Cellular and Molecular Life Sciences (2024) 81:97
https://doi.org/10.1007/s00018-024-05112-7

REVIEW

Cellular forgetting, desensitisation, stress and ageing in signalling networks. When do cells refuse to learn more?

Tamás Veres[1] · Márk Kerestély[1] · Borbála M. Kovács[1] · Dávid Keresztes[1] · Klára Schulc[1,2] · Erik Seitz[1] · Zsolt Vassy[1] · Dániel V. Veres[1,3] · Peter Csermely[1]

Received: 9 October 2023 / Revised: 9 November 2023 / Accepted: 2 January 2024

Abstract

Recent findings show that single, non-neuronal cells are also able to learn signalling responses developing cellular memory. In cellular learning nodes of signalling networks strengthen their interactions e.g. by the conformational memory of intrinsically disordered proteins, protein translocation, miRNAs, lncRNAs, chromatin memory and signalling cascades. This can be described by a generalized, unicellular Hebbian learning process, where those signalling connections, which participate in learning, become stronger. Here we review those scenarios, where cellular signalling is not only repeated in a few times (when learning occurs), but becomes too frequent, too large, or too complex and overloads the cell. This leads to desensitisation of signalling networks by decoupling signalling components, receptor internalization, and consequent downregulation. These molecular processes are examples of anti-Hebbian learning and 'forgetting' of signalling networks. Stress can be perceived as signalling overload inducing the desensitisation of signalling pathways. Ageing occurs by the summative effects of cumulative stress downregulating signalling. We propose that cellular learning desensitisation, stress and ageing may be placed along the same axis of more and more intensive (prolonged or repeated) signalling. We discuss how cells might discriminate between repeated and unexpected signals, and highlight the Hebbian and anti-Hebbian mechanisms behind the fold-change detection in the NF-κB signalling pathway. We list drug design methods using Hebbian learning (such as chemically-induced proximity) and clinical treatment modalities inducing (cancer, drug allergies) desensitisation or avoiding drug-induced desensitisation. A better discrimination between cellular learning, desensitisation and stress may open novel directions in drug design, e.g. helping to overcome drug resistance.

Keywords Allergy · Asthma · Diabetes · Habituation · Heat shock · Heart failure · Incoherent type-1 feed-forward loop · Metabolon · Mnemon · Prion · Protein translocation · Receptor downregulation · Scaffold proteins

Learning of signalling networks — at the level of their components

Molecular mechanisms of neuronal learning became well established [1]. However, much less is known about the regulation of learning at the individual, non-neuronal cells. Recent findings gave further evidence that learning, indeed occurs in unicellular organisms, as well as in individual cells of various tissues other than neurons, even in rather sophisticated forms [2]. In our paper we define cellular learning as an adaptive response to a stimulus, when the stimulus is repeated in a short time. This leaves out many classical models of learning (such as Pavlovian conditional learning) from our discussion. However, such a simplification greatly helps the identification of molecular mechanisms, which become increasingly obscured when long-term, multistep

Tamás Veres and Márk Kerestély have contributed equally to the paper.

✉ Peter Csermely
csermely.peter@med.semmelweis-univ.hu

[1] Department of Molecular Biology, Semmelweis University, Budapest, Hungary

[2] Division of Oncology, Department of Internal Medicine and Oncology, Semmelweis University, Budapest, Hungary

[3] Turbine Ltd, Budapest, Hungary

Published online: 19 February 2024

adaptation phenomena are examined, such as cell differentiation or tumour development. Several experiments in budding yeast, *Arabidopsis* or rice cells, mouse fibroblasts or murine $CD8^+$ memory cells showed the formation of molecular memory resulting in a faster, larger, more sensitive and/or more robust response after the second signal than the first [3–9].

Various molecular mechanisms induce a faster and stronger response after a repeated signal in single cells. We mention the conformational memory of intrinsically disordered proteins (IDPs) first, where the IDP transiently keeps its ordered conformation acquired after the first signal, and if the second signal arrives within the time window of the IDPs relaxation back to the disordered state, than the second signal finds the IDP in a 'conformationally-primed', 'memory'-state [10, 11]. IDPs may act like molecular switches changing the direction of signal transmission [12]. Prions are an important class of IDPs. Prion proteins may transform themselves to a β-sheet enriched prion form, which forms aggregates. In budding yeast cells the prion form of Pin1 maintained the molecular memory of a previous heat shock for many generations [4]. Oligomerizing proteins involved in cellular memory formation were called as mnemons [13, 14]. In case of the Whi3 protein present in yeast mnemon and prion states were shown to be associated, which confines the memory of deceptive courtship to the mother cell [15]. Increased association of 'conformationally-primed' IDPs with their signalling partners can be regarded as an increased network edge weight of signalling networks [10, 16].

Signal-induced protein translocation (e.g. between the cytoplasm and the mitochondria or cell nucleus) is a widespread phenomenon in the cell potentially involving thousands of human proteins [17]. Nuclear residence time of the yeast cyclin Cln3 finely tunes Whi5 inactivation by phosphorylation. Whi5 is re-activated rapidly with a half-time of ~ 12 min. Thus the Cln3/Whi5 system provides a rapidly changing short-term memory of environmental nutrient levels for yeast cells [18]. Mitochondrial translocation of the adaptor protein p66SHC was associated with the formation of hyperglycaemic cellular memory of human aortic endothelial cells [19]. Conversely, inhibition of nuclear translocation of NK-κB p65 disrupted the formation of $CD8^+$ memory T and memory B cells [20, 21]. Translocating proteins build a number of new connections in signalling networks, which, again, shows a large increase of all signalling network edge weights involved.

MicroRNAs are involved both in sensitisation- and habituation-type cellular memory formation. MiRNA-156 participated in the molecular memory formation of previous heat shock in *Arabidopsis* cells lasting for several days [6]. As an additional example for sensitisation, miRNA-21 preserved the fibrotic mechanical memory of mesenchymal stem cells [22]. As an example of habituation, both miRNA-221 and miRNA-222 were involved in the memory development of lipopolysaccharide tolerance [23]. Long non-coding RNAs (lncRNAs) played an important role in the memory formation of rice cells after drought stress [7] and the formation of $CD8^+$ memory T cells after lymphocytic choriomeningitis virus infection [24]. Increased miRNA and lncRNA levels correspond to increased network edge weights of miRNA connections in signalling networks.

Learning of signalling networks — at the network level

After the contribution of single macromolecules (proteins and RNAs) to the formation of cellular memory, we give additional three examples of more complex, system-level, signalling network-type adaptation. The first example is that of epigenetic mechanisms and chromatin memory [25]. A large variety of histone modifications and DNA methylation constitute transcriptional memory. Histone H3 lysine methylation was shown to participate in the cellular memory development of yeast [26], *Arabidopsis* [5] (specifically mediated by heat shock factors HSFA2 and HSFA3; 27], mouse fibroblast and HeLa cell sensitisation to IFN-β and -γ, respectively [8, 28], as well as in $CD8^+$ memory T cell formation [9]. DNA methylation pattern of 132 genes were changed in the development of $CD4^+$ memory T cells [29]. CRISPRoff, a single dead Cas9 fusion protein establishes DNA methylation and repressive histone modifications providing a genome-wide transcriptional memory [30]. Several studies showed the involvement of three-dimensional chromatin structure reorganization during cellular memory development in yeast [3, 31], as well as in the sensitisation to repeated IFN-γ treatment of HeLa cells [28] by the same, nuclear pore protein 100/98-mediated chromatin-reorganization process [32].

The second example of network-type cellular memory formation is that of signalling protein kinase cascades. Members of the Hog1 signalling pathway of osmotic stress in yeast remained phosphorylated even after minutes of the first stress, and 'waited' pre-activated for a faster response to a potential repeated stress [33]. Similarly, in the mitogen-activated protein kinase (MAPK) cascade different relaxation rates of individual components developed an 'activation-competent' state inducing post-activation protein phosphorylation bursts [34]. MAPK pathway members are organized by pathway scaffold proteins from fungi (e.g. Far1- and Ste5-like proteins [35]) to humans (e.g. RACK1 [36]). These proteins, once they became activated, maintain larger pathway segments pre-organized, ready to respond to the second stimulus faster, and stronger. We note that similar signalling cascade memories may be postulated in each signalling pathway. As examples the JNK and Hippo pathway

cascades are enhanced by the scaffolding proteins JIP1 and MOB1A, respectively [37, 38]. These scaffolds may prime these pathways giving a stronger second response after an initial stimulus.

The third example expands the above idea of pathway organization and consequent cellular memory formation to networks other than signalling networks, such as metabolic networks. Analysis of non-Markovian chemical reaction networks on gene expression showed that molecular memory of protein synthesis and degradation may induce feedback, bimodality and switch behaviour, and may fine tune gene expression noise, all components of molecular memory [39]. Even bacteria use their inner membrane as a scaffold [40], as well as bacterial microcompartments [41] to enhance the metabolic flux of their enzymes. Mitochondria and other intracellular compartments also function as eukaryotic organizers of metabolic processes [42]. Metabolons are multienzyme complexes that are held together by noncovalent interactions enhancing their cooperation and summative metabolic flux by substrate channelling in e.g. glycolysis, branched chain amino acid oxidation, purine biosynthesis, etc. [43–47]. All these bacterial, mitochondrial and cellular microcompartmental metabolic scaffolds, as well as metabolons are potential organizers of cellular memory.

