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PERSPECTIVE

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Epigenetic synthetic lethality as a cancer therapeutic strategy: synergy of experimental and computational approaches

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ABSTRACT

Cancer treatment is an ongoing challenge, as directly targeting oncogenic drivers is often unfeasible in many patients due to the lack of druggable targets. This has led to the exploration of alternative strategies, such as exploiting synthetic lethality (SL) relationships between genes. SL facilitates the indirect targeting of oncogenic drivers, as exemplified by the clinical success of PARP inhibitors against BRCA-mutated tumors. Advances in high-throughput perturbation screens and multi-omics technologies have deepened our understanding of SL relationships, while computational models enhance SL predictions to better reflect biological complexity. However, while numerous experimental and computational methods have been developed to identify SL interactions, difficulties remain in translating these findings into clinical applications.

This review combines recent progress on SL relationships in cancer with emerging insights into epigenetic regulation, highlighting how epigenetic drugs (epidrugs) can provide new opportunities for targeted interventions, offering a way to minimize off-target effects and enhance therapeutic precision. To advance SL-based therapies, efforts must focus not only on identifying new SL interactions but also on consolidating existing knowledge and integrating experimental and computational approaches to characterize the vulnerabilities of cancer cells. Strengthening this foundation will be critical for the effective development of SL-based cancer treatments.

PLAIN LANGUAGE SUMMARY

Synthetic Lethality (SL) describes a relationship between a pair of genes where cells remain viable if at least one gene of the pair functions normally, but die if both genes are altered (e.g. mutated) at the same time. These alterations may occur naturally or can be drug-induced. Genes are often mutated in cancer cells, so therapeutically altering the SL partner of a gene already mutated in the cancer cells leads to cell death, as both partner genes are now altered, while normal cells lacking the initial mutation are spared. As gene function can be affected by diverse alterations besides DNA mutations, the mechanisms that control gene regulation without changing the DNA sequence, referred to as epigenetics, also need to be considered. In this Perspective, we highlight the importance of integrating both genetic and epigenetic alterations while studying SL relationships, and we explore how these SL relationships can be better identified by integrating experimental and computational approaches, to understand gene-gene interactions in order to broaden the treatment possibilities.

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Synthetic lethality; epidrugs; chromatin remodeling; epigenetics; methylation; machine learning

1. Introduction

Synthetic Lethality (SL) is a molecular interaction in which the simultaneous perturbation of two or more genes leads to loss of viability. First described in 1922 by Calvin Bridges as recessive lethality, this phenomenon was observed in fruit flies (*Drosophila melanogaster*), where crossing flies with divergent eye abnormalities failed to produce offspring with a combined phenotype [1]. Further experiments in yeast models not only refined the original concept but also provided a novel approach for drug discovery focused not on the altered gene but on its synthetic lethal partner, ultimately contributing to the development of selective cancer therapies [2]. Because tumors have different molecular landscapes than normal cells, independent alterations do not result in cell death or impairment, and are often considered undruggable, such as loss-of-function mutations or overexpression. Therefore, targeting the SL partner to a tumor-specific defective gene induces cell death due to the combination of events, while sparing the normal cells without such an alteration, overcoming as well the potential lack of druggability [2–4]. Figure 1. provides a schematic overview of the synthetic lethality mechanism and its application in cancer treatments.

As interest in SL has grown, more precise terms have emerged to better classify these gene-gene interactions

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Article highlights

- Synthetic Lethal relationships are categorized to describe the complexity of genetic interactions and how they may be affected by external factors, such as pharmacological inhibition.
- The success of PARP inhibitors in BRCA-mutated tumors has fueled interest in SL-based clinical applications, which has been reinforced by the complexity of SL relationships and cases of drug resistance.
- Alterations in chromatin regulatory complexes have led to new therapeutic strategies, targeting genes in the same complexes or in their antagonists, due to the intrinsic relationship between them.
- The interplay between epigenetic and structural alterations highlights novel SL interactions that drastically expand the number of potential targets.
- Computational methods are a key tool in predicting SL relationships by integrating data from experimental studies to explore genomic networks.
- Drug perturbation data offers still untapped potential to predict SL targets and drug response.
- A better integration of computational methodologies and large-scale experimental data is needed to identify SL relationships for therapeutic strategies, so that future efforts can be built upon reliable groundwork.

leading several authors [5,6] to differentiate between two main categories, non-conditional and conditional SL (Figure 2) [2,5,6]. Non-conditional SL focusses only on gene alterations, while conditional SL accounts for specific intrinsic or extrinsic conditions that may drive the interaction beyond the aberrations already present in non-conditional SL.

In non-conditional SL, Li et al. [5] established three main categories according to the biological mechanisms affected: gene, pathway, and organelle. They include the basic SL concept at the gene level, as well as Synthetic Dosage Lethality (SDL), which expands upon the initial meaning to describe a specific subtype of SL where one gene is overexpressed, while the partner gene is underexpressed [2,5,7,8] (Figure 2). At the molecular level, they distinguish between a protein complex or single pathway vulnerability to multiple pathways being altered, recognizing how the key role of several genes in SL relationships can even reach organelle's activity, as is the case of mitochondrial-related metabolic SL. Collateral SL is also worth mentioning, as it addresses how an event in one gene leads to the loss of an adjacent passenger gene, often due to the co-deletion of tumor suppressor-associated neighboring genes. It is the loss of the collateral gene that drives this SL relationship, often with a homolog or functionally redundant gene [2,5,9]. Another closely related interaction, due to its role in therapy resistance and survival, is Synthetic Rescue (SR), where the inactivation of a vulnerable gene is compensated by adaptive alterations in another gene. Therefore, when a vulnerable gene is pharmacologically inhibited, changes in the activity of the rescuer gene may lead to drug resistance [2,5,10,11]. A schematic overview of the SL relationships described is depicted in Figure 2.

Furthermore, in conditional SL, besides the simultaneous alterations, a specific cell condition is required. These factors influencing the gene's relationships can be either internal, such as hypoxia and the presence of Reactive Oxygen Species (ROS), or external, which includes the different treatments that patients receive (Figure 2) [5,6]. These factors enable targeted combination therapies, and pharmacological inhibition in conjunction with radio- or chemotherapy. In some cases, cells may even develop drug dependency, with their metabolism adapting to the new state for survival [5,12,13]. Therefore, multi-gene interactions should also be considered as potential SL partners, since although SL relationships are more easily demonstrated between gene pairs, their regulation occurs within a complex network [2,5,6].

More recently, SL has gained interest as a strategy to explore the potential of epigenetically regulated genes. As epigenetics describes mechanisms that regulate genomic function and structural changes in DNA without altering the DNA sequence, targeting these regulatory processes increases the range of potential targets and treatments considerably. DNA methylation, histone modifications, and DNA damage response (DDR) mechanisms, together with genetic aberrations such as mutations, provide deeper insights into cellular status and broaden the landscape of therapeutic opportunities [14–17].

