

## Review

## Cancer drug resistance as learning of signaling networks

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## ABSTRACT

Drug resistance is a major cause of tumor mortality. Signaling networks became useful tools for driving pharmacological interventions against cancer drug resistance. Signaling datasets now cover the entire human cell. Recently, network adaptation became understood as a learning process. We review rapidly increasing evidence showing that the development of cancer drug resistance can be described as learning of signaling networks. During drug adaptation, the network forgets drug-affected pathways by desensitization and relearns by strengthening alternative pathways. Thus, resistant cancer cells develop a drug resistance memory. We show that all key players of cellular learning (i.e., IDPs, protein translocation, microRNAs/lncRNAs, scaffolding proteins and epigenetic/chromatin memory) have important roles in the development of cancer drug resistance. Moreover, all of them are central components of the epithelial-mesenchymal transition leading to metastases and resistance. Phenotypic plasticity was recently listed as a hallmark of cancer. We review how network plasticity induces rare, pre-existent drug-resistant cells in the absence of drug treatment. Key network methods assessing the development of drug resistance and network pharmacological interventions against drug resistance are summarized. Finally, we highlight the class of cellular memory drugs affecting cellular learning and forgetting, and we summarize current challenges to prevent or break drug resistance using network models.

## 1. Introduction

Cancer is one of the foremost causes of mortality globally. The American Cancer Society estimated 4 new cases and 1 death from cancer in every minute in 2024 in the USA alone [1]. Drug resistance continues to be the principal limiting factor in curing cancer patients. Emergence of resistance often leads to the development of a more invasive type of tumor and metastases. Thus, prevention or circumvention of drug resistance is a key task of modern anticancer pharmacology. Drug resistance often occurs by decreased drug uptake/increased drug efflux [2], by mutations in drug target(s) [3,4], by disruption of cell cycle arrest and/or apoptosis [2,5] and, importantly, by restoration of cell proliferation [5]. Important contributors to these processes are: 1.)

activation of alternative signaling pathways (by post-translational modifications, by changes both in protein/microRNA/long noncoding RNA (lncRNA) levels and in chromatin structure as well as by mutations); 2.) genomic instability leading to increased mutagenesis; 3.) changed alternative splicing and 4.) increased cellular noise [6–11].

Molecular networks of individual cells are mainly built from protein-protein interaction (PPI) networks (interactomes). In interactomes, network nodes are proteins and network edges are their physical connections. A significant part of human PPI networks participates in signal transduction by forming signaling networks (signalomes), which include several noncoding RNAs, such as microRNAs or lncRNAs. Nodes of gene regulatory networks are proteins (e.g. transcription factors, final protein products, epigenetic regulators, etc.), DNA segments and RNAs (such as

**Abbreviations:** ABC protein, adenosine triphosphate-binding cassette protein; ALK, anaplastic lymphoma kinase; CC2D1A, C2-domain containing protein 1 A; CAS, Crk-associated substrate; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; FRS2, fibroblast growth factor receptor substrate 2; GSK3, glycogen synthase kinase 3; HIF, hypoxia-inducible factor; IDP, intrinsically disordered proteins; KAT, histone lysine acetyltransferase; lncRNA, long noncoding RNA; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; MTOR, mammalian target of rapamycin; NFκB, nuclear factor-kappa B; PI3K, phosphoinositide 3-kinase; PPI, protein-protein interaction; TRPM8, transient receptor potential melastatin type-8.

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mRNAs). Genetic interaction networks are also used, where nodes are products of gene transcription and edges are correlations between their expression levels. Finally, nodes of metabolic networks are small metabolite molecules (such as oxaloacetate, citrate, etc.) and their edges are chemical reactions (associated with specific enzymes catalyzing the process) which convert metabolites to each other [5,12,13].

We focus on signaling networks, since they are involved in targeted anticancer therapy design the most. Recently, a number of signaling network datasets became available which now cover a large part or the entire human proteome [4,14–18]. Recent findings indicated that signaling networks are able to learn (i.e. produce a faster, stronger and more stable signal after a stimulus is repeated a few times). Networks learn by increasing the strength of the interactions between their components (a process, which is similar to the well-known **Hebbian learning** (see Glossary) of neuronal connections) and by network reconfiguration [19–29]. Examples of connection strength increases during **cellular learning** include the transient conformational memory of intrinsically disordered proteins (IDPs), protein translocation and increased microRNA or lncRNA levels. **Epigenetic memory**, **chromatin memory** and **scaffolding proteins** of signaling cascades are major contributors to connection strength (i.e. network edge weight) enhancement of signaling networks. Learning of individual cells builds cellular memory. Reconfiguration of the memory of healthy cells may lead to tumor transformation. Similarly, loss of **cellular memory** (**cellular forgetting** often involving pathway desensitization corresponding to the **anti-Hebbian learning** of neuronal cells) may lead to dedifferentiation, which may open the way to metastasis or cancer stem cell formation [19–27].

We first summarize the key changes in the structure of single cancer cell signaling network during drug resistance development. Next, we show how learning, memory formation and forgetting of the signaling network contribute to cancer drug resistance. We highlight the role of **network robustness** and **network plasticity**. We list key examples of network methods assessing drug resistance development. Finally, we conclude with the pharmacological possibilities of preventing or combating cancer drug resistance using **network pharmacology** and **cellular memory drugs**, i.e. drugs or drug combinations based on cellular learning or cellular forgetting.

## 2. Network structure changes in drug resistance development

**Network modules**, i.e. groups of network nodes which are more densely connected with each other than to their neighborhood, are key components of network structure. Disease modules utilize the fact that proteins associated with the same disease (like various types of cancer) tend to be co-localized in the same neighborhood of PPI networks [30]. A recent work from the group of *Albert-László Barabási* added microRNA and lncRNA connections to protein-protein interactions, thus extending the human PPI network size by 46 % and adding 132 novel disease modules to the original 505 [31].

Drug resistance associated modules of PPI networks are often called **resistomes**. The word **resistome** was originally coined for segments of bacterial PPI networks containing proteins overexpressed in antibiotics-resistant bacteria. However, the term was also expanded to several sub-networks of the human PPI network centered around key components of cancer drug resistance development, such as focal adhesions (including e.g.  $\alpha$ V $\beta$ 1-integrin and the focal adhesion kinase, FAK [32]); the mammalian target of rapamycin (mTOR [33]); nuclear factor-kappa B (NF $\kappa$ B [34]) or hypoxia-inducible factor (HIF [35]).

Network modules highlight an important role of the neighborhood of key signaling components and drug targets participating in drug resistance development. Network neighbors of cancer related proteins have a key role in cancer pathogenesis [36]. Driver mutations of cancer progression are neighbors of signature genes, whose expression can be used as a prognostic marker of metastasis and survival of breast tumors [37]. Neighbor-targeting was suggested as a key drug design strategy,

especially in late-phase cancers [12].

Signaling network modules often encode signaling pathways and their associated scaffolding proteins. Re-directing signaling from those signaling routes which became blocked by an anticancer drug (e.g. receptor tyrosine kinases/growth factor receptors by their inhibitors) to alternative pathways is a frequent mechanism of drug resistance development [38]. While the MAPK/PI3K (mitogen-activated protein kinase/phosphoinositide 3-kinase) core pathway operates mainly in differentiated cells, the Hippo-WNT-Notch-Hedgehog MYC-inducing core pathways are more characteristic to stem cells. Blocking one core pathway usually activates the other and develops drug resistance. However, as an example, the combination therapy applying PI3K/AKT inhibitors together with the WNT/ $\beta$ -catenin pathway blocker, Tankyrase repressed the growth of PI3K/AKT inhibitor-resistant colon cancer [7, 11]. We will detail network-based pharmacological interventions against drug resistance in Section 6.