Hebbian learning of signalling networks

Practically all molecular mechanisms of cellular memory formation mentioned above are satisfying the basic concept of Hebbian learning, i.e.: the increase of the connection strength of those learning components (in the initial concept: neurons) which are involved in the learning process [1, 48]. Stronger and faster binding of 'conformationally primed' IDPs, prions and mnemons, protein translocation, overexpression of miRNAs and lncRNAs, chromatin memory, scaffolded protein kinase and metabolic pathways are all examples of connection strength increases after an initial signal — serving as potential learning mechanisms of non-neuronal single cells (Fig. 1).

Obviously, single cells can not express the complexity of the learning process of multicellular networks. This is especially true to that of neuronal networks. One simple reason of this is the number of connections. While macromolecules may bind only handful of other macromolecules, neurons developed axons and dendrites, which (by their tremendously increased surface areas) allow their connections to tens of thousands of other neurons. This by itself already magnifies the structural complexity which may be achieved by neuronal networks, and allows the development of incomparably more sophisticated learning processes than those of single, non-neuronal cells.

Anti-Hebbian learning in non-neuronal cells

Hebbian learning needs to be complemented by the reverse process, where connection strengths decrease, since only Hebbian-type 'positive' changes of the system would lead to the system's over-excitation. This was first generally formalized by Oja's rule, which keeps the total of connection strengths constant during a Hebbian learning process [49].

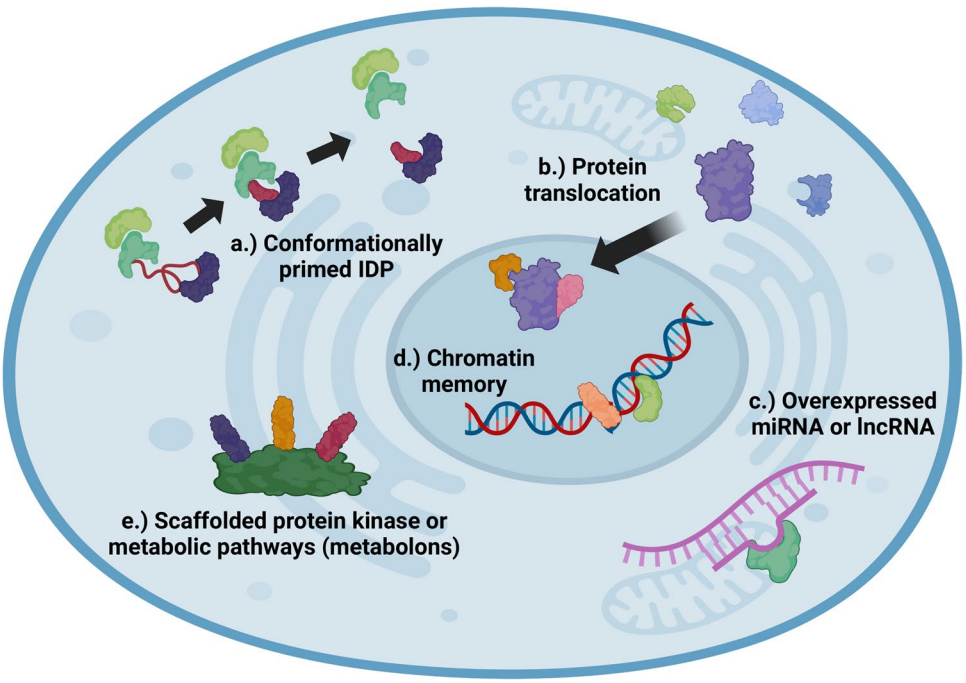

Fig. 1 Molecular mechanisms of connection strength increase by cellular Hebbian learning-type processes. **a** Stronger and faster binding of 'conformationally primed' IDPs (prions and mnemons) to their signalling partners. **b** New connection sets of translocating proteins. **c** New connections of overexpressed miRNAs and lncRNAs. **d** Chromatin memory. **e** Scaffolded protein kinase and metabolic pathways. This figure was created with BioRender.com

In cells connection strength decrease (decay) is generally introduced by cellular noise [50]. However, anti-Hebbian learning may also decrease the strength of specific connections, such as the reduced expression of the *STL1* sugar transporter gene in budding yeast cells after hyperosmotic stress [31], the diminished response of *MYC*-dependent genes after repeated dehydration stress in *Arabidopsis* [51] and the immune tolerance of macrophages after repeated lipopolysaccharide exposure [23]. Several of these direct, anti-Hebbian molecular mechanisms lead to habituation, where the cell displays a decreased response to repeated stimulation. Biological pathway network models were able to display both sensitisation (Hebbian) and habituation (anti-Hebbian) behaviour [52].

Cellular memory and forgetting

As first suggested by François Jacob and Jacques Monod in 1961 [53], individual cells also have a memory, i.e. the persistence of a cellular state, which is acquired after a stimulus. Cellular memory allows the establishment and maintenance of the identity of individual cells in heterogeneous cellular populations. Memory of the cells is manifested by bistable feedback loops or epigenetic marks conferring hysteresis and simple cognitive functions to cellular behaviour [25, 54, 55]. Intertwined feedback loops reduce cellular noise [50] and induce hysteresis, since stabilization of the 'signalling-on' state creates a resistance to return to the initial, 'signalling-off' state. While simple, hysteresis-type memory can be maintained by self-sustaining feedback loops, there seems to be a minimal network size requirement of at least 5 nodes to display richer memory functions [52].

Forgetting of organisms such as *C. elegans* is induced by cellular mechanisms, like the Musashi, MSI1-induced down-regulation of the ARP2/3 complex (playing a major role in the organization of the cytoskeleton) [56]. Increased cellular noise is a key factor of 'forgetting' in single, non-neuronal cells [50]. As a more specific example for the effect of cellular noise, robustness of the MAPK pathway becomes reduced, if environmental fluctuations (extrinsic noise) or variances of inherent chemical reaction rates (intrinsic noise) grow beyond a certain threshold [57].

We list three examples, where individual molecular mechanisms are involved in cellular 'forgetting'. First, erasure of DNA-methylation is meditated by ten-eleven translocation (TET) DNA-demethylases [58]. Second, the long non-coding RNA, originating at –2700 upstream of the budding yeast HO endonuclease, erased previous molecular memory of nutrient deprivation- or pheromone-induced cell cycle arrest [59]. Third, molecular chaperones may help the disorganization of protein sequences, thus they may act as facilitators of both molecular memory formation and cellular 'forgetting' [60]. However, currently beyond these mechanisms we do not know enough about the molecular systems regulating 'forgetting' in individual, non-neuronal cells.

We note that anti-Hebbian learning diminishes the strength of certain molecular connections, while cellular 'forgetting' may also induce a more general decrease of connection strengths. However, there is an obvious overlap between the two phenomena.

Desensitisation of signalling networks

Desensitisation of signalling responses is a general, habituation-type regulatory mechanism of signalling pathways. The most widespread way of desensitisation is receptor down-regulation by internalization (many times involving autophagy) and consequent degradation. We list here only a few examples of the many: the key plant stress signalling hormone, abscisic acid is desensitised by numerous steps of directed protein degradation [61]. An early example was the desensitisation of protein kinase C by its nonmetabolizable, long-term agonist, phorbol ester [62].

As an archetype of desensitisation G-protein-coupled receptor (GPCR) kinases (GRKs) induce arrestin binding to GPCRs, dissociating G proteins and leading to GPCR internalization [63, 64]. While short-term activation of GPCRs causes receptor desensitisation via β-arrestin-mediated decoupling from G proteins, long-term (hours to days) activation induces receptor down-regulation by internalization into vesicles, lysosomal degradation and decrease of receptor mRNAs [65]. The GPCR cardiac β-adrenoreceptors became downregulated after prolonged in vivo infusion of catecholamines in rat [66]. GPCR α1-adrenoreceptors could be downregulated by the specific α1 agonist, R-(-)-N6-(2-phenylisopropyl)adenosine in rat atria inducing their uncoupling from G proteins and loss of G_i proteins [67]. Desensitisation of rat heart contractility after sustained adenosine treatment seems to be mediated by the α1-adrenoreceptor and protein kinase C [68].

Continuous exposure of rat pancreatic islets to high glucose (300 mg/dl) induced glucose hypersensitivity after 3 h which turned to glucose insensitivity after 6 h of exposure [69]. Insulin receptor auto-antibodies (as agents able to provoke a sustained activation) induced an insulin-resistant state of glucose metabolism in 3T3-L1 adipocyte-like fatty fibroblasts after 6 h of exposure blocking an early step in insulin signalling (but leaving insulin binding ability constant) [70].

Signalling of human cells is not more complex than that of e.g. *Caenorhabditis elegans* or *Drosophila melanogaster* because of more human signalling pathways, but because of much more cross-talks between signalling pathways in humans [71]. Due to this complexity, desensitisation may

often act on different pathways than that of the provoking agent. Signalling pathways often act as 'Darwinian competitors'. If one of them becomes stronger (e.g. by a cellular learning process), it induces molecular events (such as protein phosphorylation), which desensitise (inhibit, downregulate, etc.) of 'competing' pathways. An example for this from the many is the heterologous desensitisation of G-protein-coupled receptor (GPCR) and insulin-like growth factor pathways by insulin [72]. Conversely, chronic endothelin exposure desensitises the insulin pathway [73].

