256, 2017. doi: 10.1016/j.tips.2016.11.009.

[10] X. Zhao *et al.*, "Bortezomib induces caspase-dependent apoptosis in Hodgkin lymphoma cell lines and is associated with reduced c-FLIP expression: a gene expression profiling study with implications for potential combination therapies," *Leukemia Research,* vol. 32, no. 2, pp. 275-285, 2008. doi: 10.1016/j.leukres.2007.05.024.

[11] A. Hoter and H. Y. Naim, "The functions and therapeutic potential of heat shock proteins in inflammatory bowel disease—an update," *International Journal of Molecular Sciences,* vol. 20, no. 21, p. 5331, 2019. doi: 10.3390/ijms20215331.

[12] H. H. Cheung, D. J. Mahoney, E. C. LaCasse, and R. G. Korneluk, "Down-regulation of c-FLIP Enhances death of cancer cells by smac mimetic compound," *Cancer Research,* vol. 69, no. 19, pp. 7729-7738, 2009. doi: 10.1158/0008-5472.CAN-09-1794.

[13] K. Seyrek, J. Espe, E. Reiss, and I. N. Lavrik, "The crosstalk of apoptotic and non-apoptotic signaling in CD95 system," *Cells,* vol. 13, no. 21, p. 1814, 2024. doi: 10.3390/cells13211814.