## 3. Learning, memory and forgetting of signaling networks in drug resistance

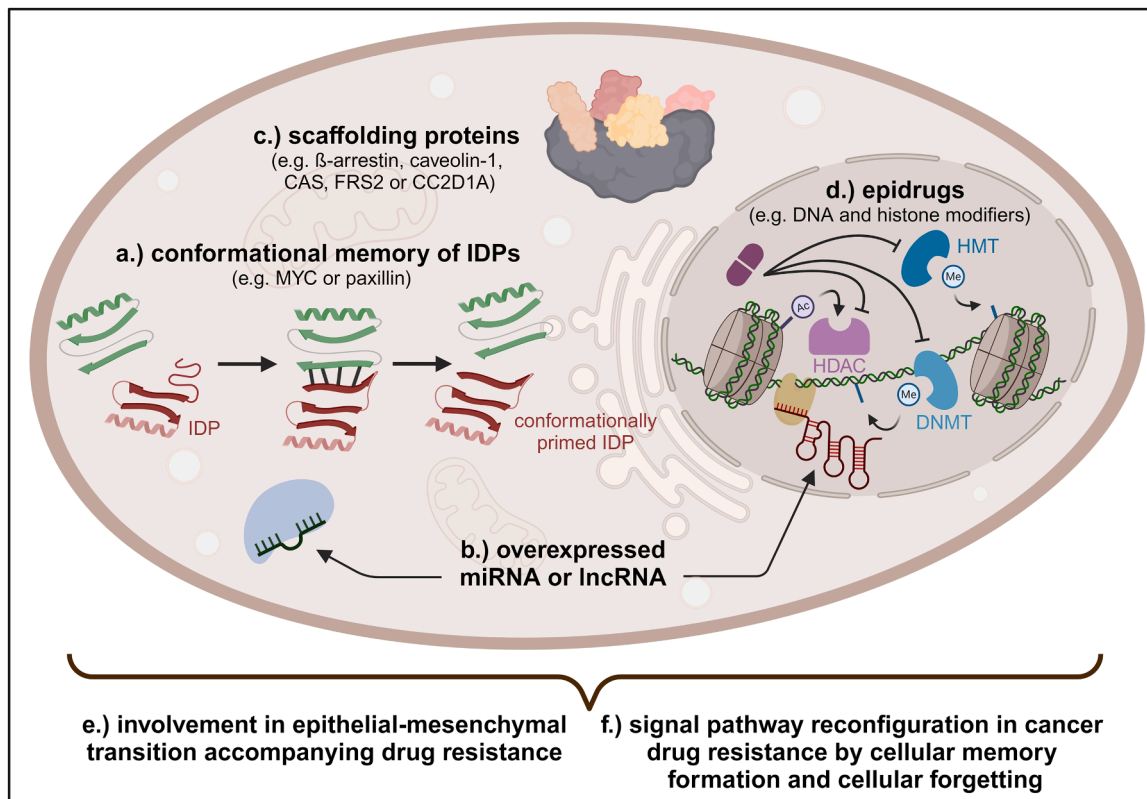
Cancer cells learn to survive in the presence of anticancer drugs. In this process, they 'forget' (i.e. desensitize, down-regulate, avoid, circumvent) a number of usual pathways which are affected by the drugs [27]. Consequently, cancer cells learn to upregulate, activate alternative pathways and develop resistance memory [39–42]. In this section, we summarize the major signaling mechanisms of these processes.

### 3.1. Cellular learning and memory mechanisms in drug resistance development

As we summarized in Section 1, cellular learning and formation of single-cell memory involves IDPs, protein translocation, scaffolding proteins, increased microRNA/lncRNA levels, as well as epigenetic and chromatin memory [19,21–28] (Fig. 1). As examples of the many, MYC and the focal-adhesion-associated paxillin are two key IDPs involved in the development of drug resistance [43]. Inhibitors of ERK (extracellular signal-regulated kinase) nuclear translocation emerged as potential agents against drug resistance [44]. Various scaffolding proteins, such as  $\beta$ -arrestin [45], caveolin-1 [46], CAS (Crk-associated substrate) family proteins [47] as well as fibroblast-growth factor receptor substrate 2 (FRS2) and C2-domain containing protein 1 A (CC2D1A) [48] are involved in resistance development against anticancer drugs blocking the MAPK/WNT/ $\beta$ -catenin, PI3K/AKT, estrogen receptor-related or ALK (anaplastic lymphoma kinase) pathways.

Both microRNAs and lncRNAs play a key role in drug resistance development [9,49,50]. MicroRNAs are small noncoding RNAs (18–22 nt in length) that act as negative regulators of gene expression through the modulation of multiple target mRNAs and by inhibition of translation. The microRNAs miR-15b, miR-16, miR-22, miR141 and miR-495 participate in the development of chemotherapy resistance [9,49]. MicroRNAs act through multiple pathways, including 1.) cell cycle and proliferation control (e.g. miR-224); 2.) survival and/or apoptosis pathways; 3.) DNA repair; 4.) drug targets; 5.) drug transporters (such as the adenosine triphosphate-binding cassette, ABC, transporter proteins); 6.) drug metabolism (e.g. miR-24; miR-508–5p) and 7.) the **epithelial-mesenchymal transition** (EMT; e.g. miR29c, miR146b, miR-200 and miR-224) [9,49,51]. MicroRNAs (such as miR-34, miR-125b, miR140 and miR215) also play a role in conveying drug resistance to cancer stem cells [49]. Thus, microRNAs act at almost all steps of cellular memory development.

lncRNAs are mRNA-like transcripts from 0.2 to ~100 kb in length that lack characteristic open reading frames. lncRNAs modulate drug metabolism (e.g. H19 and HOTAIR lncRNAs), increase drug efflux (e.g. PVT1, MRUL and MALAT1 lncRNAs), inhibit apoptosis (e.g. ERIC, PDAM, PCGEM1 and CUDR lncRNAs) and activate EMT (e.g. CCAT1 and MALAT1 lncRNAs [50]). lncRNAs (e.g. the XIST, LARRPM, LINC-PINT



**Fig. 1. Learning of signaling networks during the development of cancer drug resistance.** a.) Several key proteins of drug resistance development, such as MYC and paxillin, are IDPs contributing to cellular memory formation by their conformational memory. b.) MicroRNAs (interacting with the cell cycle, survival/apoptosis signaling, DNA repair, drug targets, drug transporters/ABC proteins and EMT) and lncRNAs (interacting with e.g. DNA-methyltransferases and ten-eleven translocation, TET dioxygenases) play an important role both in cellular learning and emergence of drug resistance. c.) Scaffolding proteins (such as  $\beta$ -arrestin, caveolin-1, CAS family proteins, fibroblast growth factor receptor substrate 2 (FRS2) or C2-domain containing protein 1 A (CC2D1A) are also involved both in learning of signaling networks and in increased drug resistance. d.) Finally, epidrugs, i.e. inhibitors of chromatin memory proteins such as DNA methyltransferase (DNMT), histone deacetylase (HDAC), histone methyltransferase and histone methylase (both abbreviated as HMT) were successfully used against drug resistance development. Ac = acetyl group. Me = methyl group. e.) All these four mechanisms of cellular memory formation (i.e. IDPs, microRNAs/lncRNAs, scaffolds and chromatin memory) are involved in epithelial-mesenchymal transition, which often accompanies drug resistance development. f.) Drug resistance development mechanisms reconfigure signaling pathways using connection strength increases and decreases corresponding to Hebbian learning (cellular memory formation), and anti-Hebbian learning (targeted cellular forgetting) at the signaling network level, respectively. Created with Biorender.com.

and WT1 lncRNAs) interact with ten-eleven translocation (TET) dioxygenases [52]. Several lncRNAs (e.g. the MIAT, LINP1, SNHG7 and HOTAIR lncRNAs) interact with DNA methyltransferases [52]. lncRNAs redirect chromatin remodeling complexes [49]. Thus, lncRNAs modulate nuclear reprogramming and the development of chromatin memory.