Stress-induced desensitisation of signalling

Desensitisation of a wide range of signals is occurring, if the cell or the animal experiences stress, such as heat shock, UV light, immobilization, or endoplasmic reticulum stress. Immobilization reduced the number of α1- and β-adrenoreceptors in rat hearts [74]. In agreement with the internalization → degradation sequence, immobilization stress first reduced the number of surface β-adrenoreceptors, and only then the total number of receptors [75]. Suppression of microRNA-16 gave a protection against acute myocardial infarction reversing β2-adrenergic receptor down-regulation in rats [76]. Epidermal growth factor (EGF) receptor down-regulation was observed in the colon cancer cell lines SW480, HT29, and DLD-1 after ultraviolet light-C treatment inhibiting cell proliferation and survival [77]. UV light-induced EGF, tumour necrosis factor (TNF) and interleukin-1 receptor down-regulation in mammalian cells activating the Jun-kinase cascade [78].

Insulin signalling desensitisation potentially leads to diabetes. Insulin receptor tyrosine phosphorylation was reduced by tunicamycin-provoked endoplasmic reticulum stress, which was reversed by the overexpression of activating transcription factor 6 (ATF6), a key signal of endoplasmic reticulum stress [79]. Similar, autophagy (but not proteasome) dependent down-regulation of insulin signalling was observed after endoplasmic reticulum stress in fat tissue of obese human subjects and 3T3-L1 adipocytes [80]. Heat stress downregulated insulin signalling in pig testicular cells [81].

Ageing-induced signalling desensitisation

Ageing can be perceived as a cumulative result of the continuous stress by free radicals and other harmful effects inducing inflammation [82–86]. Ageing is downregulating the renin-angiotensin system in rat kidneys [87]. Klotho-induced activation of the retinoic acid-inducible gene I/nuclear factor-κB (RIG-I/NF-κB) signalling pathway, as well as the subsequent production of proinflammatory mediators (TNF α and interleukin-6) and inducible nitric oxide synthase were reduced in the kidneys of aged senescence-accelerated mouse prone-8 (SAMP8) mice [88]. Downregulation of angiogenesis-related vascular endothelial growth factor (VEGF) signalling was reported in hearts of ageing rats living a sedentary lifestyle, but was recovered in ageing rats with exercise training [89]. Endoplasmic reticulum stress was activated in fatty livers of old mice by inhibiting hepatocyte nuclear factor 1 alpha (HNF1α) and downregulating farnesoid X receptor (FXR) [90]. Desensitisation of insulin receptor growth factor (in particular: downregulation of Irs1 and upregulation of Let-7 microRNA expression) was shown as a hallmark of the aged phenotype in developing B lymphocytes by a genome organization and chromatin study. These changes were associated with specific alterations in histone H3K27me3 occupancy, suggesting that Polycomb-mediated repression plays a role in precursor B cell ageing [91].

Learning, desensitisation, stress and ageing in system-level signalling: phases of the same response?

There are only a few reports of time-dependent changes in cellular signalling upon shorter *versus* longer extracellular signals. One of these was made on rat pancreatic islets, where 300 mg/dl, high concentrations of extracellular glucose induced a stronger response after 3 h, which turned to glucose insensitivity after 6 h [69]. This is clearly a two-step cellular response, where the pancreatic beta-cells first learned the presence of glucose and made a preconditioned, stronger response to them. However, after a longer time, an overload occurred and the cells turned to insensitive to glucose. Note that under natural conditions high glucose is only a temporary, postprandial event. A similar effect was observed, when 3T3-L1 cultured fat cells were exposed to insulin receptor auto-antibodies. Acute administration of anti-receptor antibodies induced a more efficient deoxyglucose uptake, while prolonged exposure led to insulin insensitivity [92]. Here again, high levels of the original agonist, insulin are also only transient, postprandial events.

If we take the examples of (1) cellular learning and development of cellular memory after a few repeated stimuli [10, 25, 54, 55]; (2) the desensitisation of signalling after a prolonged exposure to the signal [61–70] and (3) the result of the above studies [69, 92] (where in an extended timescale first learning and then desensitisation was observed) together, the conclusion can be drawn that, in fact, cellular learning and desensitisation may be consequent phases of the same response. The cell first becomes more 'alert' and more 'ready' to respond to environmental changes. However, after a prolonged stimulus its signalling network becomes

'saturated' and starts to 'protect itself' (Fig. 2). We may also add stress [74–81] and ageing [82–91] to this spectrum, where 'fatigue' of the signalling network is induced by both as examples of overloading short-term (stress) and long-term (ageing) changes (Fig. 2). We note that comparative studies of agonist-, stress- and ageing-induced desensitisation are missing. Therefore their combination on Fig. 2 is only illustrative and hypothetical.

Discrimination between repeated and unexpected signals: perhaps as also a property of single cells?

Desensitisation protects the system from the overload of inputs. At a low level of complexity overload can be understood that too many of the same signal within a certain time (where the system may adjust its thresholds defining the "too many" and the "within a certain time"). At a higher level of complexity overload also occurs, if the system is not able to make 'groups' of similar input patterns. In fact, our brain defines objects (features, categories, concepts, etc.) as groups of correlating 'suspicious coincidences'. Moreover, recognition of (and reduced response to) similar input patterns helps to highlight unexpected signals, which is essential for survival. If a layer of Hebbian learning units becomes connected by modifiable anti-Hebbian feed-backs, the resulting system is able to learn this discrimination and to recognize other principal components of an incoming, complex signal than only its first principal component [93, 94]. A well-known biological example is that of the mormyrid electric fish, which is able to eliminate predictable inputs produced by its own, regular motor output. However, this response is a general feature of cerebellum-like, laminar structures, where anti-Hebbian outputs of a deeper layer modulate outer layers (Fig. 3A) [95]. Thus using anti-Hebbian learning prevents excessive noise (i.e. regular, correlating, expected input) from masking important (i.e. unexpected) sensory information. Most sensory systems work based on the principle of fold-change detection, which allows for a proportional response to the fold-change of a signal (the unexpected) relative to the background (the repeated, regular, expected) [96]. From the complexity of learning responses of non-neuronal single cells [2] and the presence of distributed decision making in cellular signalling [97], we may expect that the widespread occurrence of anti-Hebbian learning in signalling networks (see examples above) is involved in the discrimination between repeated and unexpected signals in single, non-neuronal cells, too. Horizontal activation at a receptor-proximal level, as well as mutual inhibition at a receptor-distant level in signalling networks also point toward this expectation. For instance, in the TNF-induced NF-κB signalling, the well-studied upstream crosstalk conveyed by TNFR-associated factors (TRAFs) acts as horizontal activation at the receptor-proximal level [98]. While downstream, a network motif containing inhibition has been described that can impart fold-change detection to cell signalling circuits: the incoherent type-1 feed-forward loop (I1-FFL) (Fig. 3B) [96, 99, 100]. I1-FFL is one of the most frequently occurring network motifs in transcriptional networks [101]. Besides fold-change detection, I1-FFLs have a role in response acceleration even in yeast [102]. In an I1-FFL, X upregulates Y, while it also upregulates Z, a repressor of Y. This indirect repression of Y, coupled with the direct activation of Y, can be considered an anti-Hebbian learning mechanism. Besides NF-κB signalling, I1-FFLs were also suggested to enable fold-change detection in the nuclear levels of the transcription factors of transforming growth factor beta (TGF-β) signalling, explaining how the cells are able to give the same proportional

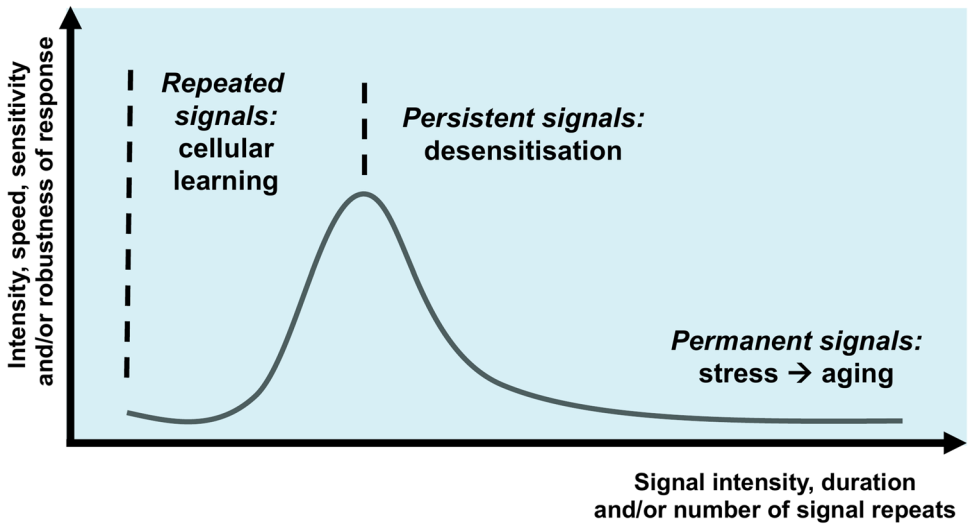

Fig. 2 Repeated signals induce cellular learning; persistent signals lead to cellular desensitisation; permanent signals (such as the accumulated signals and damage in ageing) overload the signalling network and provoke cellular stress. Note that on the contrary to the few studies showing a change from cellular learning to desensitisation in the same system [69, 92], comparative studies of agonist-, stress- and ageing-induced desensitisation are missing. Therefore, this figure is only hypothetical, illustrative and by no means quantitative