[14] N. V. Ivanisenko *et al*., "Regulation of extrinsic apoptotic signaling by c-FLIP: towards targeting cancer networks," *Trends in Cancer,* vol. 8, no. 3, pp. 190-209, 2022. doi: 10.1016/j.trecan.2021.12.002.
[15] A. Guerrache and O. Micheau, "TRAIL-non-apoptotic signalling," 2024. doi: 10.3390/cells13060521.
[16] D. R. Green, "Caspase activation and inhibition," *Cold Spring Harbor Perspectives in Biology,* vol. 14, no. 8, p. a041020, 2022. doi: 10.1101/cshperspect.a041020.
[17] P. Davidovich, C. A. Higgins, Z. Najda, D. B. Longley, and S. J. Martin, "cFLIPL acts as a suppressor of TRAIL-and Fas-initiated inflammation by inhibiting assembly of caspase-8/FADD/RIPK1 NF-κB-activating complexes," *Cell Reports,* vol. 42, no. 12, 2023. doi: 10.1016/j.celrep.2023.113476.
[18] W. d. Wang *et al*., "c-FLIP promotes drug resistance in non-small-cell lung cancer cells via upregulating FoxM1 expression," *Acta Pharmacologica Sinica,* vol. 43, no. 11, pp. 2956-2966, 2022. doi: 10.1038/s41401-022-00905-7.
[19] C. Frusteri, "Targeting immune dysregulation mediated by FLIP and putative FLIP-related pathways to develop new therapeutic approaches," 2022. 07.13 Doctoral Thesis.
[20] M. A. Hughes *et al*., "Co-operative and hierarchical binding of c-FLIP and caspase-8: a unified model defines how c-FLIP isoforms differentially control cell fate," *Molecular Cell,* vol. 61, no. 6, pp. 834-849, 2016. doi: 10.1016/j.molcel.2016.02.023.
[21] Y. Tsuchiya, O. Nakabayashi, and H. Nakano, "FLIP the Switch: Regulation of Apoptosis and Necroptosis by cFLIP," *International Journal of Molecular Sciences,* vol. 16, no. 12, pp. 30321-30341, 2015. doi: 10.3390/ijms161226232.
[22] A. Guerrache and O. Micheau, "TNF-related apoptosis-inducing ligand: non-apoptotic signalling," *Cells,* vol. 13, no. 6, p. 521, 2024. doi: 10.3390/cells13060521.
[23] A. Safa, "c-FLIP, a master anti-apoptotic regulator," *Experimental Oncology,* vol. 34, no. 3, p. 176, 2012. [Online]. Available: https://pmc.ncbi.nlm.nih.gov/articles/PMC4817998/pdf/nihms771427.pdf. [Accessed January 9, 2026].
[24] K. Newton *et al*., "cFLIP suppresses caspase-1-and MLKL-independent perinatal lethality driven by auto-processing impaired caspase-8 D387A," *Cell Death & Differentiation,* pp. 1-11, 2025. doi: 10.1038/s41418-025-01650-0.
[25] L. K. Hillert *et al*., "Dissecting DISC regulation via pharmacological targeting of caspase-8/c-FLIPL heterodimer," *Cell Death & Differentiation,* vol. 27, no. 7, pp. 2117-2130, 2020. doi: 10.1038/s41418-020-0489-0.
[26] S. Von Karstedt, A. Montinaro, and H. Walczak, "Exploring the TRAILs less travelled: TRAIL in cancer biology and therapy," *Nature Reviews Cancer,* vol. 17, no. 6, pp. 352-366, 2017. doi: 10.1038/nrc.2017.28.
[27] J. Sholl, G. D. Sepich-Poore, R. Knight, and T. Pradeu, "Redrawing therapeutic boundaries: microbiota and cancer," *Trends in Cancer,* vol. 8, no. 2, pp. 87-97, 2022. doi: 10.1016/j.trecan.2021.10.008.
[28] L. Martínez-Lostao, A. Anel, and J. Pardo, "How do cytotoxic lymphocytes kill cancer cells?," *Clinical Cancer Research,* vol. 21, no. 22, pp. 5047-5056, 2015. doi: 10.1158/1078-0432.CCR-15-0685.
[29] A. Dutton *et al*., "Expression of the cellular FLICE-inhibitory protein (c-FLIP) protects Hodgkin's lymphoma cells from autonomous Fas-mediated death," *Proceedings of the National Academy of Sciences,* vol. 101, no. 17, pp. 6611-6616, 2004. doi: 10.1073/pnas.040076510.
[30] R. Rosenzweig, N. B. Nillegoda, M. P. Mayer, and B. Bukau, "The Hsp70 chaperone network," *Nature Reviews Molecular Cell Biology,* vol. 20, no. 11, pp. 665-680, 2019. doi: 10.1038/s41580-019-0133-3.