**Epidrugs**, i.e. inhibitors of epigenetic modifying proteins, which induce epigenetic inheritance, such as DNA methyltransferase, histone deacetylase, histone methyltransferase and histone methylase were successfully used in combination with standard-of-care drugs to prevent or delay the development of drug resistance [8,9,25,53]. All these epigenetic modifications are involved in the development, maintenance and erasure of chromatin memory.

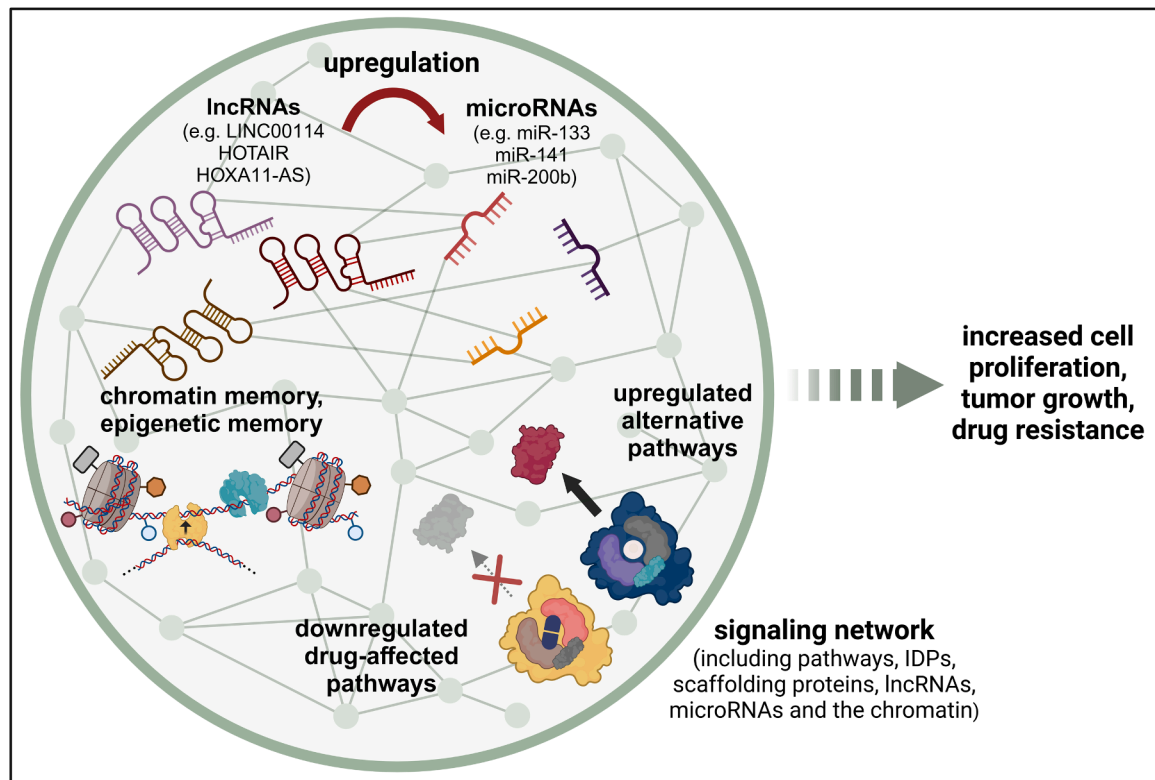
### 3.2. Interplay between cellular memory mechanisms in drug resistance development

Cellular memory mechanisms do not work independently from each other, but form a large network, and are in a continuous interplay. MicroRNAs and lncRNAs already form a network, where lncRNAs upregulate microRNA expression in several types of cancer (e.g. LINC00114 upregulates microRNA-133b in colorectal cancer, HOTAIR upregulates microRNA-141 in glioma, and HOXA11-AS upregulates microRNA-200b in non-small cell lung cancer), which leads to increased cell proliferation and tumor growth [52]. lncRNAs modify both

chromatin memory and epigenetic changes [49,50,52]. MicroRNAs, lncRNAs and the chromatin are regulated by, and also modify, the signaling network [9,49,50,52], which contains IDPs, scaffolding proteins and themselves (Fig. 2).

### 3.3. Drug resistance development as forgetting and relearning of cancer cells

In summary, all the key players of cellular learning and cellular memory formation (i.e. IDPs, protein translocation, microRNAs/lncRNAs, scaffolding proteins and epigenetic/chromatin memory) play an important role in the development of cancer drug resistance. Moreover, all of them are central components of EMT, a crucially important cellular transformation that leads to cancer metastases and accompanies the development of drug resistance [19,51,54,55]. Thus, cancer cells mobilize their entire network structure to learn survival during cancer progression. This view is in agreement with that of Shomar et al. [56], who described cancer progression as a learning process. Cancer cells reconfigure their cellular memory [26,28] through cellular forgetting and relearning [27] during drug resistance development. Drug resistance can be regarded as a form of habituation (i.e. a decrease of the response level to at least 50 % of the original response after a too frequently repeated stimulus—a concept used in neuronal learning processes [23,26]). Mechanisms of drug resistance development involve a reconfiguration of signaling pathways with both connection strength



**Fig. 2. Interplay between cellular memory mechanisms in drug resistance development.** Cellular memory mechanisms create a rich interaction network with each other. lncRNAs and microRNAs form a network, where lncRNAs upregulate microRNA expression in several types of cancer (e.g. LINC00114 upregulates microRNA-133b in colorectal cancer, HOTAIR upregulates microRNA-141 in glioma and HOXA11-AS upregulates microRNA-200b in non-small cell lung cancer), which leads to increased cell proliferation, tumor growth and drug resistance. lncRNAs modify both chromatin memory and epigenetic changes. MicroRNAs, lncRNAs and the chromatin are regulated by, and also modify, the signaling network containing downregulated drug-affected signaling pathways, upregulated alternative pathways, intrinsically disordered proteins (IDPs), scaffolding proteins, as well as lncRNAs, microRNAs and the chromatin themselves. miR = microRNA. Created with Biorender.com.

