Learning and memory in molecular networks

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Abstract

The present work examines the capacity of biological systems to encode memories via adaptive changes in molecular networks. In single cells, the rewiring of molecular networks can store information as molecular engrams. In multicellular organisms, single cells might communicate with each other and tune their molecular memories to cooperatively encode multicellular memories in tissues and organs. Learning in the whole brain might consequently be examined as a problem of individual cells learning how to form a memory together via tuning their single-cell memories to each other and a significant amount of memory content in the brain might be stored at the molecular level inside of single cells. Molecular memory formation is proposed as a universal concept to explain adaptive organism phenotypes and can elucidate memory phenomena in the brain, immune system, skeletal muscle, skin, endocrine system and during development among others. Consequently, the formation of maladaptive memories in different tissues can explain stable, environmentally-induced dysfunction in various human diseases including cancer, autoimmunity, addiction, post-traumatic stress disorder, obesity, diabetes and fibrosis. The targeting of physiological molecular memories and the creation of synthetic memories could be valuable strategies to influence organism physiology in biological engineering and therapeutic interventions.

Keywords

Memory, learning, molecular, network, engram, adaptation, maladaptation, cell, tissue

Introduction

Biological systems from unicellular lifeforms to humans encode memories at several levels of organization and throughout the whole organism to ensure physiological function. Work in the 19th and early 20th century by German researchers Ewald Hering [1] and Valentin Haecker [2] among others has suggested that memory might be a universal property of organic matter. In the 1950s, John von Neumann speculated about possible roles of a genetic memory system with self-perpetuating properties within the body and brain [3]. Since then, considerable evidence has accumulated that memory is implemented by living systems at all scales of organization and in most anatomical compartments.

Memory is defined here as a set of processes for encoding, maintaining and retrieving information within a system. I will examine molecular mechanisms for memory formation in close connection to the mammalian brain as a prime example and highlight in which other organ systems and

organisms memory can be found. I will advance novel hypotheses including that *molecular engrams* form a powerful concept class to explain biological phenotypes and that a large fraction of human diseases is caused by the formation of *maladaptive memories* in cells and tissues. While the present work is mostly focused on memory, learning in molecular networks is also examined as one way to encode meaningful molecular memories.

Memory emerges as a universally applicable and powerful concept to analyze and explain physiological and pathological phenotypes. Molecular memory in single cells in particular has a broad relevance due to it potentially being implemented similarly by all organisms across the tree of life and our increasing ability to manipulate the relevant underlying molecular substrates including DNA methylation marks, histone modification states and RNA content. It is plausible that memory is a foundational characteristic of all cells and that more complex forms of memory in multicellular organisms such as the human brain are simply cooperative extensions of evolutionarily very old mechanisms for single-cell memory formation.

Memory in single cells

Molecular memory is hypothesized to be implemented via formation and maintenance of *molecular engrams*. These engrams are sets of system configurations that constitute the memory and can be dispersed throughout the cell and organism. Constituents of a molecular memory engram can include stable DNA methylation patterns, histone modifications, long-lived changes in RNA content and phosphorylation changes in proteins. The definition is broad enough to include any memory-relevant changes at the molecular level. Molecular engrams can thus serve as explanatory concepts for phenotypes in biological systems. Importantly, as they constitute memory components, they allow analysis of memory-associated phenomena including encoding after certain stimulation patterns, erasure and modification. Epigenetic and transcriptional mechanisms are especially important in the establishment of cellular memories [4,5]. As we shall see below, molecular engrams are formed in a variety of adaptation processes in health and disease.

Previous work has demonstrated that PC12 cells display learning forms such as stimulus-selective habituation [6,7] and single mammalian cells can form short- and long-term memories [8]. Non-neural cells display the massed space learning effect [9]. Work in single-celled organisms has suggested that several single-celled species can implement complex learning behavior [10,11], including the formation of associative memories. Stentor coeruleus displays graded habituation and tunes this learning response to different stimulus parameters [12]. Different amoeba species have been reported to show associative conditioning [13]. Chemotaxis in amoeba involves cellular memory formation [14] and E. coli can form memories of swarming experience [15]. In candida albicans, single-cell cell-type memory is implemented across generations via the continuous presence of the transcription factor Wor1 [16].

In the mammalian brain, single neurons possess a large computational repertoire [17] which can support memory formation. Modeling studies suggest that individual neurons support the internal structure for single-cell associative learning [18] and neurons display complex functional network structures at the molecular level that are characteristic of learning systems including multi-node feedback mechanisms [19]. Non-synaptic plasticity also enables neuron-level learning in modelling experiments [20] and intracellular molecular networks can implement the required network structures for habituation [21].

Adaptive transcription, i.e. transcription programs which are induced by acute stimulation and control remodeling of cells to adapt to changing environmental conditions, is a promising candidate mechanism for single-cell learning and memory [22]. Adaptive transcription programs commonly involve a set of stimulus-responsive transcription factors including CREB, MEF2 and SRF, as well as several IEGs such as Fos and Egr1 which are crucial for memory formation in the brain. Adaptive transcriptional and RNA-based mechanisms might be attractive foundation mechanisms for cell memory.

The first reason is response variety, which is required to map and compute different inputs intracellularly and then encode these into memory. RNA has a vast computational capacity, leading to proposals that it can implement natural universal computation [23]. Modeling studies have shown that gene regulatory networks can support associative memory formation [24,25]. Stimulation-dependent transcriptional and RNA-related changes in neurons include, among others, mRNA induction of hundreds of genes [26] (oftentimes depending on the stimulation pattern [27]), induction of various non-coding RNAs (e.g. enhancer RNAs [28], long-non coding RNAs [29] and microRNAs [30]), alternative splicing and editing of transcripts [31,32], histone modifications [33] and DNA double strand breaks [34]. The brain also possesses a large variety of different RNA species including circular RNAs [35]. A study demonstrating the massed space learning effect in non-neural human cell lines implicates the adaptive transcription factor CREB in cellular learning [9].