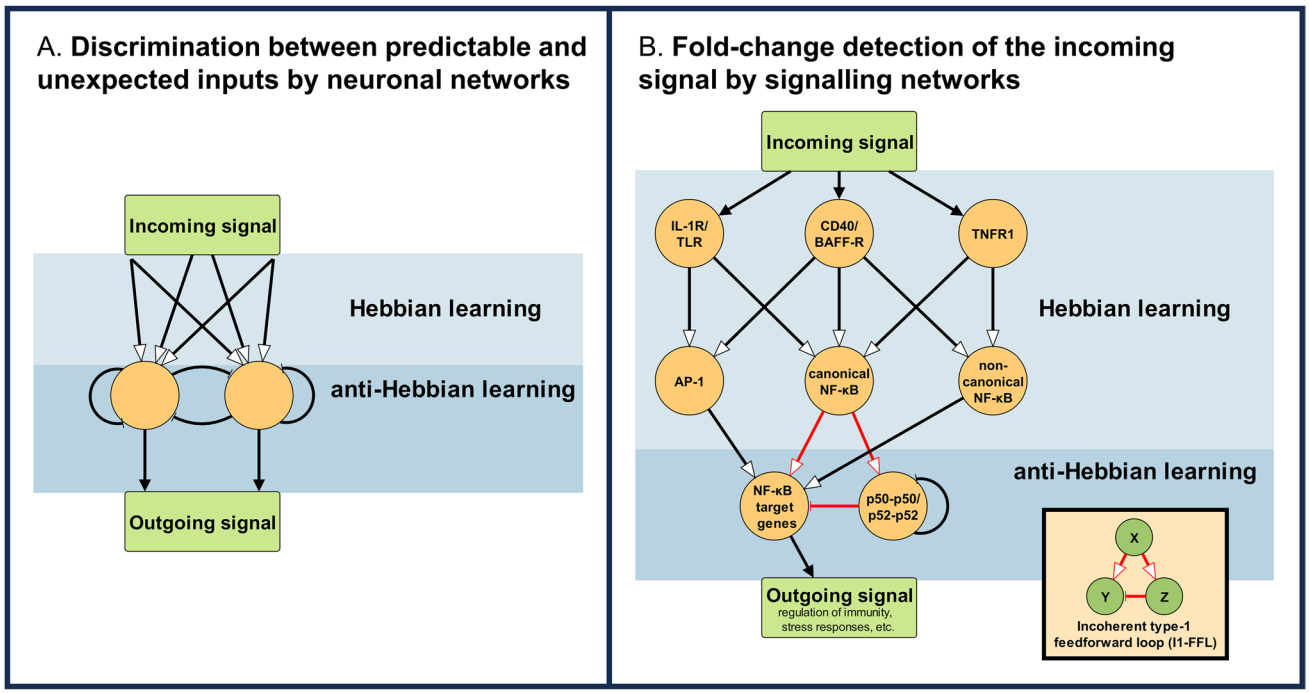

Fig. 3 Hebbian and anti-Hebbian learning layers in neuronal and signalling networks. **A** Schematic representation of the combination of Hebbian- and anti-Hebbian learning layers, which result in the discrimination between predictable and unexpected inputs. The cerebellum-like laminar structure of the figure is widespread in various animal and human neuronal networks [95] and was also shown to work in computational neural networks [93, 94]. Note that self-inhibitory connections ('autapses') are not necessarily needed for the circuit. **B** Proposed Hebbian and anti-Hebbian learning layers in the NF-κB signalling. Receptor proximally, the signalling of multiple receptors can lead to the activation of the NF-κB pathway through TRAFs. Concurrently, some can lead to the activation of the adjacent AP-1 signalling pathway [98]. This constitutes a horizontal activation in the proposed Hebbian learning layer in the upstream signalling. In the downstream signalling, AP-1 and the non-canonical NF-κB pathway modulate NF-κB target genes (e.g. interleukin-8, interleukin-6). The canonical NF-κB (RelA-p52 heterodimer) has also been shown [100] to upregulate the formation of the transcriptionally inactive p50-p50/p52-p52 homodimers that act as competitors to NF-κB for κB sites in the target genes' promoters. These interactions, highlighted in red, constitute a Type-1 incoherent feed-forward loop (I1-FFL, see inset) that can be understood as an anti-Hebbian learning mechanism. This system enables fold-change detection of the incoming signal in NF-κB nuclear levels, that is analogous to discrimination between predictable and unexpected inputs. This figure was created with yEd Graph Editor

response, even though the nuclear level of transcription factors can vary greatly from cell to cell [96]. The occurrence of I1-FFLs in major signalling pathways suggests that this learning mechanism may be a rather general feature of signalling networks. Even still, to decide whether discrimination between repeated and unexpected signals is also a property of single cells, future experiments are required.

Applications of cellular learning and 'forgetting' in pharmacology and drug design

Mimicking cellular learning (memory) became a recent hit in drug design. Chemically-induced proximity between two adjacent signalling proteins (a new drug design paradigm [103, 104]) is actually copying Hebbian learning of the cell [10]. In this 'cellular learning scenario' chemical proximity-developing drugs induce targeted posttranslational modifications of key, otherwise undruggable proteins. In the reversed, anti-Hebbian learning model, chemically-induced proximity promotes the selective degradation of the target [105, 106].

Drug resistance can be conceptualised in a learning network model as habituation. Biological networks may contain nodes, where stimulation breaks the habituation (drug resistance) developed by the network [52]. Limited drug tolerance can be conceptualised as sensitisation in a learning network model, most simply by displaying a hysteresis-type response. Interestingly, breaking of sensitisation was much rarer phenomenon in a model of 35 biological networks than that of habituation [52]. However, the break of allergy-induced sensitisation against drugs became a carefully manageable clinical modality in the last decades — as we will describe in the following paragraphs.

Signal desensitisation plays a major role in anti-cancer therapy, which can be regarded as 'the archetype' of therapeutic intervention consequences in a number of other

diseases. As an example for the first modality of protocols, the anti-cancer agent, 90 kDa heat shock protein (Hsp90) inhibitors induce a desensitisation of the EGF receptor via p38 MAPK-mediated phosphorylation at Ser1046/1047 of the EGF receptor in human pancreatic cancer cells. Here drug-induced desensitisation of the cancer-promoting growth factor signal is a mode of action to avoid disease [105]. As an example for the second modality of consequences, gastric cancer cells become desensitised to trastuzumab-treatment by upregulation of MUC4 expression and by catecholamine-induced β2-adrenoreceptor activation. Here desensitisation, i.e. the development of drug resistance is an unwanted consequence of drug treatment [106]. As a third modality of therapeutic interventions, response-desensitisation (i.e. breaking the sensitisation of unwanted side-reactions for the drug) is a general goal in cancer therapy, where patients often develop sensitivity towards the administered drugs [107, 108].

Supporting the notion that cancer therapy experiences are '*pars pro toto*' for other conditions, increased hypersensitivity to drugs (e.g. for aspirin and non-steroid anti-inflammatory drugs, NSAIDs in patients with heart disease or inflammatory diseases; for insulins, penicillin or other antibiotics) became a general phenomenon in the past 25 years due to the widespread and intensive drug use. Therefore, carefully administered drug-desensitisation protocols became more and more important in the clinical practice [109, 110]. Similarly, drug-induced desensitisation of cellular mechanisms of action is also a general phenomenon in a number of non-cancer treatment protocols, including that of β-adrenergic agonists in asthma [111], diabetes [112, 113] or heart failure [114].

Conclusion

In our previous work [10] we gave several examples for cellular learning [3–9] (i.e. the formation of cellular memory [25, 52–55]), and showed that cellular learning can be perceived as Hebbian learning [48] of signalling networks, where learning is accompanied by strengthening of those protein–protein, protein-microRNA and chromatin interactions, which participate in the learning process [10]. In this review we give the first description of cellular forgetting, and we summarize our current knowledge on the other side of the coin: when signalling networks 'refuse' to learn more, and become desensitised by prolonged presence of the provoking signal, by stress or ageing.

Cellular learning proceeds using several molecular mechanisms, such as conformational memory of (IDPs), prions and mnemons [10–16], protein translocation [18–21], as well as miRNAs and lncRNAs [6, 7, 22–24]. System level responses of cellular learning include chromatin memory [3, 5, 8, 9, 25–32], signalling protein kinase cascades [33–38], as well as network responses other than those of signalling networks, such as metabolic reaction networks and metabolons [40–47].

Besides Hebbian learning [10] by the molecular mechanisms listed in the previous paragraph, non-neural cells also display anti-Hebbian learning, where connection strengths decrease between the signalling network components [23, 31, 51, 52]. Cells are also able to 'forget' using TET DNA-demethylases, lncRNAs or molecular chaperones [58–60] besides developing a cellular memory.

A cellular habituation-type of response is the development of desensitisation. This often involves first decoupling of signalling network components from each other followed by receptor internalization and downregulation [61–70]. This may be displayed by cross-desensitisation, where prolonged exposure for a pathway agonist induces the desensitisation of other pathway(s) [72, 73]. A specific condition of generally increased signal intensity and/or complexity is stress, which desensitises a wide range of signals [74–81]. Ageing can be perceived as a result of cumulative stress [82–86], which downregulates a large number of signalling pathways [87–91].

Here we propose that cellular learning, desensitisation, stress and ageing may be placed as responses along the same axis of more and more intensive (more and more prolonged, or more and more often repeated) signals (Fig. 2). We pose the question, whether single cells may also display discrimination between repeated and unexpected signals, a common property of neuronal and artificial neural networks (Fig. 3A) [93–95]. As a first step in answering this question, we present fold-change detection enabling I1-FFLs as anti-Hebbian learning mechanisms that are potentially general features of signalling networks given their occurrence in prominent signalling pathways like NF-κB (Fig. 3B) and TGF-β signalling [96, 98–101].