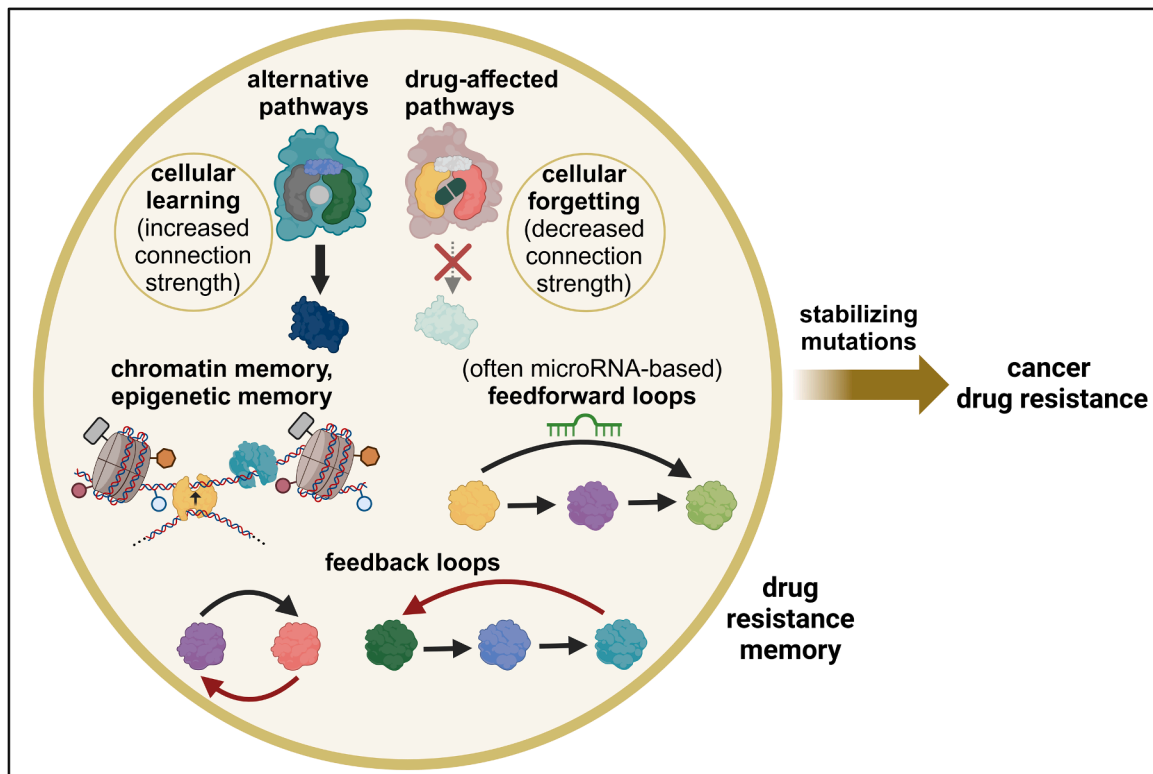
(i.e. network edge weight) increases and decreases. Connection strength increases correspond to Hebbian learning (cellular memory formation [19]). Connection strength decreases correspond to anti-Hebbian learning (targeted cellular forgetting [27]). Thus, signaling networks both forget, and relearn during drug resistance development using a number of mechanisms, including the desensitization of drug-affected pathways, upregulation of alternative pathways, feedback loops, (often microRNA-based) feedforward loops, chromatin memory and consequent, stabilizing mutations [7,11,39–42]. We note that more complex patterns of memory than loop-structures (such as multiple feedback loops or concatenated feedforward loops) also often occur in networks [22,23,28,29], and networks may also develop memory through their recurring dynamic states without consolidating a specific structural pattern [23]. All these processes lead to the development of drug resistance memory [39–42,57,58] (Fig. 3; see also Section 4.).

#### 4. Network plasticity as an inducer of drug resistance

Phenotypic plasticity of cells was recently incorporated as a hallmark of cancer [59], and it induces drug resistance [60]. Plasticity of the epithelial-mesenchymal transition is an important mark of its contribution to cancer metastasis [61]. Network plasticity, i.e. the ability of fast network reconfigurations as a response to external stimuli, and network robustness are both increased in cancer cells, which leads to the appearance and maintenance of dynamically changing cellular heterogeneity [39,60,61].

##### 4.1. Network plasticity in the development of an early, rare drug-resistant cell population

Adaptation of the signaling network induces acquired resistance in the whole cell population. However, network plasticity helps the emergence of intrinsic drug-resistance in a rare subpopulation (approximately one of 3000 cells) of cancer cells even in the absence of drug treatment. Moreover, this transient drug-resistant state may become stabilized and live through two to six generations of dividing cancer cells. Dynamic and long-lived, rare but coordinated fluctuations in gene expression (including long transcriptional bursts) are major sources of pre-existent drug-resistant cells. These and other sources of noise (such as the fluctuating protein conformations of IDPs or higher chromatin accessibility) are crucially important to raise cellular heterogeneity (including pre-existent drug-resistant cells) in cancer cell populations [24,25,42,57,58,62]. These pre-existent drug-resistant cells have been shown to become often dormant, reducing their proliferation rate, which helps their initial escape from several anticancer drugs targeting cell division mechanisms [56]. In breast cancer cells treated by protein kinase/phosphatase inhibitors, the signaling network has been shown to become heterogeneously resistant to the drug, which shows an important sign of network plasticity [63]. Importantly, network plasticity and the relatively high noise of cancer cells themselves re-induce the drug dependent state, if the drug administration is ceased. This is the reason why re-sensitization to a repeated drug challenge occurs, and why 'drug holiday' became an important treatment option for cancer patients [64,65] (see Section 6.1.).



**Fig. 3. Forgetting and relearning of signaling networks during cancer drug resistance development.** Cancer cells reconfigure their cellular memory through cellular forgetting and relearning during drug resistance development. This process involves the reconfiguration of the signaling network with both connection strength increases and decreases corresponding to Hebbian learning (cellular memory formation) and anti-Hebbian learning (targeted cellular forgetting), respectively. Forgetting and relearning mobilizes a number of mechanisms, including the desensitization of drug-affected pathways, upregulation of alternative pathways feedback loops, (often microRNA-based) feedforward loops, chromatin memory and consequent, stabilizing mutations. We note that more complex patterns of memory than loop-structures (such as multiple feedback loops or concatenated feedforward loops) also often occur in networks, and networks may also develop memory through their recurring dynamic states without consolidating a specific structural pattern. These lead to the development of drug resistance memory. Created with Biorender.com.

#### 4.2. Drug-resistant cell plasticity induced by the tumor microenvironment

Tumor microenvironment increases the plasticity of cancer cells, which helps the emergence of their drug-resistant phenotype [66]. As an important example of this process, cancer-associated fibroblasts increase the plasticity of tumor organoids, i.e. 3D multicellular clusters derived from patient tumors. A crucial part of this transition is the shift from a proliferative state to a slow-cycling, dormant state, which protects cancer cells from chemotherapy [67]. Tumor microenvironment helps the metabolic reprogramming of cancer cells, which leads to an enhanced plasticity of the epithelial-mesenchymal transition [68]. Due to the hypoxic environment, cancer cells lose the oxidative phosphorylation in their mitochondria. However, after their epithelial-mesenchymal transition, they may regain oxidative phosphorylation (increasing their metabolic plasticity, as well as helping their motility and drug resistance) by receiving mitochondria from surrounding mesenchymal stem cells [69]. Tumor microenvironment also helps the activation of stemness pathways, which leads to cancer stem cell formation [70]. Cancer stem cells have an extremely plastic network structure [71]. Importantly, cancer cells also increase the plasticity of their neighbors, such as that of tumor-associated macrophages, which leads to macrophage-myofibroblast and macrophage-neuron transitions [72]. By increasing the plasticity of their neighborhood, cancer cells convert their surrounding environment to a supportive niche [73].