Accordingly, the first approved drugs that capitalize on SL relationships are PARP (Poly-(ADP-Ribose) Polymerase)

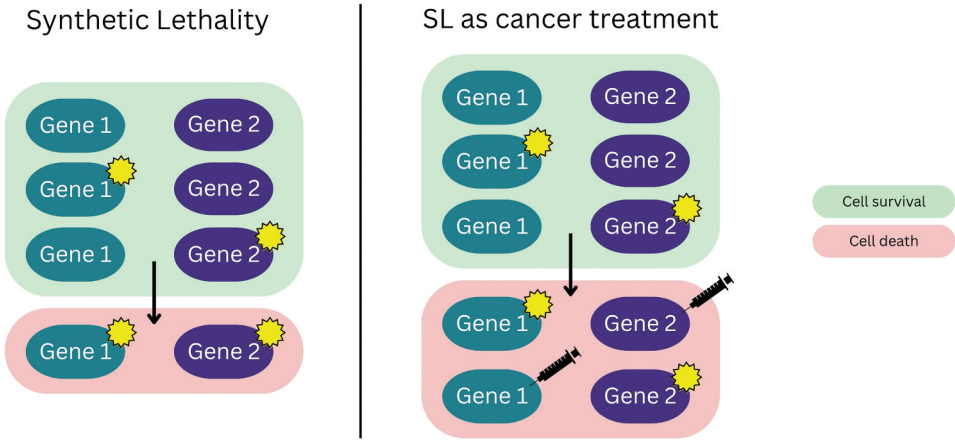

Figure 1. Synthetic Lethality (SL) as a cancer treatment strategy. SL occurs when the simultaneous alteration of two genes, such as mutations or copy-number alterations, leads to cell death, while the alteration of just one of these genes does not affect cell viability. This relationship can be exploited in cancer treatment by targeting the SL partner of an altered gene. In the figure, the scenarios in green boxes represent viable cells while the red boxes represent a lethal combination; the yellow asterisk marks an alteration, and the syringe represents the treatment.

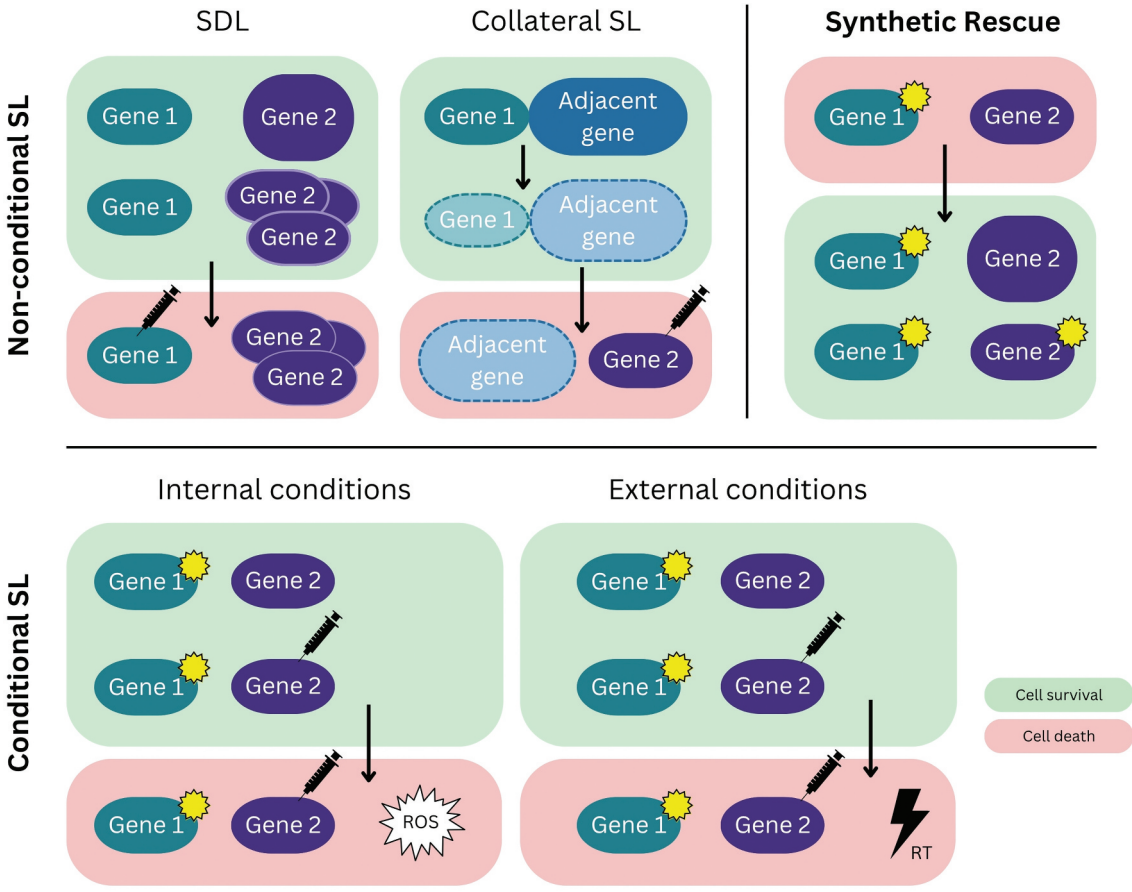

Figure 2. Categorization of the synthetic lethality relationships. Synthetic Dosage Lethality (SDL) refers to cases where one gene is either overexpressed or amplified, and another alteration in the second gene leads to cell death. Collateral SL occurs when the deletion of a second adjacent gene drives the lethal interaction. In contrast, Synthetic Rescue describes a scenario where a second alteration compensates for the initial defect, restoring cell viability. In conditional SL, the environmental factors, either internal or external, may drive the SL relationship. In the figure, filled genes represent expressed genes, empty genes indicate deletions, the yellow asterisk marks an alteration, enlarged genes represent overexpression, duplicated genes represent gene amplification, the syringe represents the treatment, the star symbolizes internal factors such as reactive oxygen species (ROS), and the lightning bolt represents external factors such as radiotherapy (RT).

inhibitors. Since then, more DDR inhibitors have been developed and are currently being tested in different cancer types, to target genes such as ATM (Ataxia Telangiectasia Mutated) and ATR (Ataxia Telangiectasia and Rad3 related) serine/threonine kinases [18,19]. A recent review by Ngoi et al. [2] provides (as Supplementary Table S1 and S2) two comprehensive lists detailing completed and ongoing clinical trials and preclinical studies which include many epigenetic targets.