Finally, we summarize applications of signalling network learning and desensitisation in clinical treatments discriminating between five scenarios (Fig. 4): 1.) when cellular Hebbian learning is mimicked by chemically-induced proximity between signalling network components [103, 104]; 2.) when cellular anti-Hebbian learning is mimicked by chemically-induced proximity of protein degradation [104, 105]; 3.) when desensitisation of unwanted signalling (such as that in cancer) is the mechanism of drug action [105]; 4.) when desensitisation of wanted signalling occurs, and should be avoided (in cancer, asthma, diabetes or heart failure [106, 110–114]); and finally, 5.) when sensitisation against a drug occurs by allergic reaction, which also should be minimized (in cancer, inflammatory diseases, diabetes or infections [107, 109, 110]).

We hope that our summary will prompt further investigations of the phenomena, when cells learn (develop

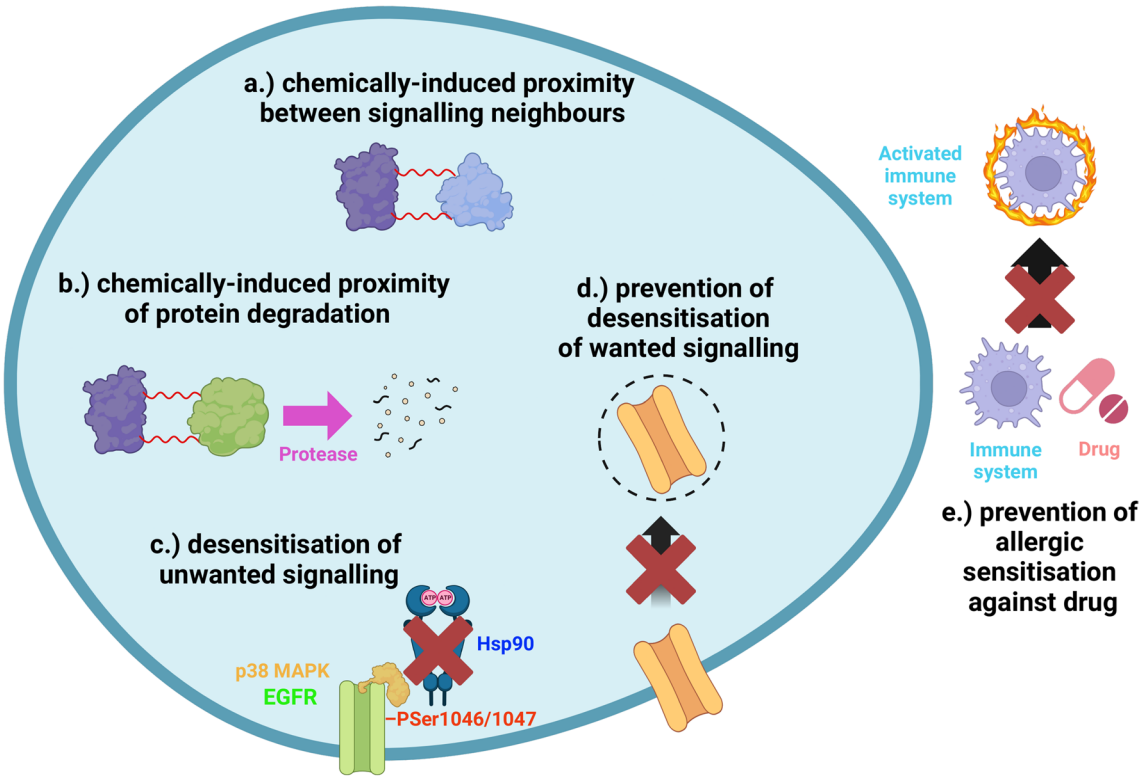

Fig. 4 Clinical treatments for and against Hebbian and anti-Hebbian learning of the signalling network. **a** Cellular Hebbian learning is mimicked by chemically-induced proximity between signalling network components. **b** Anti-Hebbian learning is mimicked by chemically-induced proximity of protein degradation. **c** Desensitisation (drug-induced anti-Hebbian learning) of unwanted signalling (such as that in cancer). **d** Prevention of desensitisation of wanted signalling (cellular anti-Hebbian learning) in cancer, asthma, diabetes or heart failure. **e** Prevention of allergy-induced sensitisation (Hebbian learning) against the drug in cancer, inflammatory diseases, diabetes or infections. This figure was created with BioRender.com

cellular memory) by Hebbian learning-type processes, and when they 'refuse' to learn more, i.e. become desensitised (display anti-Hebbian learning, i.e. cellular 'forgetting') by prolonged exposure to environmental signals, by stress or by ageing. It is an interesting question, how much desensitisation remains specific for the given pathway, and how much it is displayed as cross-desensitisation of other pathways, or as a general forgetting (desensitisation) of many (if not all) pathways. While agonist-induced desensitisation is mostly the former, directed type desensitisation against the same pathway (or selected different pathways), stress- and ageing-induced desensitisation are usually more widespread phenomena involving a larger segment of the signalling network. We predict that network methodologies will greatly help the discrimination between these scenarios.

Author contributions PC initiated the idea, wrote the initial draft and finalized the manuscript. TV and MK finalized paper figures and contributed to key concepts. All authors participated in the interpretation of initial ideas and writing the manuscript.

Funding Open access funding provided by Semmelweis University. This work was supported by a grant from the Hungarian Science Foundation (OTKA K131458) and by the Thematic Excellence Programme (Tématerületi Kiválósági Program TKP2021-EGA-24) of the Ministry for Innovation and Technology in Hungary, within the framework of the Molecular Biology thematic program of the Semmelweis University.

Availability of data and material This review study does not contain parts which require the deposit of data or other material.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval and consent to participate This study required no ethics approval and consent to participate.

Consent for publication All authors provided consent for publication of this work.