#### 4.3. Resistance memory: stabilization of the early, drug-resistant state

The network plasticity-induced, pre-existent, rare drug-resistant state may acquire a long-lasting stability and may generally characterize (almost) the entire cancer cell population after a (longer) drug treatment. Such resistance-stabilization is helped by a number of mechanisms inducing resistance memory of cancer cells. Multiple layers of feedback loops play an important role in the development (e.g. by positive feedback loops) and maintenance (e.g. by negative feedback loops or by microRNA-based feedforward loops) of cellular resistance memory [39–42]. Chromatin memory is also an important contributor to resistance memory development [57,58]. Resistance memory becomes stabilized in several cell generations by mutations, which may also induce cancer stem cell formation [42,57]. Signaling memory is robust to noise. Lowered noise (by e.g. tissue integration of previously migrating drug-resistant cancer cells) helps the maintenance of the drug-resistant state. However, in a few cases (especially in high stress conditions, and in cancer cells having a gradual kill curve needing higher drug levels), noise may also increase the development of resistance memory [39,42].

#### 4.4. Network robustness in drug resistance development

The seminal paper of Hiroaki Kitano [39] on cancer as a robust system defined network robustness as an ability of cellular adaptation (learning), as well as tolerance of fluctuations in protein-protein interactions and stochastic noise (of e.g. transcriptional and translational processes). Robustness of molecular networks is enhanced by feedback

controls, redundancy (i.e. the property that functionally equivalent network parts, such as signaling pathways can substitute each other) and network modularity (i.e. separation of network groups from each other to prevent the spread or amplification of local perturbations). Cancer cells display an increased robustness, which is enhanced by multiple layers of feedback loops and genomic instability, as well as by cellular heterogeneity [39]. Cellular heterogeneity leads to various interactions between tumor cell types, stromal cells, the extracellular matrix, immune cells and the vasculature increasing the robustness further [39]. Protein-protein interaction and gene regulatory networks of cancer cells have higher robustness than those of healthy cells [40].

Networks with an onion structure (i.e. a structure having a dense, central core of network nodes surrounded by consecutive layers of more and more peripheral nodes, where intra-layer connections are denser than inter-layer connections) was shown to be much more robust both to attacks of its hubs (i.e. nodes having the highest number of neighbors) or of randomly selected nodes [74]. Core/periphery network structures with distinct peripheral network modules weakly attached to the network core but not to other peripheral node groups were also shown to display a high robustness [75]. It is an open question whether such onion or other core/periphery structures play a role in drug resistance development.

Key publications from *László-Albert Barabási* and his group described network controllability, where a few nodes direct networks to a desired state (i.e. from cell proliferation to apoptosis) [76], as well as network resilience (i.e. the ability of networks to adjust their structure to retain functionality when errors, failures and environmental changes, such as cancer drug treatments occur [77]). However, until now, neither controllability nor network resilience changes were calculated for cancer cells acquiring drug resistance. As a first step of these investigations, the important contributions from *Michael Levin* and colleagues [22,23,26,29] showed that transcriptional networks possess memory (which

increases during differentiation), and are more controllable to break habituation (which corresponds to drug resistance development) than random pairs.

## 5. Network methods assessing the development of drug resistance

Structural analysis of protein-protein interaction networks extended with microRNAs and lncRNAs revealed the existence of disease modules, i.e. densely connected groups of network nodes associated with e.g. several types of cancer [31]. Drug resistance-associated network module analysis identified e.g. SPTBN1 (a cytoskeletal component of the spectrin family), LSMP1 (a protein protecting the lysosomal membrane against hydrolysis), miR-92a, miR-124 and additional 17 microRNAs, as well as the lncRNAs UCA1, GAS5 and LINC-ROR as drug resistance-associated proteins or noncoding RNAs, respectively [49,78,79]. Assessment of drug resistance development requires the comparison of two or more network structures of the drug-sensitive and the (increasingly) drug-resistant cells. This is usually performed by machine learning methods or by network common component analysis. These methods identified e.g. the keratin gene family (KRT5, KRT6A, KRT13, KRT14 and KRT15) as proteins involved in the development of gefitinib and erlotinib resistance, as well as the histone deacetylase inhibitor trichostatin A as a candidate adjuvant for the prevention/reversion of docetaxel resistance [53,80] (Table 1).

Since the function of signaling networks is crucially linked to the transmission of perturbations, methods related to network dynamics became increasingly important to analyze the development of drug resistance. However, the assessment of network dynamics is computationally costly. Therefore, initially only relatively small (up to a few dozen nodes) dynamic signaling networks were examined, where Boolean dynamics were often applied. Boolean dynamics use activating

**Table 1**  
Network methods assessing the development of drug resistance.

| Method's name                              | Network                                                      | Cancer type                                             | Brief description                                                                                                                                                   | Ref.     |
|--------------------------------------------|--------------------------------------------------------------|---------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| <b>Methods assessing network structure</b> |                                                              |                                                         |                                                                                                                                                                     |          |
| Disease module                             | PPI + microRNA + lncRNA                                      | Various                                                 | Determination of local network modules of disease-associated gene products                                                                                          | [31]     |
|                                            | Gene coexpression network                                    | Hepatocellular carcinoma                                | Drug-resistance associated network module identification                                                                                                            | [114]    |
|                                            | MicroRNA + lncRNA + drugs                                    | Various                                                 | RNA/drug network association and network module identification using machine learning                                                                               | [49, 78] |
| DRdriver                                   | Gene regulatory network of specific, drug-resistant patients | 8 cancer types                                          | Networks of resistance-specifically mutated genes, their regulators and targets, drivers of most differentially expressed gene identified by genetic algorithm      | [115]    |
| NetSCCA                                    | Multilayer gene networks                                     | Gefitinib- and erlotinib-sensitive and -resistant cells | EGFR CRISPR knockout screen combined with network-constrained sparse common component analysis of sensitive and resistant cells                                     | [80]     |
| DryNetMC                                   | Time course RNASeq gene regulatory network                   | Glioma                                                  | Network topology, network entropy and expression dynamics characterization on a ~50 node network                                                                    | [116]    |
| <b>Methods analyzing network dynamics</b>  |                                                              |                                                         |                                                                                                                                                                     |          |
| Boolean                                    | 51 node dynamic signaling network                            | Breast cancer                                           | Boolean dynamic model of 6 signaling pathways (IGF1R, HER2/3, PI3K, MAPK, AKT, mTORC, ER)                                                                           | [84]     |
|                                            | MALAT-miR-145-KLF4-BMI1-Sp1                                  | Non-small cell lung cancer                              | Regulatory circuits of miR-145                                                                                                                                      | [82]     |
|                                            | FLT3 tyrosine kinase internal tandem duplication network     | Acute myeloid leukaemia                                 | Personalized predictive models of the signaling landscape of affected patients                                                                                      | [81]     |
| Boolean and protein translocation          | Epithelial-mesenchymal transition                            | Various                                                 | Shows different functions before and after protein translocation                                                                                                    | [51]     |
| Global sensitivity analysis                | ErbB2/3 signaling network                                    | Ovarian cancer                                          | Multiparametric network perturbations using 54 ordinary differential equations and 91 parameters                                                                    | [117]    |
| Pathway dynamics analysis                  | Signaling network of 14 phosphoproteins                      | Colorectal                                              | Pathway dynamics analysis from phosphoprotein patterns after drug perturbations                                                                                     | [83]     |
| VESPA                                      | Signaling network 7-point phosphoproteomic time series       | Colorectal                                              | Virtual enrichment signaling protein analysis: machine learning of drug perturbation adaptations                                                                    | [85]     |
| Turbine                                    | Simulated Cell                                               | Various                                                 | Difference equation-based simulation of signal propagation in a large-scale human signaling network to reveal best few from 66,348 drug combination/cell line pairs | [86]     |

or inhibiting connections. The signaling status of each network node is described by ON or OFF states. Thus, Boolean dynamics is binary: showing either full activation or full inhibition. The interplay of connections is marked by the logical operators AND, OR and NOT. AND means that the involved connections are all needed for activation. OR means that any one of them is enough. NOT inverts the node status: if it was ON, it becomes OFF, and vice versa [81–84].