[31] D. Balchin, M. Hayer-Hartl, and F. U. Hartl, "Recent advances in understanding catalysis of protein folding by molecular chaperones," *FEBS Letters,* vol. 594, no. 17, pp. 2770-2781, 2020. doi: 10.1002/1873-3468.13844.
[32] M. P. Mayer, "The Hsp70-chaperone machines in bacteria," *Frontiers in Molecular Biosciences,* vol. 8, p. 694012, 2021. doi: 10.3389/fmolb.2021.694012.
[33] Y. J. Dawood, M. A. Mahdi, A. H. Jumaa, R. Saad, and R. M. Khadim, "Evaluation of LH, FSH, oestradiol, prolactin and tumour markers CEA and CA-125 in sera of Iraqi patients with endometrial cancer," *Scripta Medica,* vol. 55, no. 4, pp. 419-426, 2024. doi:10.5937/scriptamed55-49925.
[34] M. E. Murphy, "The HSP70 family and cancer," *Carcinogenesis,* vol. 34, no. 6, pp. 1181-1188, 2013. doi: 10.1093/carcin/bgt111.
[35] P. Yan, T. Wang, M. L. Guzman, R. I. Peter, and G. Chiosis, "Chaperome networks–redundancy and implications for cancer treatment," *HSF1 and Molecular Chaperones in Biology and Cancer, Advances in Experimental Medicine and Biology,* vol. 1243, pp. 87-99, 2020. doi: 10.1007/978-3-030-40204-4_6.
[36] D. Kunachowicz, M. Król-Kulikowska, W. Raczycka, J. Sleziak, M. Błażejewska, and J. Kulbacka, "Heat shock proteins, a double-edged sword: significance in cancer progression, chemotherapy resistance and novel therapeutic perspectives," *Cancers,* vol. 16, no. 8, p. 1500, 2024. doi: 10.3390/cancers16081500.
[37] M. K. Singh *et al*., "Heat shock response and heat shock proteins: Current understanding and future opportunities in human diseases," *International Journal of Molecular Sciences,* vol. 25, no. 8, p. 4209, 2024. doi: 10.3390/ijms25084209.
[38] M. Shevchenko, E. Servuli, Z. Albakova, L. Kanevskiy, and A. Sapozhnikov, "The role of heat shock protein 70 kDa in asthma," *Journal of Asthma and Allergy,* pp. 757-772, 2021. doi: 10.2147/JAA.S288886.
[39] J. Y. Kim, S. Barua, M. Y. Huang, J. Park, M. A. Yenari, and J. E. Lee, "Heat shock protein 70 (HSP70) induction: chaperonotherapy for neuroprotection after brain injury," *Cells,* vol. 9, no. 9, p. 2020, 2020. doi: 10.3390/cells9092020.
[40] Z. Albakova, G. A. Armeev, L. M. Kanevskiy, E. I. Kovalenko, and A. M. Sapozhnikov, "HSP70 multi-functionality in cancer," *Cells,* vol. 9, no. 3, p. 587, 2020. doi: 10.3390/cells9030587.
[41] W. Wang, B. Cheng, L. Miao, Y. Mei, and M. Wu, "Mutant p53-R273H gains new function in sustained activation of EGFR signaling via suppressing miR-27a expression," *Cell Death & Disease,* vol. 4, no. 4, pp. e574-e574, 2013. doi: 10.1038/cddis.2013.97.
[42] G. Hu *et al*., "The long noncoding RNA HOTAIR activates the Hippo pathway by directly binding to SAV1 in renal cell carcinoma," *Oncotarget,* vol. 8, no. 35, p. 58654, 2017. doi: 10.18632/oncotarget.17414.
[43] T. T. Al-Mahdwi, A. M. Said, I. M. Hade, Y. S. Yasin, and A. H. Jumaa, "Synergistic cytotoxic impact of linagliptin-ciprofloxacin combination on cervical cancer cell line: insights into targeting heat shock protein 60," *Asian Pacific Journal of Cancer Prevention: APJCP,* vol. 26, no. 6, p. 2117, 2025. doi: 10.31557/APJCP.2025.26.6.2117.
[44] M. A. Mahdi, A. H. Jumaa, Y. J. Dawood, and K. Jabbar, "Bio synthesis of silver nanoparticle using reseda lutea water extract and estimating their anti-cancer impact," *International Journal of Pharmaceutical Sciences and Nanotechnology (IJPSN),* vol. 18, no. 2, pp. 7929-7945, 2025. doi: 10.37285/ijpsn.2025.18.2.5.