References

1. Kandel ER, Dudai Y, Mayford MR (2014) The molecular and systems biology of memory. Cell 157(1):163–186. https://doi.org/10.1016/j.cell.2014.03.001
2. Gershman SJ, Balbi PE, Gallistel CR, Gunawardena J (2021) Reconsidering the evidence for learning in single cells. Elife 10:e61907. https://doi.org/10.7554/eLife.61907
3. D'Urso A, Takahashi YH, Xiong B, Marone J, Coukos R, Randise-Hinchliff C, Wang JP, Shilatifard A, Brickner JH (2016) Set1/COMPASS and mediator are repurposed to promote epigenetic transcriptional memory. Elife 5:e16691. https://doi.org/10.7554/eLife.16691
4. Chernova TA, Chernoff YO, Wilkinson KD (2017) Prion-based memory of heat stress in yeast. Prion 11(3):151–161. https://doi.org/10.1080/19336896.2017.1328342
5. Liu N, Avramova Z (2016) Molecular mechanism of the priming by jasmonic acid of specific dehydration stress response genes in *Arabidopsis*. Epigenetics Chromatin 9:8. https://doi.org/10.1186/s13072-016-0057-5
6. Stief A, Altmann S, Hoffmann K, Pant BD, Scheible WR, Bäurle I (2014) *Arabidopsis* miR156 regulates tolerance to recurring environmental stress through SPL transcription factors. Plant Cell 26(4):1792–1807. https://doi.org/10.1105/tpc.114.123851
7. Li P, Yang H, Wang L, Liu H, Huo H, Zhang C, Liu A, Zhu A, Hu J, Lin Y, Liu L (2019) Physiological and transcriptome analyses reveal short-term responses and formation of memory under drought stress in rice. Front Genet 10:55. https://doi.org/10.3389/fgene.2019.00055
8. Kamada R, Yang W, Zhang Y, Patel MC, Yang Y, Ouda R, Dey A, Wakabayashi Y, Sakaguchi K, Fujita T, Tamura T, Zhu J, Ozato K (2018) Interferon stimulation creates chromatin marks and establishes transcriptional memory. Proc Natl Acad Sci U S A 115(39):E9162–E9171. https://doi.org/10.1073/pnas.1720930115
9. Pace L, Goudot C, Zueva E, Gueguen P, Burgdorf N, Waterfall JJ, Quivy JP, Almouzni G, Amigorena S (2018) The epigenetic control of stemness in CD8(+) T cell fate commitment. Science 359(6372):177–186
10. Csermely P, Kunsic N, Mendik P, Kerestély M, Faragó T, Veres DV, Tompa P (2020) Learning of signaling networks: molecular mechanisms. Trends Biochem Sci 45(4):284–294. https://doi.org/10.1016/j.tibs.2019.12.005
11. Tompa P (2016) The principle of conformational signaling. Chem Soc Rev 45(15):4252–4284. https://doi.org/10.1039/c6cs00011h
12. Van Roey K, Gibson TJ, Davey NE (2012) Motif switches: decision-making in cell regulation. Curr Opin Struct Biol 22(3):378–385. https://doi.org/10.1016/j.sbi.2012.03.004
13. Caudron F, Barral Y (2014) Mnemons: encoding memory by protein super-assembly. Microb Cell 1(3):100–102. https://doi.org/10.15698/mic2014.01.134
14. Reichert P, Caudron F (2021) Mnemons and the memorization of past signaling events. Curr Opin Cell Biol 69(4):127–135. https://doi.org/10.1016/j.ceb.2021.01.005
15. Lau Y, Oamen HP, Grogg M, Parfenova I, Saarikangas J, Hannay R, Nichols RA, Hilvert D, Barral Y, Caudron F (2022) Whi3 mnemon association with endoplasmic reticulum membranes confines the memory of deceptive courtship to the yeast mother cell. Curr Biol 32(5):963–974. https://doi.org/10.1016/j.cub.2022.01.002
16. Csermely P, Korcsmáros T, Kiss HJ, London G, Nussinov R (2013) Structure and dynamics of molecular networks: a novel paradigm of drug discovery: a comprehensive review. Pharmacol The 138(3):333–408. https://doi.org/10.1016/j.pharmthera.2013.01.016
17. Mendik P, Dobronyi L, Hári F, Kerepesi C, Maia-Moço L, Buszlai D, Csermely P, Veres DV (2019) Translocatome: a novel resource for the analysis of protein translocation between cellular organelles. Nucleic Acids Res 47(D1):D495–D505. https://doi.org/10.1093/nar/gky1044
18. Qu Y, Jiang J, Liu X, Yang X, Tang C (2020) Non-epigenetic mechanisms enable short memories of the environment for cell cycle commitment. bioRxiv. https://doi.org/10.1101/2020.08.14.250704v1
19. Paneni F, Mocharla P, Akhmedov A, Costantino S, Osto E, Volpe M, Lüscher TF, Cosentino F (2012) Gene silencing of the mitochondrial adaptor p66(Shc) suppresses vascular hyperglycemic memory in diabetes. Circ Res 111(3):278–289. https://doi.org/10.1161/circresaha.112.266593
20. Ramon S, Bancos S, Serhan CN, Phipps RP (2014) Lipoxin A_4 modulates adaptive immunity by decreasing memory B-cell responses via an ALX/FPR2-dependent mechanism. Eur J Immunol 44(2):357–369. https://doi.org/10.1002/eji.201343316
21. Pallett MA, Ren H, Zhang RY, Scutts SR, Gonzalez L, Zhu Z, Maluquer de Motes C, Smith GL (2019) Vaccinia virus BBK E3 ligase adaptor A55 targets importin-dependent NF-κB activation and inhibits $CD8^+$ T-Cell memory. J Virol 93(10):e00051-e119. https://doi.org/10.1128/JVI.00051-19
22. Li CX, Talele NP, Boo S, Koehler A, Knee-Walden E, Balestrini JL, Speight P, Kapus A, Hinz B (2017) MicroRNA-21 preserves the fibrotic mechanical memory of mesenchymal stem cells. Nat Mater 16(3):379–389. https://doi.org/10.1038/nmat4780
23. Seeley JJ, Baker RG, Mohamed G, Bruns T, Hayden MS, Deshmukh SD, Freedberg DE, Ghosh S (2018) Induction of innate immune memory via microRNA targeting of chromatin remodelling factors. Nature 559(7712):114–119. https://doi.org/10.1038/s41586-018-0253-5
24. Hudson WH, Prokhnevska N, Gensheimer J, Akondy R, McGuire DJ, Ahmed R, Kissick HT (2019) Expression of novel long noncoding RNAs defines virus-specific effector and memory $CD8^+$ T cells. Nat Commun 10(1):196. https://doi.org/10.1038/s41467-018-07956-7
25. Berenguer J, Celià-Terrassa T (2021) Cell memory of epithelial-mesenchymal plasticity in cancer. Curr Op Cell Biol 69(4):103–110. https://doi.org/10.1016/j.ceb.2021.01.001
26. Sump B, Brickner DG, D'Urso A, Kim SH, Brickner JH (2022) Mitotically heritable, RNA polymerase II-independent H3K4 dimethylation stimulates INO1 transcriptional memory. Elife 11:e77646. https://doi.org/10.7554/eLife.77646
27. Friedrich T, Oberkofler V, Trindade I, Altmann S, Brzezinka K, Lämke J, Gorka M, Kappel C, Sokolowska E, Skirycz A, Graf A, Bäurle I (2021) Heteromeric HSFA2/HSFA3 complexes drive transcriptional memory after heat stress in Arabidopsis. Nat Commun 12(1):3426. https://doi.org/10.1038/s41467-021-23786-6
28. Gialitakis M, Arampatzi P, Makatounakis T, Papamatheakis J (2010) Gamma interferon-dependent transcriptional memory via relocalization of a gene locus to PML nuclear bodies. Mol Cell Biol 30(8):2046–2056. https://doi.org/10.1128/MCB.00906-09

29. Komori HK, Hart T, LaMere SA, Chew PV, Salomon DR (2015) Defining CD4 T cell memory by the epigenetic landscape of CpG DNA methylation. J Immunol 194(4):1565–1579. https://doi.org/10.4049/jimmunol.1401162
30. Nuñez JK, Chen J, Pommier GC, Cogan JZ, Replogle JM, Adriaens C, Ramadoss GN, Shi Q, Hung KL, Samelson AJ, Pogson AN, Kim JYS, Chung A, Leonetti MD, Chang HY, Kampmann M, Bernstein BE, Hovestadt V, Gilbert LA, Weissman JS (2021) Genome-wide programmable transcriptional memory by CRISPR-based epigenome editing. Cell 184(9):2503–2519. https://doi.org/10.1016/j.cell.2021.03.025
31. Meriem ZB, Khalil Y, Hersen P, Fabre E (2019) Hyperosmotic stress response memory is modulated by gene positioning in yeast. Cells 8(6):582. https://doi.org/10.3390/cells8060582
32. Light WH, Freaney J, Sood V, Thompson A, D'Urso A, Horvath CM, Brickner JH (2013) A conserved role for human Nup98 in altering chromatin structure and promoting epigenetic transcriptional memory. PLoS Biol 11(3):e1001524. https://doi.org/10.1371/journal.pbio.1001524
33. You T, Ingram P, Jacobsen MD, Cook E, McDonagh A, Thorne T, Lenardon MD, de Moura AP, Romano MC, Thiel M, Stumpf M, Gow NA, Haynes K, Grebogi C, Stark J, Brown AJ (2012) A systems biology analysis of long and short-term memories of osmotic stress adaptation in fungi. BMC Res Notes 5:258. https://doi.org/10.1186/1756-0500-5-258
34. Mitra T, Menon SN, Sinha S (2018) Emergent memory in cell signaling: Persistent adaptive dynamics in cascades can arise from the diversity of relaxation time-scales. Sci Rep 8(1):13230. https://doi.org/10.1038/s41598-018-31626-9
35. Côte P, Sulea T, Dignard D, Wu C, Whiteway M (2011) Evolutionary reshaping of fungal mating pathway scaffold proteins. MBio 2(1):e00230-e310. https://doi.org/10.1128/mBio.00230-10
36. Klímová Z, Bráborec V, Maninová M, Čáslavský J, Weber MJ, Vomastek T (2016) Symmetry breaking in spreading RAT2 fibroblasts requires the MAPK/ERK pathway scaffold RACK1 that integrates FAK, p190A-RhoGAP and ERK2 signaling. Biochim Biophys Acta 1863:2189–2200. https://doi.org/10.1016/j.bbamcr.2016.05.013
37. Lee PC, Beyrakhova K, Xu C, Boniecki MT, Lee MH, Onu CJ, Grishin AM, Machner MP, Cygler M (2020) The Legionella kinase LegK7 exploits the Hippo pathway scaffold protein MOB1A for allostery and substrate phosphorylation. Proc Natl Acad Sci U S A 117(25):14433–14443. https://doi.org/10.1073/pnas.2000497117
38. Kant S, Standen CL, Morel C, Jung DY, Kim JK, Swat W, Flavell RA, Davis RJ (2017) A protein scaffold coordinates SRC-mediated JNK activation in response to metabolic stress. Cell Rep 20(12):2775–2783. https://doi.org/10.1016/j.celrep.2017.08.025
39. Zhang J, Zhou T (2019) Markovian approaches to modeling intracellular reaction processes with molecular memory. Proc Natl Acad Sci U S A 116(47):23542–23550. https://doi.org/10.1073/pnas.1913926116
40. Wang Y, Wang Y, Wu Y, Suo Y, Guo H, Yu Y, Yin R, Xi R, Wu J, Hua N, Zhang Y, Zhang S, Jin Z, He L, Ma G (2023) Using the inner membrane of *Escherichia coli* as a scaffold to anchor enzymes for metabolic flux enhancement. Eng Life Sci 23(2):e2200034. https://doi.org/10.1002/elsc.202200034
41. Kennedy NW, Mills CE, Nichols TM, Abrahamson CH, Tullman-Ercek D (2021) Bacterial microcompartments: tiny organelles with big potential. Curr Opin Microbiol 63:36–42. https://doi.org/10.1016/j.mib.2021.05.010
42. Aon MA, Cortassa S (2015) Function of metabolic and organelle networks in crowded and organized media. Front Physiol 5:523. https://doi.org/10.3389/2Ffphys.2014.00523
43. Srere PA (1985) The metabolon. Trends Biochem Sci 10(3):109–110
44. Tian T, Fan J, Elf SE (2021) Metabolon: a novel cellular structure that regulates specific metabolic pathways. Cancer Commun (Lond) 41(6):439–441. https://doi.org/10.1002/cac2.12154
45. Zhu Y, Jin L, Shi R, Li J, Wang Y, Zhang L, Liang CZ, Narayana VK, De Souza DP, Thorne RF, Zhang LR, Zhang XD, Wu M (2022) The long noncoding RNA glycoLINC assembles a lower glycolytic metabolon to promote glycolysis. Mol Cell 82(3):542–554. https://doi.org/10.1016/j.molcel.2021.11.017
46. Patrick M, Gu Z, Zhang G, Wynn RM, Kaphle P, Cao H, Vu H, Cai F, Gao X, Zhang Y, Chen M, Ni M, Chuang DT, DeBerardinis RJ, Xu J (2022) Metabolon formation regulates branched-chain amino acid oxidation and homeostasis. Nat Metab 4(12):1775–1791. https://doi.org/10.1038/s42255-022-00689-4
47. Pedley AM, Pareek V, Benkovic SJ (2022) The purinosome: a case study for a mammalian metabolon. Annu Rev Biochem 91:89–106. https://doi.org/10.1146/annurev-biochem-032620-105728
48. Hebb DO (1949) The Organization of Behavior. Wiley & Sons, New York
49. Oja E (1982) Simplified neuron model as a principal component analyzer. J Mathem Biol 15(3):267–273. https://doi.org/10.1007/2FBF00275687
50. Acar M, Becskei A, van Oudenaarden A (2005) Enhancement of cellular memory by reducing stochastic transitions. Nature 435(7039):228–232. https://doi.org/10.1038/nature03524
51. Liu N, Ding Y, Fromm M, Avramova Z (2014) Different gene-specific mechanisms determine the "revised-response" memory transcription patterns of a subset of *A. thaliana* dehydration stress responding genes. Nucleic Acids Res 42(9):5556–5566. https://doi.org/10.1093/nar/gku220
52. Biswas S, Clawson W, Levin M (2023) Learning in transcriptional network models: computational discovery of pathway-level memory and effective interventions. Int J Mol Sci 24(1):285. https://doi.org/10.3390/ijms24010285
53. Jacob F, Monod J (1961) On the regulation of gene activity. Cold Spring Harb Symp Quant Biol 26:389–401. https://doi.org/10.1101/SQB.1961.026.01.024
54. Burrill DR, Silver PA (2010) Making cellular memories. Cell 140(1):13–18. https://doi.org/10.1016/j.cell.2009.12.034
55. Koseska A, Bastiaens PI (2017) Cell signaling as a cognitive process. EMBO J 36(5):568–582. https://doi.org/10.15252/embj.201695383
56. Hadziselimovic N, Vukojevic V, Peter F, Milnik A, Fastenrath M, Fenyves BG, Hieber P, Demougin P, Vogler C, de Quervain DJ, Papassotiropoulos A, Stetak A (2014) Forgetting is regulated via Musashi-mediated translational control of the Arp2/3 complex. Cell 156(6):1153–1166. https://doi.org/10.1016/j.cell.2014.01.054
57. Wang J, Zhang K, Wang E (2008) Robustness and dissipation of mitogen-activated protein kinases signal transduction network: underlying funneled landscape against stochastic fluctuations. J Chem Phys 129(13):135101. https://doi.org/10.1063/1.2985621
58. Hore TA, von Meyenn F, Ravichandran M, Bachman M, Ficz G, Oxley D, Santos F, Balasubramanian S, Jurkowski TP, Reik W (2016) Retinol and ascorbate drive erasure of epigenetic memory and enhance reprogramming to naïve pluripotency by complementary mechanisms. Proc Natl Acad Sci U S A 113(43):12202–12207. https://doi.org/10.1073/pnas.1608679113
59. Yu Y, Yarrington RM, Chuong EB, Elde NC, Stillman DJ (2016) Disruption of promoter memory by synthesis of a long noncoding RNA. Proc Natl Acad Sci U S A 113(34):9575–9580. https://doi.org/10.1073/pnas.1601793113