2. Clinical applications and challenges of synthetic lethality: the case of PARP inhibitors

SL-based cancer therapies have been implemented in the clinic as first-line treatment, such as PARP inhibitors (PARPi) in breast and ovarian cancer in patients with BRCA-mutated tumors. The three most well-known PARP members—PARP1, PARP2, and PARP3—are all involved in DNA repair mechanisms, both detecting and repairing single-strand breaks (SSBs) through base excision repair (BER) and double-strand breaks (DSBs) via homologous recombination (HR) or non-homologous end-joining (NHEJ). Similarly, BRCA1 and BRCA2, while being mutually exclusive, play distinct but indispensable roles in HR. Interestingly, despite initial assumptions that, when the HR pathway is broken, BRCA-defective cells cannot repair DNA damage in the presence of PARPi through any of the aforementioned mechanisms, the complexity of this SL relationship has gradually been uncovered, revealing a more intricate mechanism than previously thought [20,21]. Thanks to the development of several PARPi with different degrees of catalytic inhibition and trapping activity —such as olaparib, veliparib, talazoparib, and saruparib—it has been shown that both functions are required for cell death. Specifically, PARP1 trapping onto DNA is essential to convert SSBs into DSBs, causing enough genomic instability that a deregulated NHEJ pathway is unable to compensate for or rescue HR inactivity, ultimately leading to the death of BRCA-mutated cells [6,16].

Unfortunately, treatment with PARPi often results in drug resistance, as tumor cells adapt to counter the loss of fitness. This adaptation can occur through various mechanisms: by altering PARP1 (in some cases to prevent DNA trapping), by genetic reversion to restore BRCA1 or BRCA2 functions, or by mutations occurring in functionally related genes such as TP53BP1 (Tumor Protein P53 Binding Protein 1) [21,22].

Despite these challenges, novel therapies are currently under development, both at clinical and preclinical stages, following the success of PARPi. Ngoi et al. [2] provide an overview of pre-clinical and clinical trials on SL agents,

focused on relationships around DNA damage response (DDR), signaling and repair mechanisms, as well as DNA replication and cell division, metabolic reprogramming, and epigenetic regulation for different cancer types [15,16]. Among them, DNA polymerase θ (POLQ) trials are of special relevance, as when DNA repair pathways are compromised (especially when TP53BP1 is also defective), cells become dependent on error-prone Theta-Mediated End-Joining (TMEJ), also known as alternative DNA end-joining (Alt-EJ), where POLQ plays a key role. Because POLQ has been identified as a SL partner to BRCA1 and BRCA2, several studies on POLQ inhibitors are currently being conducted to assess their efficacy as monotherapy or in combination with PARPi [2,23–25]. One specific inhibitor (ART558) has been shown to also trap POLQ on DNA in its closed conformation, suppressing PARPi resistance [23].

3. Exploring chromatin complex alterations and epigenetic synthetic lethality for precision oncology

Currently, most efforts to identify and exploit SL relationships have focused on DDR pathways, such as targeting ATR and ATM, because of their upstream role in these pathways. Inhibitors are being tested for these two proteins (ATRi or ATMi, accordingly), as several SL partners have been identified [18,19]. For example, epigenetic silencing of SLFN11 (Schlafen Family Member 11) in esophageal cancer or FAM110C (Family With Sequence Similarity 110 Member C) in pancreatic cancer are SL with ATMi or ATRi, respectively. In both cases, DNA methylation is a sensitive marker and upon the consequent loss of expression due to epigenetic silencing, the cancer cells become susceptible to inhibition [18,19].

However, in recent years, increasing attention has been paid to other DNA-related processes. Essential mechanisms like DNA replication and transcription rely on DNA accessibility, which is regulated by several chromatin remodeling family complexes, including SWI/SNF (SWItch/Sucrose Non-Fermentable), ISWI (Imitation SWItch), Polycomb (Polycomb-group or PcG proteins), NuRD (Nucleosome Remodelling and Deacetylase), and INO80 (INOsitol requiring 80). For instance, PBRM1 (Polybromo 1) is a specific SWI/SNF complex subunit implicated not only in maintaining chromosomal stability but also on ATM-dependent DNA repair pathways. Loss of PBRM1 has been found to be SL in renal cancer with both PARPi and ATRi, promoting replication stress, while PBRM1 deficiency also sensitizes cells to PARPi [26].

Notably, due to their high mutation frequency, several other SWI/SNF subunits are under the spotlight for the development of novel SL therapeutic strategies, particularly ARID1A (AT-Rich Interaction Domain 1A) and SMARCA4/2 (SWI/SNF Related BAF Chromatin Remodeling Complex Subunit ATPase 4/2) [2,27,28].

Multiple potential SL partners have been proposed for these genes in various studies, and their characterization has led to diverse therapeutic strategies. These include targeting genes within the same complexes, such as BRD9 (Bromodomain Containing 9), SMARCC1 (SWI/SNF Related BAF Chromatin Remodeling Complex Subunit C1), or even paralogues of the mutated genes (ARID1B, SMARCA2/4), to completely inhibit their activity [27]. Another approach involves inhibiting antagonist complexes like PRC2 (Polycomb Repressive Complex 2) to rescue SWI/SNF activity [14,27,29]. Additionally, targeting seemingly unrelated genes, such as AURKA (Aurora kinase A), involved in cell cycle and division, has also shown potential SL behavior [29].

Among these targets, perturbations in KEAP1 (Kelch-like ECH-Associated Protein 1) have been identified as an SL mechanism in ARID1A-deficient cells in clear cell ovarian carcinoma (CCOC), unrelated to its function as NRF2 (nuclear factor erythroid 2-related factor 2) activator [30]. While the authors propose dual inhibition of ATR and KEAP1 —as ATR is also a SL partner of ARID1A and SMARCA4 (mainly observed in lung cancer) [31–33]— targeting both the SWI/SNF complex and KEAP1 could offer a potential therapeutic strategy, particularly given KEAP1's role in therapy resistance via alterations in the KEAP-NRF2 system [34–36].

Recently, KLF5 (Krüppel-like transcription factor 5) was proposed as a potential SL partner for ARID1A. The loss of KLF5 in ARID1A-deficient cells mimics the inhibition of BRD4 (Bromodomain Containing 4), which is toxic for these cells. When ARID1A is lost from chromatin remodeling complexes, transcription becomes dependent on BRD4, which in turn requires KLF5 to be recruited to the chromatin, rendering KLF5 a potential therapeutic target [33]. Moreover, KLF5 has been implicated in promoting resistance via KEAP1 inhibition in esophageal squamous cell carcinoma, emerging as a potential target to overcome resistance [36]. This also helps further defining the SL relationship between ARID1A and KEAP1.

SMARCA4 is frequently inactivated in lung and ovarian cancers, including small cell carcinoma of the ovary hypercalcemic type (SSCOHT), a rare pediatric malignancy. Recently, it has been demonstrated that SMARC4-deficient cells become dependent on lysine-specific histone demethylases KDM6A (also known as UTX, ubiquitously transcribed X chromosome tetratricopeptide repeat protein) and KDM6B (also known as JMJD3, Jumonji domain-containing protein 3) due to impaired epigenetic regulation of H3K27 marks. As a result, these tumors are highly sensitive to KDM6 inhibitors such as GSK-J4. The dual loss of SMARCA4 and KDM6 functions induces lethal chromatin rigidity and transcriptional silencing in both lung and ovarian cancer models, including patient-derived orthotopic xenografts (PDOXs) from SCCOHT, where GSK-J4 treatment significantly impaired tumor growth and prolonged survival [37].