[45] A. R. Stankiewicz, G. Lachapelle, C. P. Foo, S. M. Radicioni, and D. D. Mosser, "Hsp70 inhibits heat-induced apoptosis upstream of mitochondria by preventing Bax translocation," *Journal of Biological Chemistry,* vol. 280, no. 46, pp. 38729-38739, 2005. doi: 10.1074/jbc.M509497200.

[46] S. R. Salih, K. N. Abdulla, A. K. Awn, Y. S. Yasin, and A. H. Jumaa, "Impact of esomeprazole, ciprofloxacin and their combination on cervical cancer cell line proliferation: A focus on heat shock protein 70 modulation," *Asian Pacific Journal of Cancer Prevention: APJCP,* vol. 26, no. 7, p. 2455, 2025. doi: 10.31557/APJCP.2025.26.7.2455.

[47] G. Çetin, S. Klafack, M. Studencka-Turski, E. Krüger, and F. Ebstein, "The ubiquitin–proteasome system in immune cells," *Biomolecules,* vol. 11, no. 1, p. 60, 2021. doi: 10.3390/biom11010060.

[48] Y. J. Dawood, R. Saad, M. A. Mahdi, and A. H. Jumaa, "Evaluation of LDH, AFP, β-hCG and tumour markers CEA and CA-125 in Sera of Iraqi patients with ovarian cancer," *Scripta Medica,* vol. 56, no. 2, pp. 275-282, 2025. doi: 10.5937/scriptamed56-56933.

[49] A. J. Ambrose and E. Chapman, "Function, therapeutic potential, and inhibition of Hsp70 chaperones," *Journal of Medicinal Chemistry,* vol. 64, no. 11, pp. 7060-7082, 2021. doi: 10.1021/acs.jmedchem.0c02091.

[50] M. A. Mahdi, A. H. Jumaa, and Y. J. Dawood, "Clinical investigation of IL-31, TOS and GSH in the Sera of gastric cancer females patients in Iraq," *Asian Pacific Journal of Cancer Prevention: APJCP,* vol. 26, no. 2, p. 587, 2025. doi: 10.31557/APJCP.2025.26.2.587.

[51] B. Nitzsche, M. Höpfner, and B. Biersack, "Synthetic small molecule modulators of Hsp70 and Hsp40 chaperones as promising anticancer agents," *International Journal of Molecular Sciences,* vol. 24, no. 4, p. 4083, 2023. doi: 10.3390/ijms24044083.

[52] S. R. Salih, A. H. Majeed, K. M. Hussein, Y. S. Yasin, and A. H. Jumaa, "Dual drug repurposing in cervical cancer: the synergistic cytotoxic effect of dapagliflozin-etoricoxib and its predicted modulation of PI3K/Akt/mTOR signaling via molecular docking," *Asian Pacific Journal of Cancer Biology,* vol. 10, no. 4, pp. 821-835, 2025. doi: 10.31557/APJCB.2025.10.4.821-835.

[53] M. J. Braunstein *et al.*, "Antimyeloma effects of the heat shock protein 70 molecular chaperone inhibitor MAL3-101," *Journal of Oncology,* vol. 2011, no. 1, p. 232037, 2011. doi: 10.1155/2011/232037.

[54] B. Preti *et al.*, "Discovery and Structure–Activity Relationship Studies of Novel Adenosine A1 Receptor-Selective Agonists," *Journal of Medicinal Chemistry,* vol. 65, no. 21, pp. 14864-14890, 2022. doi: 10.1021/acs.jmedchem.2c01414.

[55] J. Hosfelt *et al.*, "An allosteric inhibitor of bacterial Hsp70 chaperone potentiates antibiotics and mitigates resistance," *Cell Chemical Biology,* vol. 29, no. 5, pp. 854-869. e9, 2022. doi: 10.1016/j.chembiol.2021.11.004.

[56] Z. Albakova, Y. Mangasarova, and A. Sapozhnikov, "Heat shock proteins in lymphoma immunotherapy," *Frontiers in Immunology,* vol. 12, p. 660085, 2021. doi: 10.3389/fimmu.2021.660085.

[57] H. Feng, R. Yang, Y. Du, Y. Liu, and F. Niu, "Research and development progression of oridonin for hematological malignancies therapy," *Current Medicinal Chemistry,* vol. 32, no. 23, pp. 4713-4724, 2025. doi: 10.2174/0109298673273034231215190811.

[58] K. Wen, Z. Fu, X. Wu, J. Feng, W. Chen, and J. Qian, "Oct-4 is required for an antiapoptotic behavior of chemoresistant colorectal cancer cells enriched for cancer stem cells: effects associated with STAT3/Survivin," *Cancer Letters,* vol. 333, no. 1, pp. 56-65, 2013. doi: 10.1016/j.canlet.2013.01.009.