Boolean methods identified (among many others) the JNK pathway and miR-145 potentially playing a role in drug resistance of acute myeloid leukemia and non-small cell lung cancer, respectively [81,82]. Co-blockade of glycogen synthase kinase 3 (GSK3) and the MYC/CDK4/CDK6 axis (or GSK3 and mTORC1) were also shown as potential treatment options in case of MEK (mitogen-activated protein kinase kinase) inhibitor (or PI3K inhibitor) resistance [83,84]. Propagation of multiple perturbations in larger signaling networks emerged as a modeling option only recently. Analysis of time series of phospho-proteomic patterns during drug treatment [85] is a promising method to study drug resistance development and to propose treatment options to prevent or inhibit its emergence. The Simulated Cell model uses discrete-time difference equation–based perturbation propagation in a large-scale signaling network. This method results in an *in silico* estimate of cell survival after drug treatment. The model calculates the continuous state of signaling nodes between full inhibition and full activation. Simulated Cell uses manually curated signaling networks customized to specific cancer cells by RNA expression and mutation patterns. The method was successfully used to predict the best few from 66,348 drug combination/cell line pairs [86].

## 6. Network pharmacology and cellular memory drugs combating drug resistance

Combination therapy emerged early on as an important treatment modality against cancer. Network pharmacology uses the rich information encoded by molecular networks of cancer cells to suggest drug combinations based on the network proximity of potential drug target proteins in e.g. disease modules, i.e. densely connected network node groups associated with the particular type of cancer [87,88].

### 6.1. Network pharmacology–based therapy options against drug resistance

Network-based combination therapy options include blocking different targets a.) in the same pathway; b.) in redundant pathways (using isoforms, e.g. Ras/K-Ras/H-Ras, EGFR/ErbB2/3, etc.); c.) in parallel pathways (like the pairs RTK/JAK-STAT or Hippo-YAP1/WNT- $\beta$ -catenin, both pairs stimulating cell proliferation); and in d.) compensatory pathways (like MAPK inducing sufficiently high protein levels and PI3K/AKT/mTOR inducing cell growth, both needed for proliferation [7,11]). An important recent development that the paradoxical activation of the MAPK pathway (by e.g. the PP2A inhibitor LB-100) together with cell cycle checkpoint inhibition by WEE1 or CHK1 inhibitors developed resistant cells that have not increased but much reduced tumorigenicity [89]. Recent work examined 684 drug combinations in 97 cancer cell lines using a large-scale dynamic model of cancer cell signaling networks and showed the synergy between drugs affecting DNA damage response pathways. The easy interpretability of network models helps to understand synergy mechanisms, which is at least as important in clinical applications as synergy itself [86]. These approaches may significantly speed up the drug development process and may lead to the discovery of unusual drug combinations, which often suggest a repurposing of existing drugs against completely different diseases than cancer. Network methods may also bring nonconventional drug targets to the discovery-channel, like those network neighbors which are adjacent network nodes to proteins involved in cancer development [12,36,37].

Ceasing anticancer therapy administration may lead to re-

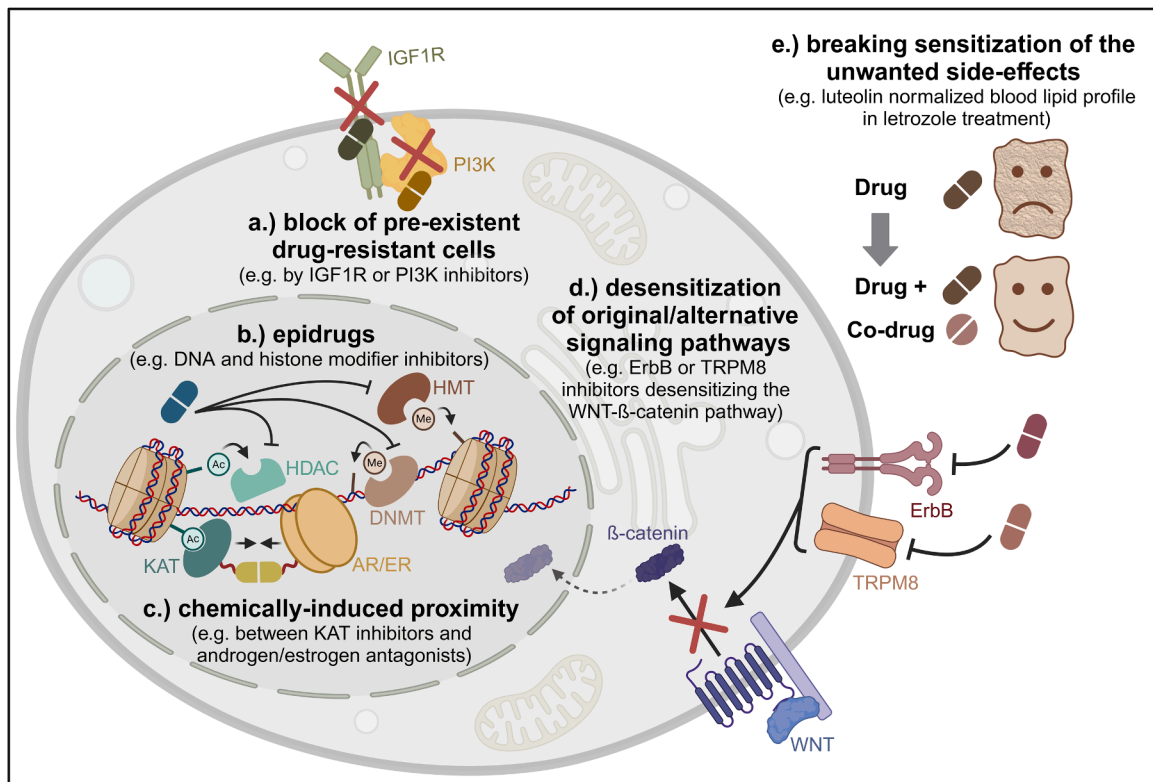
sensitization against the drug due to network plasticity-induced changes in the already existing drug-resistant cells (which often have not yet acquired mutations or extensive network changes stabilizing the drug-resistant state). Intermittent treatment protocols (including 'drug holidays') became an important treatment option in gefitinib-resistant lung adenocarcinoma or encorafenib/vemurafenib-resistant melanoma [64,65,90]. As Sui Huang used the Nietzschean saying for cancer cells: "what does not kill me, makes me stronger", chemotherapy treatments often induce very aggressive tumors, which complete an epithelial-mesenchymal transition, with increased metastatic potential and cancer stem cell formation. Here, cancer cells are shifted to 'rebellious', more malignant attractor states by the stress and (partial) cell killing by the treatment itself [91]. Maintenance therapy, i.e. a therapy with extended duration (and potentially with lower drug doses) was introduced as early as 1956 [92]. Differentiation therapy is a successful option in acute promyelocytic leukemia, with a combined treatment of retinoic acid and arsenic. Differentiation therapy may re-differentiate cancer stem cells to progenitor cells incapable of self-renewal, reduce cancer cell heterogeneity, induce cell dormancy and may reverse the EMT [39,93,94].