To highlight the importance and interest in these genes, we have performed a systematic search in Scopus to find cancer research publications from the last 5 years mentioning synthetic lethality and chromatin, either in the title or the abstract. We found 267 papers mentioning 109 different genes that we manually curated to properly classify the found pairs as SL or not. In Figure 3., we present a summary of the chromatin regulatory genes (CRGs) most commonly identified in a SL-pair, the number of SL relationships they establish, as well as the most represented chromatin regulatory complexes or gene superfamilies, classified in Table 1. according to their function. The full methodology and curated

table can be found in Supplementary File S1 and Supplementary Table S1, respectively.

3.1. The Goldilocks principle in epigenetic regulation

An intriguing concept recently introduced in the context of epigenetic vulnerabilities is the so-called "Goldilocks phenomenon" [27]. This principle refers to cases where cancer cells require an intermediate activity level of certain genes—neither too high nor too low—to sustain tumorigenesis. For example, a partial reduction in SWI/SNF complex activity may support oncogenic programs, whereas complete loss or full restoration of its function is detrimental to cell viability [27]. These dosage-sensitive dependencies open up therapeutic

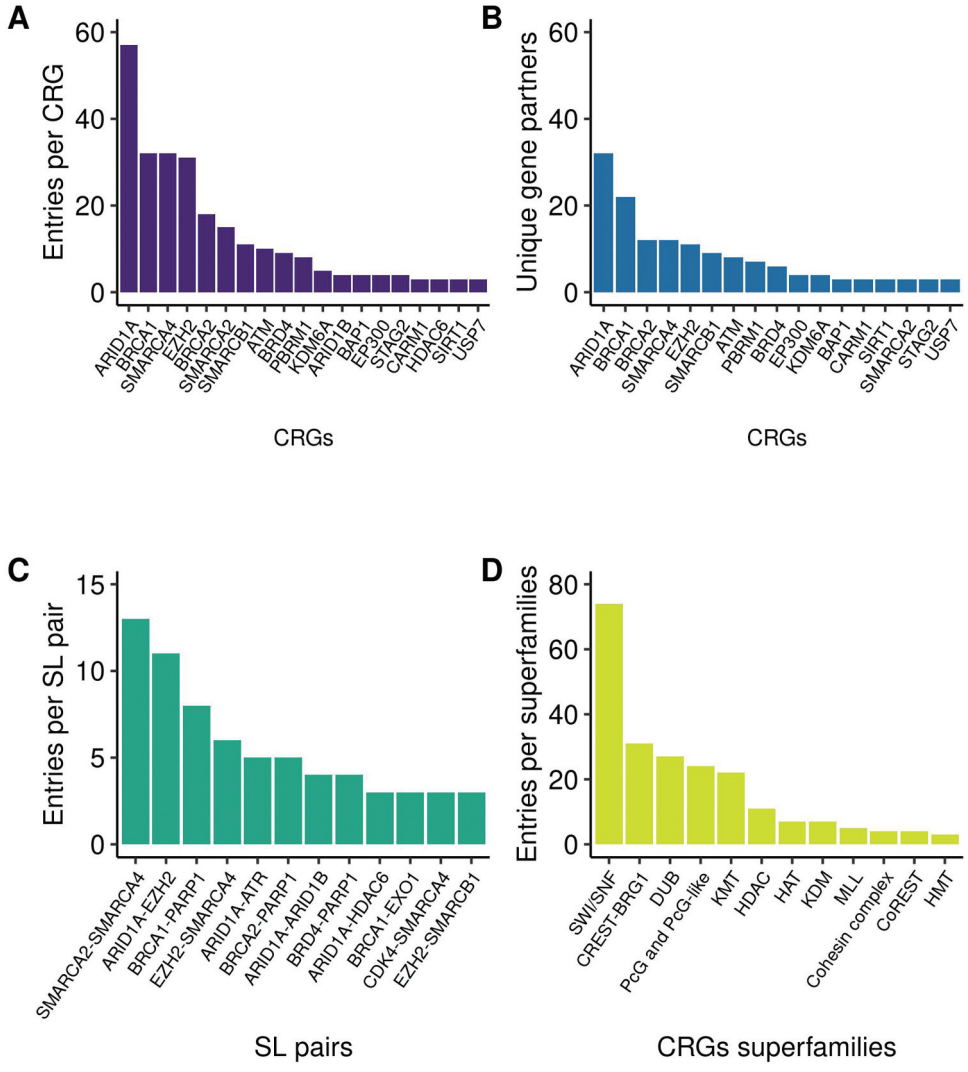

Figure 3. Overview of SL relationships involving CRGs identified through manual curation of systematic literature search. Only SL pairs reported in at least three independent sources are included. (A) frequency of each CRG reported as part of an SL relationship, (B) number of unique SL partner genes identified for each CRG, (C) frequency of each reported SL pair, and (D) number of unique complexes or functional superfamilies for the CRGs in a SL pair.

Table 1. Overview of chromatin remodelers' families.

WRITERS	**Methylation**	
	DNA methyltransferases (DNMTs)	Histone methyltransferases (HMTs) Histone lysine methyltransferase (KMTs) Arginine methyltransferases (PRMTs)
	Acetylation	
	–	Histone lysine acetyltransferase (HATs or KATs)
ERASERS	**Methylation**	
	DNA demethylation	Lysine demethylases (KDMs or HDMs)
	Acetylation	
	–	Histone or lysine deacetylase (HDACs or KDACs)
READERS	**Methylation**	
	DNA methylation	Histone methylation
	Acetylation	
	–	Histone acetylation

opportunities by targeting either SWI/SNF or Polycomb Repressive Complexes (PRCs) to perturb this fragile balance. In breast cancer, it was demonstrated that intermediate expression levels of SMARCD1 (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily D member 1), were associated with poorer prognosis compared to both low and high expression levels [38]. This observation suggests a narrow window of tolerated expression, consistent with the "Goldilocks" model. Additionally, the study identified other SWI/SNF subunits as potential "essential expression-restricted" genes, further expanding the potential treatment opportunities [38].

In these cases, the SL relationship relies on a partially altered complex that has already modified the cell's phenotype. Targeting a second gene to inhibit its activity leads to cell death. While the somewhat active complex is required for cell survival, in other cases, complete alteration of the complex is needed for tumorigenesis (Knudson's two-hit theory) [15,39]. Thus, even if a SL relationship is identified between two genes, unless the altered gene is completely inactivated, the relationship may not be strong enough. Dual inhibition of the initial gene and the SL partner may be needed to achieve an effective therapeutic response (Figure 4).