[59] F. Simonetta and F. Bertoni, "An epigenetic signature in CD19-CAR T cells predicts clinical outcome," *Trends in Cancer,* vol. 8, no. 2, pp. 81-82, 2022. doi: 10.1016/j.trecan.2021.12.005.

[60] A. Jarad, *et al.*, "Diabetic wound healing enhancement by Tadalafil," *International Journal of Pharmaceutical Research*, vol 12, no. 3, p841, 2020. doi: 10.31838/ijpr/2020.12.03.121.

[61] M. A. Vostakolaei, L. Hatami-Baroogh, G. Babaei, O. Molavi, S. Kordi, and J. Abdolalizadeh, "Hsp70 in cancer: A double agent in the battle between survival and death," *Journal of Cellular Physiology,* vol. 236, no. 5, pp. 3420-3444, 2021. doi: 10.1002/jcp.30132.

[62] J. Yang, Z. Liu, S. Perrett, H. Zhang, and Z. Pan, "PES derivative PESA is a potent tool to globally profile cellular targets of PES," *Bioorganic & Medicinal Chemistry Letters,* vol. 60, p. 128553, 2022. doi: 10.1016/j.bmcl.2022.128553.

[63] K. Kwong *et al.*, "In vivo manipulation of the protein homeostasis network in rhabdomyosarcoma," *Oncotarget,* vol. 16, p. 681, 2025. doi: 10.18632/oncotarget.28764.

[64] R. Mitra, C. M. Adams, W. Jiang, E. Greenawalt, and C. M. Eischen, "Pan-cancer analysis reveals cooperativity of both strands of microRNA that regulate tumorigenesis and patient survival," *Nature Communications,* vol. 11, no. 1, p. 968, 2020. doi: 10.1038/s41467-020-14713-2.

[65] W. Yang *et al.*, "Mebendazole induces ZBP-1 mediated PANoptosis of acute myeloid leukemia cells by targeting TUBA1A and exerts antileukemia effect," *Journal of Advanced Research,* 2025. doi: 10.1016/j.jare.2025.02.013.

[66] B. S. Kumar, P. K. Gopal, A. Gurao, and R. Verma, "Binary role of heat shock proteins in cancer immunotherapy: A detailed perspective," in *Heat Shock Proteins in Inflammatory Diseases*, A.A. Alexander and P.K. Asaur Eds. Springer, 2020, pp. 387-405. doi: 10.1007/7515_2020_34.

[67] G. Courties *et al.*, "In vivo RNAi-mediated silencing of TAK1 decreases inflammatory Th1 and Th17 cells through targeting of myeloid cells," *Blood,* vol. 116, no. 18, pp. 3505-3516, 2010. doi: 10.1182/blood-2010-02-269605.

[68] T. E. Chavas *et al.*, "A macrophage-targeted platform for extending drug dosing with polymer prodrugs for pulmonary infection prophylaxis," *Journal of Controlled Release,* vol. 330, pp. 284-292, 2021. doi: 10.1016/j.jconrel.2020.11.031.

[69] A. B. Meriin, V. L. Gabai, J. Yaglom, V. I. Shifrin, and M. Y. Sherman, "Proteasome inhibitors activate stress kinases and induce Hsp72: diverse effects on apoptosis," *Journal of Biological Chemistry,* vol. 273, no. 11, pp. 6373-6379, 1998. doi: 10.1074/jbc.273.11.6373.

[70] F. Freisleben *et al.*, "Mebendazole mediates its anti-leukemic effects by proteasomal degradation of GLI transcription factors via inhibition of HSP70/90-chaperone activity in acute myeloid leukemia in a preclinical and clinical setting," *Blood,* vol. 134, p. 5050, 2019. doi: 10.1182/blood-2019-129973.

[71] F. Dal Piaz *et al.*, "Chemical proteomics reveals HSP70 1A as a target for the anticancer diterpene oridonin in Jurkat cells," *Journal of Proteomics,* vol. 82, pp. 14-26, 2013. doi: 10.1016/j.jprot.2013.01.030.