60. Tompa P, Csermely P (2004) The role of structural disorder in the function of RNA and protein chaperones. FASEB J 18(11):1169–1175. https://doi.org/10.1096/fj.04-1584rev
61. Ali A, Pardo JM, Yun DJ (2020) Desensitization of ABA-signaling: the swing from activation to degradation. Front Plant Sci 11:379. https://doi.org/10.3389/fpls.2020.00379
62. Hepler JR, Earp HS, Harden TK (1988) Long-term phorbol ester treatment down-regulates protein kinase C and sensitizes the phosphoinositide signaling pathway to hormone and growth factor stimulation. evidence for a role of protein kinase C in agonist-induced desensitization. J Biol Chem 263(16):7610–7619
63. Premont RT, Gainetdinov RR (2007) Physiological roles of G protein-coupled receptor kinases and arrestins. Annu Rev Physiol 69:511–534. https://doi.org/10.1146/annurev.physiol.69.022405
64. Moore CA, Milano SK, Benovic JL (2007) Regulation of receptor trafficking by GRKs and arrestins. Annu Rev Physiol 69:451–482. https://doi.org/10.1146/annurev.physiol.69.022405.154712
65. Rajagopal S, Shenoy SK (2018) GPCR desensitization: Acute and prolonged phases. Cell Signal 41:9–16. https://doi.org/10.1016/j.cellsig.2017.01.024
66. Chang HY, Klein RM, Kunos G (1982) Selective desensitization of cardiac beta adrenoceptors by prolonged in vivo infusion of catecholamines in rats. J Pharmacol Exp Ther 221(3):784–789
67. Lee HT, Thompson CI, Hernandez A, Lewy JL, Belloni FL (1993) Cardiac desensitization to adenosine analogues after prolonged R-PIA infusion in vivo. Am J Physiol 265(6 Pt 2):H1916–H1927. https://doi.org/10.1152/ajpheart.1993.265.6.H1916
68. Perlini S, Khoury EP, Norton GR, Chung ES, Fenton RA, Dobson JG Jr, Meyer TE (1998) Adenosine mediates sustained adrenergic desensitization in the rat heart via activation of protein kinase C. Circ Res 83(7):761–771. https://doi.org/10.1161/01.res.83.7.761
69. Purrello F, Rabuazzo AM, Anello M, Patanè G (1996) Effects of prolonged glucose stimulation on pancreatic beta cells: from increased sensitivity to desensitization. Acta Diabetol 33(4):253–256. https://doi.org/10.1007/BF00571559
70. Karlsson FA, Van Obberghen E, Grunfeld C, Kahn CR (1979) Desensitization of the insulin receptor at an early postreceptor step by prolonged exposure to antireceptor antibody. Proc Natl Acad Sci U S A 76(2):809–813. https://doi.org/10.1073/pnas.76.2.809
71. Korcsmáros T, Farkas IJ, Szalay MS, Rovó P, Fazekas D, Spiró Z, Böde C, Lenti K, Vellai T, Csermely P (2010) Uniformly curated signaling pathways reveal tissue-specific cross-talks and support drug target discovery. Bioinformatics 26(16):2042–2050. https://doi.org/10.1093/bioinformatics/btq310
72. Dalle S, Imamura T, Rose DW, Worrall DS, Ugi S, Hupfeld CJ, Olefsky JM (2002) Insulin induces heterologous desensitization of G-protein-coupled receptor and insulin-like growth factor I signaling by downregulating beta-arrestin-1. Mol Cell Biol 22(17):6272–6285. https://doi.org/10.1128/MCB.22.17.6272-6285.2002
73. Ishibashi KI, Imamura T, Sharma PM, Huang J, Ugi S, Olefsky JM (2001) Chronic endothelin-1 treatment leads to heterologous desensitization of insulin signaling in 3T3-L1 adipocytes. J Clin Invest 107(9):1193–1202. https://doi.org/10.1172/JCI11753
74. Torda T, Yamaguchi I, Hirata F, Kopin IJ, Axelrod J (1981) Quinacrine-blocked desensitization of adrenoceptors after immobilization stress or repeated injection of isoproterenol in rats. J Pharmacol Exp Ther 216(2):334–338
75. De Blasi A, Fratelli M, Wielosz M, Lipartiti M (1987) Regulation of beta adrenergic receptors on rat mononuclear leukocytes by stress: receptor redistribution and down-regulation are altered with aging. J Pharmacol Exp Ther 240(1):228–233
76. Liu J, Sun F, Wang Y, Yang W, Xiao H, Zhang Y, Lu R, Zhu H, Zhuang Y, Pan Z, Wang Z, Du Z, Lu Y (2017) Suppression of microRNA-16 protects against acute myocardial infarction by reversing beta2-adrenergic receptor down-regulation in rats. Oncotarget 8(12):20122–20132. https://doi.org/10.18632/oncotarget.15391
77. Adachi S, Yasuda I, Nakashima M, Yamauchi T, Kawaguchi J, Shimizu M, Itani M, Nakamura M, Nishii Y, Yoshioka T, Hirose Y, Okano Y, Moriwaki H, Kozawa O (2011) Ultraviolet irradiation can induce evasion of colon cancer cells from stimulation of epidermal growth factor. J Biol Chem 286(29):26178–26187. https://doi.org/10.1074/jbc.M111.240630
78. Rosette C, Karin M (1996) Ultraviolet light and osmotic stress: activation of the JNK cascade through multiple growth factor and cytokine receptors. Science 274(5290):1194–1197. https://doi.org/10.1126/science.274.5290
79. Tang X, Shen H, Chen J, Wang X, Zhang Y, Chen LL, Rukachaisirikul V, Jiang HL, Shen X (2011) Activating transcription factor 6 protects insulin receptor from ER stress-stimulated desensitization via p42/44 ERK pathway. Acta Pharmacol Sin 32(9):1138–1147. https://doi.org/10.1038/aps.2011.75
80. Zhou L, Zhang J, Fang Q, Liu M, Liu X, Jia W, Dong LQ, Liu F (2009) Autophagy-mediated insulin receptor down-regulation contributes to endoplasmic reticulum stress-induced insulin resistance. Mol Pharmacol 76(3):596–603. https://doi.org/10.1124/mol.109.057067
81. Li N, Xiao Y, Wang H, Zhong Y, Yang H, Huang K (2023) Insulin desensitization and cell senescence induced by heat stress in pig testicular cell model. Anim Biotechnol 19:1–10. https://doi.org/10.1080/10495398.2023.2214246
82. Holliday R (1997) Understanding ageing. Philos Trans R Soc Lond B Biol Sci 352(1363):1793–1797. https://doi.org/10.1098/rstb.1997.0163
83. Kirkwood TB, Austad SN (2000) Why do we age? Nature 408(6809):233–238. https://doi.org/10.1038/35041682
84. Sőti C, Csermely P (2007) Aging cellular networks: chaperones as major participants. Exp Gerontol 42(1–2):113–119. https://doi.org/10.1016/j.exger.2006.05.017
85. Ferrucci L, Wilson DM 3rd, Donegà S, Gorospe M (2022) The energy-splicing resilience axis hypothesis of aging. Nat Aging 2(3):182–185. https://doi.org/10.1038/s43587-022-00189-w
86. Walker KA, Basisty N, Wilson DM 3rd, Ferrucci L (2022) Connecting aging biology and inflammation in the omics era. J Clin Invest 132(14):e158448. https://doi.org/10.1172/JCI158448
87. Jung FF, Kennefick TM, Ingelfinger JR, Vora JP, Anderson S (1995) Down-regulation of the intrarenal renin-angiotensin system in the aging rat. J Am Soc Nephrol 5(8):1573–1580. https://doi.org/10.1681/ASN.V581573
88. Zeng Y, Wang PH, Zhang M, Du JR (2016) Aging-related renal injury and inflammation are associated with downregulation of Klotho and induction of RIG-I/NF-κB signaling pathway in senescence-accelerated mice. Aging Clin Exp Res 28(1):69–76. https://doi.org/10.1007/s40520-015-0371-y
89. Iemitsu M, Maeda S, Jesmin S, Otsuki T, Miyauchi T (2006) Exercise training improves aging-induced downregulation of VEGF angiogenic signaling cascade in hearts. Am J Physiol Heart Circ Physiol 291(3):H1290–H1298. https://doi.org/10.1152/ajpheart.00820.2005
90. Xiong X, Wang X, Lu Y, Wang E, Zhang Z, Yang J, Zhang H, Li X (2014) Hepatic steatosis exacerbated by endoplasmic reticulum stress-mediated downregulation of FXR in aging mice. J Hepatol 60(4):847–854. https://doi.org/10.1016/j.jhep.2013.12.003
91. Koohy H, Bolland DJ, Matheson LS, Schoenfelder S, Stellato C, Dimond A, Várnai C, Chovanec P, Chessa T, Denizot J, Manzano Garcia R, Wingett SW, Freire-Pritchett P, Nagano T, Hawkins P, Stephens L, Elderkin S, Spivakov M, Fraser P, Corcoran AE, Varga-Weisz PD (2018) Genome organization and chromatin analysis identify transcriptional downregulation