In addition, an interesting case is that of TIP60 (Tat-interactive protein 60-kDa, also known as KAT5 or Lysine Acetyltransferase 5), a haploinsufficient tumor suppressor gene [40,41] whose expression is required for cell survival. It is often downregulated in several cancer types such as breast and colon [41,42], and it has been confirmed that its complete inhibition leads to apoptosis. This is not only the case when TIP60 expression is already suppressed, but also in cases where it is upregulated instead, such as in anaplastic thyroid cancer cells [43]. While targeting only TIP60 may offer a therapeutic approach for many cancer types, TIP60 inhibition has also been explored in refractory cancer cells in combination with other treatments. For example, in cisplatin-resistant squamous cell carcinoma cells [44], TIP60 overexpression upregulates ΔNp63α protein, promoting such resistance, while its inhibition sensitizes the cells to the cisplatin treatment. Similarly, in glioma cells, it has been shown that downregulating TIP60 increases sensitivity to ionizing radiation [40]. Therefore, to properly exploit TIP60 as a therapeutic target, it is key to understand these tissue- and cancer-specific roles.

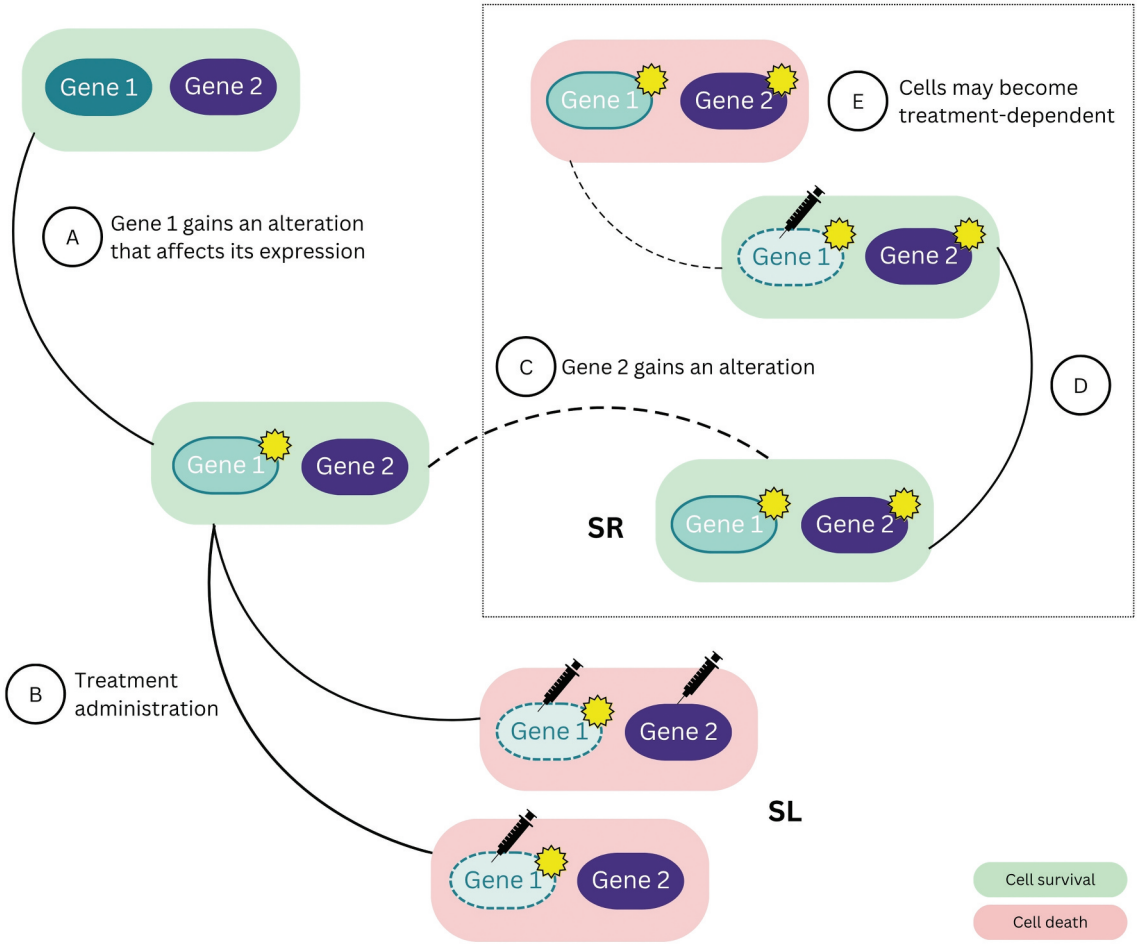

Figure 4. The Goldilocks phenomenon. (A) upon Gene 1 acquiring an alteration, its expression diminishes; however, the expression levels are within the required values to ensure the cell's survival. (B) Gene 1 can be targeted to completely inhibit its expression, also in combination with Gene 2 inhibition if they are a SL pair. (C) In some cases, the cells will rescue Gene 1 by inducing a second alteration in Gene 2 (SR). In those cases, the new adaptation may have made the cells to become dependent on the given treatment (D), so stopping treatment (E) leads to cell death. In the figure, filled genes represent expressed genes, clear genes represent reduced expression levels, and empty genes with a dashed line indicate complete loss of expression, the yellow asterisk marks an alteration, and the syringe represents the treatment.

The Goldilocks or expression-restricted anomaly has also been described in relation to Polycomb Repressive complexes. In *Drosophila*, the level of highly conserved histone modification H2Aub1 (Histone H2A monoubiquitination) is a key regulatory element in cancer, controlled just-right via PRC1 (Polycomb repressive complex 1) and PR-DUB (Polycomb repressive deubiquitinase) to balance gene repression [45,46].

In the case of PRC2, EZH2 (Enhancer of Zeste Homolog 2) gain-of-function mutations in lymphoma increase H3K27me3 (tri-methylation of lysine 27 on histone H3 protein) levels. However, treatment with PRC2 inhibitors results in a secondary mutation that ensures cell survival. Surprisingly, when the treatment is removed, hypermethylation surpasses the tolerable limit, provoking cell death, as the cells become dependent on the drug to maintain the balance necessary for survival [47,48].

While the Goldilocks phenomenon may regulate survival under normal conditions, it could also respond to a synthetic rescue adaptation. However, in this case, a secondary change in external conditions might limit cell survival (Figure 4).