### 6.2. Cellular memory drugs: an emerging new option against drug resistance

The signaling network of the cell can be trained to reconfigure its cellular memory [26–28,95]. A large number of the above listed treatment options use cellular memory drugs, i.e. drugs affecting the formation of cellular memory (differentiation therapy) or the induction of cellular forgetting ('drug holidays', maintenance therapy; Fig. 4). Several emerging treatment protocols use sequential therapy, where first a drug against the network plasticity-induced pre-existent drug-resistant cells is administered, which is then followed by targeted therapy (such as e.g. that of combined BRAF, MEK, etc. inhibitors). These drugs include IGF1-receptor inhibitors, PI3K inhibitors, or epidrugs, i.e. inhibitors of epigenetic modifying enzymes, such as DNA-methyltransferases, histone deacetylases, histone methyltransferases or histone demethylases. Importantly, histone deacetylase inhibition cannot erase network plasticity-induced, apoptosis-inducing JNK-impaired, vincristine- or anisomycin-resistant neuroblastoma cells. However, histone deacetylase inhibition improves drug response by restoring drug-induced, apoptosis-promoting JNK activity within the drug-resistant subpopulation of neuroblastoma cells [8,24,25,57].

The recent drug design strategy of chemically induced proximity mimics Hebbian-learning of signaling networks in the sense that it strengthens the interaction between two signaling network neighbors. This strategy has recently been suggested to link the epidrugs histone lysine acetyltransferase (KAT) inhibitors to androgen or estrogen receptor antagonists [96,97].

Therapy options (such as those mentioned before against the drug-resistant subpopulation of cancer cells) may induce cellular forgetting that breaks the (stochastically pre-existent or developing) habituation against the anticancer drug [19,23,26,27]. Desensitization of the 'always-on' cancer-specific signaling pathway induces cellular forgetting. The rich repertoire of emerging drug development directions to break ErbB signaling by disrupting protein-protein interactions of the ErbB receptor or by proteolysis/lysosome-targeting chimeras of ErbB [98] provides important examples of targeted cellular forgetting. Drug-induced desensitization of the cancer-promoting alternative growth signal is another mode to modify cellular memory (such as that by inhibitors of Transient receptor potential melastatin type-8, TRPM8, which desensitize the alternative WNT/ $\beta$ -catenin pathway [99]). Breaking of sensitization against the unwanted side effects of the anticancer drug may be an important co-therapy option (e.g. the coadministration of the flavonoid luteolin, with the aromatase inhibitor letrozole, besides the standard care of coadministered vitamin D and calcium, normalized the otherwise impaired blood lipid profile [100]).



**Fig. 4. Cellular memory drugs against drug resistance.** Cellular memory drugs are drugs affecting the formation of cellular memory (such as the development and stabilization of alternative signaling pathways maintaining cancer cell viability) or the induction of cellular forgetting (such as desensitization of pathways to drug inhibition). a.) Drugs against network plasticity-induced, pre-existent drug-resistant cells that emerge as a rare subpopulation in cancer cell heterogeneity before the anticancer drug administration (e.g. IGF1R or PI3K inhibitors). b.) Epidrugs, i.e. inhibitors of epigenetic modifying enzymes, e.g. DNA-methyltransferases (DNMT), histone deacetylases (HDAC), histone methyltransferases or histone demethylases (both abbreviated as HMT). Ac = acetyl group. Me = methyl group. c.) Chemically induced proximity: mimicking Hebbian learning of signaling neighbors, e.g. linking histone lysine acetyltransferase (KAT) inhibitors to androgen or estrogen receptor (AR and ER, respectively) antagonists. d.) Drug-induced desensitization of the original or alternative cancer promoting growth signal (e.g. inhibition of ErbB or TRPM8 desensitizing the WNT/ $\beta$ -catenin pathway). e.) Breaking sensitization to the unwanted side effects of anticancer drugs (e.g. the coadministration of luteolin broke the sensitization of blood lipid profile induced by letrozole). Created with Biorender.com.

## 7. Concluding remarks and future perspectives

We reviewed the development of cancer drug resistance as a cellular learning process of signaling networks. In this process, the signaling network plasticity (due to stochastic fluctuations) of the heterogeneous cancer cells first develops a rare (one in ~3000) subpopulation of pre-existent drug-resistant cells. In the presence of anticancer drugs, cancer cells forget their original state by downregulating drug-affected signaling proteins, by decreasing drug-affected connection strengths of signaling partners and by desensitizing drug-affected signaling pathways. Cancer cells also relearn to strengthen (i.e. upregulate, increase connection strengths and sensitize) alternative pathways. This latter is analogous to the Hebbian learning process of inter-neuronal connections. In the presence of the drug, the pre-existent resistant cell population becomes dominant (also because non-resistant cells die out) and develops drug resistance memory. We showed that all key players of the cellular learning process (such as IDPs, protein translocation, micro-RNAs/lncRNAs, scaffolding proteins and epigenetic/chromatin memory) are documented to be involved in drug resistance development. Importantly, all of them are involved in epithelial-mesenchymal transition, which accompanies drug resistance and leads to metastasis formation. We listed methods related to network structure or dynamics that assess drug resistance. We summarized the involvement of network pharmacology in opening new directions to understand resistance development. Finally, we highlighted cellular memory drugs affecting cellular memory and cellular forgetting and showed that these cellular memory drugs a.) erase the rare pre-existent drug-resistant cells as a pre-

treatment before targeted anticancer therapy; b.) mimic Hebbian learning of signaling networks by chemically induced proximity; c.) affect chromatin memory by DNA and/or histone modifications; d.) desensitize the original or alternative cancer promoting signaling; e.) break sensitization to unwanted side effects.

Future studies are needed for the further exploration and validation of therapeutic strategies related to network pharmacology, cellular learning and cellular forgetting. Network pharmacology-related inquiries may examine whether the onion structure of networks [74] becomes more prevalent in signaling networks of drug-resistant cells than in drug sensitive cells. Similarly, the enrichment of core/periphery network structures with distinct peripheral network modules weakly attached to the network core but not to other peripheral node groups [75] during cancer drug resistance development needs to be explored. Importantly, changes of neither network controllability [76] nor network resilience [77] were studied in drug-resistant cells in enough detail yet. Similarly, little attention was focused on network neighbors [12,36,37] of proteins known to be involved in drug resistance development. All these may drive the attention to novel potential drug targets, which may be successfully explored in combating cancer drug resistance.

Therapeutic modalities utilizing the plasticity of cancer cell networks require a much larger effort to bring their full potential to clinical practice. The appropriate scheduling of 'drug holidays' [64,65,90] including their onset, duration, sequence, reoccurrence, etc. deserves much greater attention. Combination of intermittent and maintenance therapies to conventional therapies is also an area getting less attention

than required.

Cellular memory drugs (i.e. drugs affecting cellular learning and cellular forgetting) are only rarely examined and used in the clinical practice yet. Sequential therapy, administering first cellular memory drugs against pre-existing drug-resistant cells displaying a large network plasticity (e.g. IGF1-receptor inhibitors, PI3K inhibitors or epidrugs) followed by targeted therapy [8,24,25,57], needs more studies. Cellular memory drugs inducing chemically induced proximity [96,97] will certainly be an area expanding in the future. Targeted cellular forgetting of continuously active signaling pathways (such as that of the EGF receptor [98]) or desensitizing drug-induced alternative pathways (like that of the WNT/ $\beta$ -catenin pathway [99]) will also have greater attention in the future. These efforts will help to set the balance of drug administration strategies to kill enough cancer cells (Huang, 2020) but still limit the pressure for drug resistance development.