of insulin-like growth factor signaling as a hallmark of aging in developing B cells. Genome Biol 19(1):126. https://doi.org/10.1186/s13059-018-1489-y
92. Grunfeld C, Jones DS, Shigenaga JK (1985) Autoantibodies against the insulin receptor dissociation of the acute effects of the antibodies from the desensitization seen with prolonged exposure. Diabetes 34(3):205–211. https://doi.org/10.2337/diab.34.3.205
93. Rubner J, Schulten K (1990) Development of feature detectors by self-organization. Biol Cybern 62:193–199. https://doi.org/10.1007/BF00198094
94. Földiák P (1990) Forming sparse representations by local anti-Hebbian learning. Biol Cybern 64:165–170. https://doi.org/10.1007/BF02331346
95. Roberts PD, Leen TK (2010) Anti-hebbian spike-timing-dependent plasticity and adaptive sensory processing. Front Comput Neurosci 4:156. https://doi.org/10.3389/fncom.2010.00156
96. Adler M, Alon U (2018) Fold-change detection in biological systems. Curr Opin Syst Biol 8:81–89. https://doi.org/10.1016/j.coisb.2017.12.005
97. Bromberg KD, Ma'ayan A, Neves SR, Iyengar R (2008) Design logic of a cannabinoid receptor signaling network that triggers neurite outgrowth. Science 320:903–909. https://doi.org/10.1126/science.1152662
98. Oeckinghaus A, Hayden MS, Ghosh S (2011) Crosstalk in NF-κB signaling pathways. Nat Immunol 12(8):695–708. https://doi.org/10.1038/ni.2065
99. Goentoro L, Shoval O, Kirschner MW, Alon U (2009) The incoherent feedforward loop can provide fold-change detection in gene regulation. Mol Cell 36(5):894–899. https://doi.org/10.1016/j.molcel.2009.11.018
100. Lee RE, Walker SR, Savery K, Frank DA, Gaudet S (2014) Fold change of nuclear NF-κB determines TNF-induced transcription in single cells. Mol Cell 53(6):867–879. https://doi.org/10.1016/j.molcel.2014.01.026
101. Alon U (2007) Network motifs: theory and experimental approaches. Nat Rev Genet 8(6):450–461. https://doi.org/10.1038/nrg2102
102. Mangan S, Itzkovitz S, Zaslaver A, Alon U (2006) The incoherent feed-forward loop accelerates the response-time of the gal system of Escherichia coli. J Mol Biol 356(5):1073–1081. https://doi.org/10.1016/j.jmb.2005.12.003
103. Stanton BZ, Chory EJ, Crabtree GR (2018) Chemically induced proximity in biology and medicine. Science 359(6380):1117. https://doi.org/10.1126/science.aao5902
104. Peng Y, Liu J, Inuzuka H, Wei W (2023) Targeted protein post-translational modifications by chemically induced proximity for cancer therapy. J Biol Chem 299(4):104572. https://doi.org/10.1016/j.jbc.2023
105. Adachi S, Yasuda I, Nakashima M, Yamauchi T, Yamauchi J, Natsume H, Moriwaki H, Kozawa O (2010) HSP90 inhibitors induce desensitization of EGF receptor via p38 MAPK-mediated phosphorylation at Ser1046/1047 in human pancreatic cancer cells. Oncol Rep 23(6):1709–1714. https://doi.org/10.3892/or_00000815
106. Shi M, Yang Z, Hu M, Liu D, Hu Y, Qian L, Zhang W, Chen H, Guo L, Yu M, Song L, Ma Y, Guo N (2013) Catecholamine-Induced β2-adrenergic receptor activation mediates desensitization of gastric cancer cells to trastuzumab by upregulating MUC4 expression. J Immunol 190(11):5600–5608. https://doi.org/10.4049/jimmunol.1202364
107. Vega A, Jimenez-Rodriguez TW, Barranco R, Bartra J, Diéguez MC, Doña I, Fernández-Rivas M, Gandolfo-Cano M, Gastaminza-Lasarte G, González-Mancebo E, de la Hoz CB, Sánchez-Morillas L, Torres MJ, Berges-Gimeno MP, Muñoz-Cano R (2021) Hypersensitivity reactions to cancer chemotherapy: Practical recommendations of ARADyAL for diagnosis and desensitization. J Investig Allergol Clin Immunol 31(5):364–384. https://doi.org/10.18176/jiaci.0712
108. Alen Coutinho I, Costa Sousa F, Cunha F, Frutuoso C, Ribeiro C, Loureiro C, Águas F, Todo BA (2022) Key elements in hypersensitivity reactions to chemotherapy: experience with rapid drug desensitization in gynaecological cancer in a Tertiary Hospital. Eur Ann Allergy Clin Immunol 54(6):265–276. https://doi.org/10.23822/EurAnnACI.1764-1489.207
109. Yang BC, Castells MC (2022) The who, what, where, when, why, and how of drug desensitization. Immunol Allergy Clin North Am 42(2):403–420. https://doi.org/10.1016/j.iac.2021.12.004
110. Cernadas JR, Brockow K, Romano A, Aberer W, Torres MJ, Bircher A, Campi P, Sanz ML, Castells M, Demoly P, Pichler WJ (2010) European network of drug allergy and the EAACI interest group on drug hypersensitivity. general considerations on rapid desensitization for drug hypersensitivity - a consensus statement. Allergy 65(11):1357–1366. https://doi.org/10.1111/j.1398-9995.2010.02441.x
111. Morris HG (1980) Drug-induced desensitization of beta adrenergic receptors. J Allergy Clin Immunol 65(2):83–86. https://doi.org/10.1016/0091-6749(80)90190-6
112. Ball AJ, Flatt PR, McClenaghan NH (2000) Desensitization of sulphonylurea- and nutrient-induced insulin secretion following prolonged treatment with glibenclamide. Eur J Pharmacol 408(3):327–333. https://doi.org/10.1016/s0014-2999(00)00782-2
113. Irwin N, McKinney JM, Bailey CJ, Flatt PR, McClenaghan NH (2010) Effects of metformin on BRIN-BD11 beta-cell insulin secretory desensitization induced by prolonged exposure to sulphonylureas. Diabetes Obes Metab 12(12):1066–1071. https://doi.org/10.1111/j.1463-1326.2010.01294.x
114. Tilley DG, Rockman HA (2006) Role of beta-adrenergic receptor signaling and desensitization in heart failure: new concepts and prospects for treatment. Expert Rev Cardiovasc Ther 4(3):417–432. https://doi.org/10.1586/14779072.4.3.417