4. Interplay of epigenetics and chromosomal changes in synthetic lethality

While chromatin remodeling complexes represent a well-defined axis of epigenetic vulnerability, additional layers of epigenetic regulation—such as DNA methylation, histone modifications, and structural genomic changes—also contribute to SL interactions, thereby expanding the therapeutic landscape. An illustrative example of how epigenetic and structural alterations converge to create SL vulnerabilities is the case of TACC2 (Transforming Acidic Coiled-Coil Containing Protein 2) in esophageal cancer. Loss of TACC2 expression, driven by either copy number alterations or promoter hypermethylation, results in the repression of CDK1A, creating a dependency on CDK activity. In this context, SL arises from the inhibition of CDK1/2, which proves selectively toxic in TACC2-inactivated cells. The proposed therapeutic strategy includes either pharmacological CDK inhibition or combined approaches involving CDK inhibitors and siRNA-mediated targeting of TACC2 [49].

Another recent study identified PELO (Pelota MRNA Surveillance and Ribosome Rescue Factor) as a potential therapeutic target in cancers harboring large deletions in chromosome 9p21.3 or exhibiting microsatellite instability (MSI-H). Through large-scale CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) knockout screens, PELO was identified as a dependency in tumors with a disrupted superkiller complex (SKIc) function, either from stabilizer gene FOCAD (Focadhesin) loss or SKI3 (SKI3 Subunit of Superkiller Complex) mutations. PELO and SKIc analogous roles in mRNA degradation outline a synthetic lethal interaction where PELO inhibition may be exploited therapeutically in a substantial subset of tumors, including those resistant to immune checkpoint inhibitors [50].

The interplay between epigenetic enzymes and cellular stress pathways also gives rise to synthetic lethal vulnerabilities, as illustrated by the functional crosstalk between DNMT3A (DNA (cytosine-5)-methyltransferase 3A) and HDAC6 (Histone deacetylase 6) in lung cancer. In this setting, DNMT3A has been identified as a synthetic lethal partner of HDAC6 in a HIF-1 (Hypoxia-Inducible Factor 1)-dependent manner, underscoring how epigenetic dysregulation can modulate hypoxia-adaptive signaling. Notably, this interaction appears to be specific to DNMT3A, as other members of the DNMT family do not display the same dependency. The combined loss of DNMT3A and pharmacological inhibition of HDAC activity triggers cell death via upregulation of VHL (Von Hippel–Lindau) and the subsequent downregulation of HIF-1, disrupting hypoxia-driven survival mechanisms [51].

5. Computational methods for synthetic lethality prediction

Several screening methods have been employed to identify clinically relevant SL partners, based on gene silencing strategies such as knockdowns or knockouts. RNA interference (RNAi) screens use small interference RNA (siRNA) or short-hairpin RNA (shRNA) in cancer and non-cancer cell lines to knockdown single genes (e.g., project DRIVE [52]); while CRISPR-based systems can knockout single or multiple genes, (CRISPR inhibition, CRISPRi) or mimic gain-of-function events (CRISPR activation, CRISPRa) in cell lines, which may be grown as 2D or 3D cultures, or even in *in vivo* models [2,53,54].

The results from such experiments represent valuable information regarding gene-gene interaction as a key resource for SL prediction. Large databases compile these gene-gene interactions (Table 2). The largest database to date for human cell lines is the Cancer Dependency Map project (DepMap) [55], which includes data from the Score [53] and Achilles projects from the Sanger Institute (315 CRISPR cell lines, and 966 drug screen cell lines) and the Broad Institute [55] (1064 CRISPR cell lines, and 915 drug screen cell lines), respectively. Alternatively, CellMap collects data from yeast screenings (7,837 genes) [56], providing a global genetic interaction network [57]. Specifically created

Table 2. Databases for cell line-based pharmacological perturbation screenings.

Database	Screening/Analysis method	Data Type	Database publication
DepMap	CRISPR, RNAi (Achilles, Score)	Gene dependency data across cancer cell lines	Tsherniak et al. [55]
Project DRIVE	RNAi, shRNA	Gene knockdown data from cancer cell lines	McDonald et al. [52]
Score	CRISPR (Sanger Institute)	Gene knockout screens in cancer cell lines	Behan et al. [53]
Achilles	CRISPR (Broad Institute)	Gene essentiality screens across diverse cancer types	Tsherniak et al. [55]
CellMap	Yeast genetic screening	Genetic interaction networks in yeast	Costanzo et al. [56]
SynLethDB 3.0	Multiple (CRISPR, RNAi, literature curation, computational predictions)	Synthetic lethality gene pairs across species	Wang et al. [58]; Guo et al. [59]

Table 3. Summary of SL computational methods.

Model type	Model	Model name	Model publication
Statistical methods	DAISY	Data Mining SL	Jerby-Arnon et al. [62]
	MiSL	Mining Synthetic Lethals	Sinha et al. [63]
	ISLE	Identification of clinically relevant SL	Lee et al. [64]
	SiLi	Statistical inference-based SL identification	Yang et al. [72]
Network methods	IDLE	Identifying Dosage Lethality Effects	Megchelenbrink et al. [65]
	Fast-SL	Fast SL	Pratapa et al. [66]
Classical ML methods	SL^2MF	Matrix factorization model for SL prediction	Liu et al. [69]
	GRSMF	Graph regularized self-representative matrix factorization	Huang et al. [70]
	CMFW	MF with a matrix-specific weight (W)	Liany et al. [71]
	DiscoverSL	Discover SL	Das et al. [73]
	CMF	Collective matrix factorization	Singh and Gordon [74]
Deep learning methods	DDGCN	Dual-dropout graph convolutional network	Cai et al. [68]
	KG4SL	Knowledge graph for SL	Wang et al. [75]
	KR4SL	Knowledge Graph Reasoning for SL	Zhang et al. [76]
	SLKG	Synthetic Lethality Knowledge Graph	Zhang et al. [77]
	GCATSL	Graph contextualized attention network for SL	Long et al. [78]
	SLMGAE	SL Multi-view Graph Auto-Encoder	Hao et al. [79]
	MGE4SL	Multi-Graph Ensemble Neural Network for SL	Lai et al. [80]
	SLGNN	Synthetic Lethality knowledge graph neural network	Zhu et al. [81]
	PTGNN	Pre-Training Graph Neural Networks	Long et al. [82]
	PiLSL	Pairwise interaction learning-based graph neural network	Liu et al. [83]
	NSF4SL	Negative-sample-free contrastive learning for SL	Wang et al. [84]

for SL, SynLethDB and its latest update SynLethDB 3.0 offer a comprehensive collection of SL gene pairs in multiple species from various sources, including biochemical assays, public databases, computational predictions, and manually curated data from literature and text mining [58,59]. It has 51,411 known SL pairs for all 5 species, and over 1,777,000 predicted pairs. An overview of available databases for pharmacological perturbation screenings is presented in Table 2 [52,53,55,56,58,59].

These databases serve as valuable resources for computational prediction models aimed at overcoming the inherent limitations of experimental screenings, which are often time-consuming and unrealistic due to the highly combinatorial nature of SL gene pair analyses. Several distinct methods have been developed to identify SL relationships, integrating biological knowledge as needed [60,61].