Translation of the therapeutic concepts into clinical practice has many challenges. As an example of these, Biswas et al. [22] examined 35 gene regulatory networks possessing several types of memories and reported a significant variability of their responses to treatment sequences and durations. An important contribution is the recent study of Kukushkin et al. [95] reporting that the training of two non-neural, immortalized cell lines distributed across multiple sessions produced a stronger memory than the same amount of training applied in a single episode. This property (also called massed training) is highly conserved across the animal kingdom and is observed at both the behavioral and the synaptic level [95]. These findings suggest that actual effects of drug treatments may exhibit a strong history dependence—a concept remaining largely under-explored in clinical settings.

However, recent studies on large dynamic networks examined the sensitivity of KRAS-mutated molecular subgroups to PD-(L)1 immunotherapy in 776 patients [101], performed *in silico* clinical trials suggesting patient stratification and selecting the best-responder patient cohort [102], conducted an N-of-1 *in silico* clinical trial designing a successful therapy for a relapsed glioblastoma patient [103] and provided *in silico* drug combination screens in a short time revealing the best few from 66,348 drug combination/cell line pairs [86]. Creation and simulation of proteome-wide models is greatly helped by artificial intelligence (AI) technology [104,105]. These advances increase the hope that even larger dynamic network models may bring us closer to clinical applications.

There are several limitations to this study. The network methods we listed in Table 1. and our conclusions are based mostly on information about signaling networks. However, there are quite a few studies examining protein-protein interaction networks, including those which extended these PPI networks with microRNAs and/or lncRNAs. Since signaling networks constitute a major subnetwork of the combined PPI/microRNA/lncRNA network, and since molecular networks very often behave self-similarly [12], we expect that the results obtained with PPI networks or extended PPI networks are valid for signaling networks, too. As an example of this, the disease module concept of *László-Albert Barabási* was first shown in PPI networks, then extended to PPI/microRNA/lncRNA networks and also proved to be valid in signaling networks [31,106]. However, the precise examination of the similarity between PPI and signaling networks, and the possibility of extending these conclusions to gene regulatory networks, gene interaction networks or metabolic networks, are open questions for future studies.

Since we discussed learning of signaling networks, we concentrated on the development of acquired resistance. However, several points mentioned (such as network plasticity-induced cellular heterogeneity) cover intrinsic resistance as well. Except for the role of the tumor microenvironment in the development of cancer cell plasticity (Section 4.2.), we concentrated on the learning of single-cell signaling networks. Learning and forgetting during the development of drug resistance by the cell-cell network of cancer, stromal and immune cells is an important area of future studies.

Our current knowledge on signaling network dynamics during drug

resistance development is rather limited. This is mainly because of the limited size of the signaling networks examined in these studies. Recent developments extended human interactomes and signaling networks to the proteome level covering ~20 thousand human proteins [15,16,18]. However, even the largest currently published dynamic network models have only between 2 and 3.6 thousand nodes [86,101–103] (in the currently used version #8 of the Simulated Cell model, the network size grew to 8 thousand nodes; Daniel V. Veres, personal communication). What are the challenges to reach proteome-wide drug resistance models? Current datasets often use different identifiers, which prevents their easy combination. Only a segment of the data is experimentally verified, and a significant portion of them is only predicted. Both network data and models need to be more interoperable and reproducible [107]. Current, intensive community efforts [107–110] may solve these challenges in the future.

Finally, our conclusions give a valid description of the development of drug resistance in cancer cells. However, we note that there are several similarities to antibiotic resistance, antimicrobial resistance and resistance in diseases other than cancer. As examples of these, the concepts of the resistome and compensation of alternative signaling pathways were also coined in antibiotic resistance development [32,111], and even plants involve their chromatin memory in their defense responses [112]. Recently, an excellent review was published about the similarities of drug resistance development in bacteria, fungi and cancer cells [113]. However, the examination of the extent of this similarity will require further studies.

Our rapidly increasing knowledge about molecular networks of cancer cells has already provided a very powerful armament to combat the development of drug resistance. Significant improvements of the last years in network dynamics measurements opened an especially important new area here. We hope that our study summarizing the concept of cellular learning and cellular forgetting in understanding drug resistance development at the network level will prompt further studies of this exciting field.

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## CRediT authorship contribution statement

**Csermely Peter:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Veres Dániel:** Writing – review & editing, Conceptualization. **Schule Klára:** Writing – review & editing. **Kerestély Márk:** Writing – review & editing. **Keresztes Dávid:** Writing – review & editing, Visualization. **Kovács Borbála:** Writing – review & editing. **Szarka Levente:** Writing – review & editing.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Peter Csermely and Márk Kerestély report financial support provided by Ministry for Innovation and Technology in Hungary. Daniel V. Veres reports a relationship with Turbine Ltd. that includes: employment and equity or stocks. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Patient consent for publication

Not applicable.

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## Glossary

- Anti-Hebbian learning:** decrease of those connection strengths (network edge weights) which participated in the transmission of a stimulus that was repeated too often, or became too large or continuous. Anti-Hebbian learning is also a form of cellular forgetting.
- Cellular forgetting:** occurs continuously as a result of cellular noise. However, cells can also induce forgetting of special signaling pathways, which became too frequently used by too often repeated or continuous signals. This often happens by desensitization or pathway reconfiguration.
- Cellular learning:** adaptation of single, non-neuronal cell networks to produce a faster, stronger and more stable response to external stimuli repeated a few times. Often involves increasing strength of those network interactions which participated in the signal transmission after the repeated stimulus.
- Cellular memory:** persistent changes in molecular networks (especially signaling networks) of individual cells after a repeated stimulus.
- Cellular memory drugs:** drugs or drug combinations based on cellular memory formation or cellular forgetting mechanisms.
- Chromatin memory:** altered 3D chromatin structure providing different accessibility of genes for transcription after a repeated signal. Histone and DNA modifications play key roles in chromatin memory development.
- Epigenetic memory:** chromatin memory induced by a previous signal, which is heritable through cell generations.
- Epidrugs:** inhibitors of the epigenetic modifying proteins DNA methyltransferase, histone deacetylase, histone methyltransferase and histone methylase inducing epigenetic inheritance.
- Epithelial-mesenchymal transition (EMT):** a process where epithelial cells lose their cell polarity and cell-cell adhesion and gain migratory and invasive properties to become mesenchymal cells. EMT induces cancer metastases and may lead to cancer stem cell formation.
- Hebbian learning:** increase of those connection strengths (network edge weights) which participated in the transmission of a repeated stimulus.
- Network module:** a group of network nodes having a denser connection structure than their connection density with nodes in adjacent modules.
- Network pharmacology:** a novel area of drug design using molecular networks to suggest treatments, such as appropriate drug combinations.
- Network plasticity:** ability of fast network reconfigurations in response to external stimuli. Network plasticity is achieved, e.g. by network noise, conformational plasticity of IDPs and fast reconfiguration of feedback loops.
- Network robustness:** ability to maintain key cellular functions through cellular learning

and through tolerance of fluctuations in protein-protein interactions and cellular noise of stochastic molecular processes. Becomes enhanced by feedback controls, redundancy (i.e. functionally equivalent network parts) and by network modularity.

**Scaffolding proteins:** proteins, which connect adjacent signaling components, and thus make their interaction stronger, faster and more robust against cellular noise.