Hypothesis-based methods require prior knowledge to predict SL, such as identifying SL pairs that are co-expressed but presenting mutually exclusive alterations to avoid cell death. Specific pipelines have been developed for these methods, such as DAISY (Data mining Synthetic lethality [62]), which applies three parallel statistical inference strategies to cancer genomic data, MiSL (Mining Synthetic Lethals [63]), which identifies SL partners for specific mutated genes in pan-cancer data from The Cancer Genome Atlas (TCGA), and ISLE (Identification of clinically relevant Synthetic Lethality [64]), which mines TCGA data to predict drug responses. While these methods are relatively straightforward, they are limited by the known SL pairs available in the databases. In contrast, network-based methods are more extensive, analyzing protein-protein interactions or signaling networks. For example, IDLE (Identifying Dosage Lethality Effects [65]), predicts SDL from metabolic models, while Fast-SL [66] identifies SL in metabolic networks. These and similar methods are discussed in more detail in several publications [60,61].

The advancement in machine learning (ML) has led to the development of various algorithms for SL prediction. Most fall under the scope of supervised ML, which identifies patterns from labeled observations (known SL or non-SL pairs), learning the relationships between the input values and this label to subsequently recognize them in new observations. These algorithms integrate multi-omics data from the abovementioned databases (Table 2), along with SL key traits, such as gene co-expression and the presence or absence of mutually exclusive alterations to predict novel SL pairs.

Within ML, deep learning (DL) methods represent a more intricate subset that identifies nonlinear relationships across multiple layers, often building graphs or networks that mimic cellular systems. This allows DL methods to better capture SL relationships beyond paired genes. Nevertheless, both ML and DL approaches require known SL and non-SL pairs to be properly trained and are typically improved by incorporating other biological knowledge, such as protein-protein interactions or pathway data. Some methods, like matrix factorization (MF), can be implemented in an unsupervised manner, overcoming the need for labeled data [60,61,67–71]. A summary of SL computational methods is presented in Table 3 [62–66,68–84].

5.1. Computational modelling

To fully explore SL relationships, it is crucial to identify targetable SL partners and potential drugs that can act against them. High-throughput perturbation screening experiments have been performed in several cell lines in order to uncover vulnerabilities from multi-omics data across diverse cancer types. Notable initiatives, such as PRISM [85], the Genomics of Drugs Sensitivity in Cancer (GDSC) [86,87], and the Cancer Therapeutic Response Portal (CTRP) [88], have contributed to this effort. However, although this data has been integrated in some of the previously mentioned computational methods (e.g., DAISY [62], MiSL [63], and ISLE [64]), it is often only included in the refinement steps and is not fully leveraged. This is largely because most approaches primarily focus on multi-omics data and do not fully capitalize on the perturbation data's potential [89,90].

To better use the available perturbation data, several new computational approaches have been developed, many of which integrate single-cell RNA-seq (scRNA-seq) data. Some methods, such as scGen [91], scVIDR [92], and CellOracle [93], are broadly aimed at perturbation prediction, while others, like beyondcell [94], scDEAL [95] and scRank [96] are specifically designed for drug-response predictions. Thanks to their novelty, most of these models are continually updated. However, incorporating scRNA-seq data adds an extra layer of complexity and often disregards existing data.

As highlighted by Srivatsa et al. [89], perturbation data is frequently used as a validation tool rather than as a predictive resource for SL interactions. They propose a novel framework that combines mutated genes with perturbed genes to predict SL based on drug response, aiming to better harness the power of perturbation data in therapeutic contexts.

6. Future perspectives

In this work, we show that several approaches, both wet-lab and computational, have been developed to predict synthetic lethality. However, despite the amount of knowledge gained from screening methods and their computational integration, there is still much work to be done. In many cases, the proposed SL pairs are not yet being used as therapeutic targets, even though clinical trials involving these targets have been—and continue to be—conducted.

In wet-lab methods, detailed information can be obtained at multiple levels for the studied SL pairs within specific cancer types, ranging from cell lines to *in vivo* models. However, one of the key challenges in identifying SL is defining bona fide negative pairs—genes that cannot exhibit an SL relationship. It is quite difficult to prove through perturbation screenings (as done to determine SL pairs) that these genes are entirely unrelated, especially accounting for the complex network interactions between genes.

On the other hand, while *in silico* methods offer significantly faster and cheaper exploration of multiple gene combinations in a shorter time, they are dependent on existing data, which may not always be available for a given cancer type or specific omics data. Wet-lab identification efforts do not always translate into computational resources, creating a gap in the data available for computational methods. This limitation is especially pronounced in DL models, which require vast amounts of data. The lack of negative-labeled data further restricts model performance, as many algorithms require both positive and negative cases for proper training. Nevertheless, some strategies are being developed to overcome these challenges, such as NSF4SL (Negative Sampling Free for SL), which avoids the use of negative pairs [84].

Unfortunately, the disconnect between computational methods and biological data fuels a feedback loop. As DL algorithms often function as black boxes, they are often overlooked by the biological community due to their poor interpretability. Simultaneously, commonly used data repositories such as TCGA and DepMap continue to grow, but the ML methods themselves are not always kept up to date [60,84]. To bridge this gap between wet-lab experiments and computational models, careful curation and preprocessing of data is essential. Integrating as much available data as possible and exploring gene networks holistically could provide valuable insights (Figure 5). Future studies should focus on a dual outcome: not only identifying SL pairs but also considering how results obtained in experimental settings would be used to train or validate computational methods, or how genes predicted by these models should be experimentally tested, respectively. In this context, more interpretable ML methods could better help predict synthetic lethality in ways that are both understandable and reproducible, while allowing for bidirectional sharing of new data.

Furthermore, incorporating new knowledge into these models, particularly in the field of epigenetics, is crucial. While many current approaches focus on DNA repair mechanisms, there is increasing interest in DNA-associated processes, such as DNA methylation and chromatin accessibility, studied through techniques like ATAC-seq (assay for transposase-accessible chromatin). Initially, increased methylation in promoter CpG islands was linked to gene silencing, but later studies revealed a more complex relationship. For instance, positive correlations between methylation and gene expression have been found, especially in gene body or downstream regions. Additionally, methylation of enhancer regions, though less explored than promoter methylation, may play an important role in transcription regulation [97–101].

The complexity of methylation marks—both in terms of their presence or absence across methylation sites—creates a challenging puzzle in gene expression regulation. Further studies are needed to understand how gene expression is regulated via methylation, first in normal cells to establish baseline methylation profiles in normal cells, which can then be later compared to cancer cells to identify alterations. By integrating this regulatory layer with existing knowledge on gene networks, new potential SL pairs can be identified.

Similarly, histone modifications are another key aspect of epigenetic regulation that could offer new insights into cell regulation and potential therapeutic strategies. Histones, beyond serving as scaffolds for DNA packaging, dynamically modulate chromatin accessibility through several post-translational modifications. Enzymes involved in these processes are classified as "writers," "erasers," or "readers," depending on their role in adding, removing or interpreting modifications, respectively (Table 1). Mutations in these enzymes and the histones themselves can alter chromatin dynamics and present new targets for pharmacological inhibition, potentially revealing additional SL genes.

Therefore, when accounting for all these epigenetic mechanisms, it is clear that despite its abundance, the use of gene expression is largely untapped, since its use has been limited to co-expression and differential expression analyses. Underlaying mechanisms like copy number alterations, DNA methylation, or chromatin accessibility have not been fully leveraged. By establishing baseline levels of gene expression in normal versus cancerous cells, these mechanisms can be characterized and targeted as the root cause of altered expression profiles.

This brings us to the growing attention on epigenetic drugs, also known as epidrugs. Epidrugs target enzymes involved in epigenetic regulation, such as DNA methyltransferases (DNMT), histone deacetylases (HDAC), histone

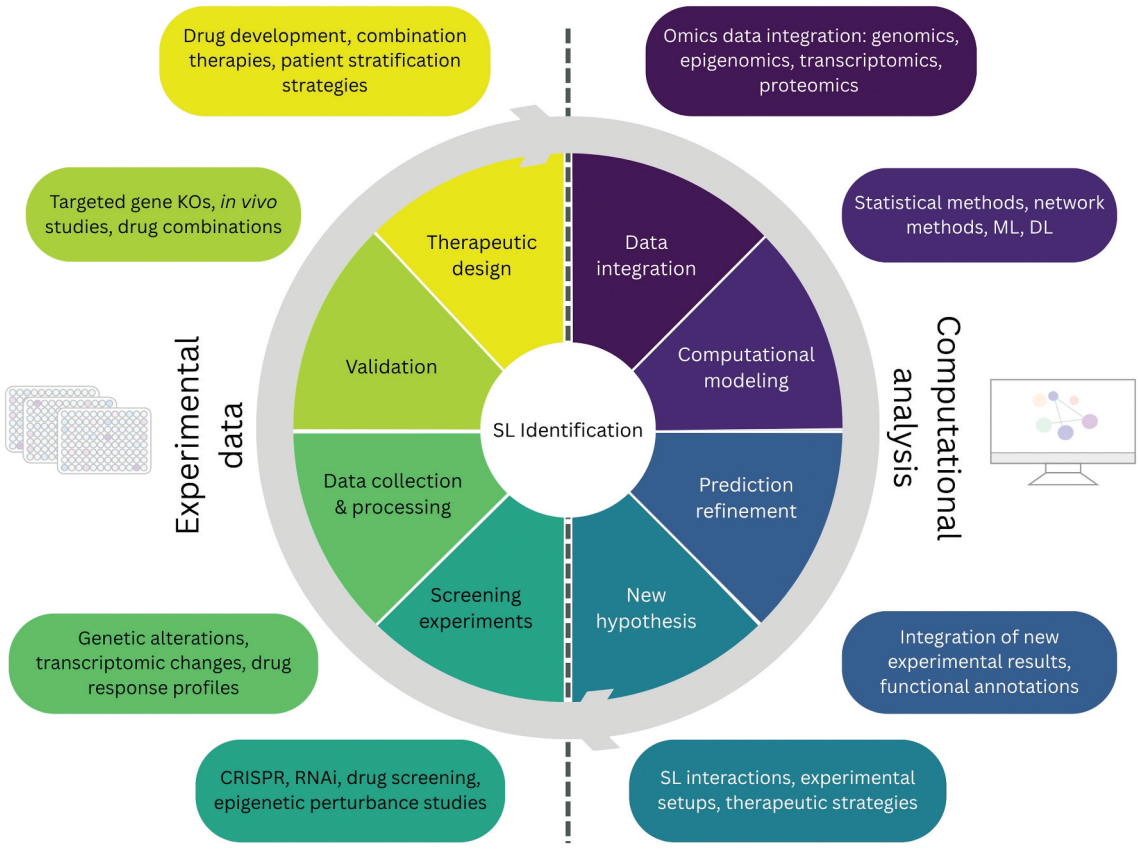

Figure 5. Integrative workflow for synthetic lethality discovery. The circular diagram illustrates the iterative process of SL identification, combining experimental and computational approaches. The computational half (right side) consists of data integration, computational modeling, prediction refinement, and new hypothesis generation, feeding back into experimental testing. This experimental half (left side) includes screening experiments, data collection & processing, validation and therapeutic design. The results obtained will be the computational method's input.

methyltransferases (HMT) and bromodomain and extra-terminal motif proteins (BET). Although several inhibitors targeting these enzymes are approved for cancer treatment (e.g., DNMTi, HDACi, HMTi), their non-specificity due to the highly conserved nature of these enzymes and the dynamic nature of epigenetic regulation often lead to off-target toxicities. Synthetic lethality offers a promising avenue to reduce these off-target effects, as the presence of the acquired alteration in cancer cells could reduce toxicity to healthy cells. SL relationships can be established between both epigenetic and non-epigenetic alterations and an epigenetic target, as exemplified by the SWI/SNF and PCR2 complexes discussed earlier.

While current efforts to identify SL interactions often focus on specific gene pairs in particular cancer subtypes, it may be time to take a step back and reassess the data collected in detail. A deeper understanding of the biological systems under study is needed, achieved by integrating and interpreting existing data. This includes starting with control cases and moving on to disease states. While more data will undoubtedly be helpful, its quality is key. Bridging the gap between wet-lab and computational methods will allow us to better understand how they can complement each other. As we explore the broader landscape of SL, we must characterize gene networks more thoroughly to identify new targets. Epigenetic mechanisms are not just another layer of regulation, but a critical system that should be fully incorporated into SL research.

By reevaluating our current knowledge and exploring novel or repurposed drug combinations, we can better harness the potential of SL in cancer therapy. To truly advance the field, the next step is not just about pushing forward but ensuring that we build a solid foundation-, fone that integrates current insight, strengthens our understanding of biological systems, and refines our methodologies. Only by doing so can we fully exploit synthetic lethality and develop more effective, targeted therapeutic strategies.

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Author contributions

Maria Farina-Morillas, Jose A. Seoane and Miguel F. Segura conceptualized the manuscript. Maria Farina-Morillas prepared the original draft under supervision of Jose A. Seoane. Laia Ollé-Monràs conducted the systematic literature search. Laia Ollé-Monràs, Maria Farina-Morillas, Silvana CE Maas, and Jose A. Seoane manually curated the literature search. Maria Farina-Morillas and Isabel de Rojas-P conceptualized the figures, under the supervision of Jose A. Seoane and Miguel F. Segura, respectively. Maria Farina-Morillas, Laia Ollé-Monràs, Isabel de Rojas-P, and Silvana CE Maas critically revised the draft. All the authors contributed to the writing and gave their approval for the final manuscript.

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