One crucial prerequisite for cellular memory formation via adaptive transcription would be the ability to parse different input parameters and map them to transcriptomic changes. The transcription factor Npas4 is induced differentially according to stimulus and regulated by a distinct signaling cascade in medium spiny neurons that relays specific input information to the genome [36]. While traditional IEGs such as Arc and Fosb are regulated by dopamine signaling, MAPK and PKA, Npas4 is uncoupled from all of these pathways and instead regulated by calcineurin [36]. Similar to Npas4, the Fos promoter and its enhancers contain elements that mediate differential induction to different neuronal inputs [37]. Another way in which the cell maps different circuit inputs to transcriptional output is through proteins like DARPP-32 which is phosphorylated differently at several amino acid residues in response to different stimuli [38,39] and subsequently regulates transcription via PP-1. CRE and SRE gene regulatory elements are differentially induced by calcium influx through different types of calcium channels (VDCCs and NMDARs) [40]. I have previously explored ways in which RNA-based transcription circuits can implement a “neuronal network within a neuron” [41], for instance via formation of Hopfield networks in nucleic acid replacement cascades.

Additionally, RNA is an attractive candidate substrate for cellular long-term memory formation because experimental results show that nuclear RNAs can persist for the whole life of an animal *in vivo* [42]. RNA-based memory is also involved in horizontal and vertical memory transfer in C. elegans [43-45], making it possible that these mechanisms are evolutionarily conserved and important in mammalian neurons. Another potential mechanism to diversify RNA for memory encoding is RNA editing which has been shown to be important in the regulation of brain function, including A-to-I-editing [46,47] and m6A methylation which is involved in learning and memory [48].

An important mechanism to control RNA content involves epigenetic regulation of transcription which is a central way of encoding cellular memory across the tree of life [49-51]. In the brain, chromatin plasticity is a determining factor for recruitment of neurons into a memory engram [52] and site-specific epigenetic editing has causal roles in learning [53]. DNA methylation is a central

mechanism in cellular memory formation [54,55] and for memory encoding in the brain [56]. The DNA methylase Dnmt3a for instance is involved in regulating activity-dependent transcription and memory formation [57,58]. Dnmt3a2 is induced by dopamine receptor stimulation in MSNs and it regulates D1R-dependent gene inductions [59]. Interestingly, Glanzman and colleagues have established a link between DNA methylation and RNA-based memory transfer by finding that transfer of habituation by RNA injection in Aplysia requires the activity of DNA methyltransferases [60]. These findings are in line with mechanisms demonstrating a reversal of the central dogma, in which information can flow from RNA to DNA [61].

Molecular memory formation during physiological function

In multicellular organisms including humans, molecular memory formation happens throughout the whole body.

For the brain, memory is one of its main functions and seemingly relatively well studied. Yet, there are important explanatory gaps in standard paradigms that could be resolved through concepts of molecular memory formation. A classic example for a model of neuronal learning is associative memory formation via Hebbian plasticity in which multi-cell memory circuits form through timing-dependent synaptic plasticity [62]. In a strong version of this view, a single cell by itself is not able to encode memory content, as synapses generally require two or more cells. Over time, several challenges to the hypothesis that memory formation in the brain happens exclusively via synaptic plasticity mechanisms such as LTP have emerged [63-67]. These include, among others, unaffected learning performance in AMPA- and NMDAR-knockout animals which show a complete elimination of LTP in targeted memory circuits but intact learning performance [68,69], extensive synaptic turnover in memory-relevant circuits [70,71], intact memory after significant remodeling of the brain in metamorphosis in different insects [72-75], the retainment of memory in planaria after decapitation and regrowth from tail fragments [76,77], transfer of learned information between animals in different species via RNA and other brain extracts [78-83], transfer of acquired information via RNA within the same animals [84], RNA-based transfer of learned information in C. elegans horizontally between individuals [44] and vertically between generations [43-45], RNA-based transfer of habituation in Aplysia [85], the dissociation of synaptic plasticity and long-term memory in Aplysia [86], and the recovery of memory after amnestic treatments which inhibit synaptic plasticity [87]. In the above experiments, storage or transfer of the memory-relevant information via synaptic plasticity is unlikely which calls for the investigation of additional memory mechanisms in the brain. I hypothesize here that single-cell memories will be important functional building blocks for more complex multicellular memories in the brain and that an important approach to the study of memory will involve analysis of multicellular network memory as a problem of individual cells learning how to form a memory together. In line with the challenges to synaptic plasticity as the only mechanism to store information in memory, several researchers have proposed alternative memory models in which cells are able to store memory content within themselves. Gallistel proposes that at least certain memory contents are coded by a cell-intrinsic molecular mechanism [67]. Gershman advances a model in which intracellular memory and synaptic plasticity serve complementary functions in that intracellular memory codes for the parameters of a generative model and synaptic plasticity optimizes an inference model [66]. In line with the proposition that computation by chemistry is energetically cheaper by orders of magnitude than by neural spiking and synaptic mechanisms [88], and the fact that evolutionarily old cellular mechanisms exist to encode memory across the tree of life from unicellular organisms to

mammalian brains, it seems plausible that single neurons could learn and form memories themselves. As mentioned above, one important problem is how to connect single-cell learning to cooperative multi-cell learning. Adaptive transcription has been shown to be able to build this bridge between the cellular and network levels. For instance, Fos is involved in establishing place cell tuning [89] and Npas4 implements a circuit-wide logic controlling neuronal network excitation-inhibition balance [90].

In the immune system, a general function of memory is to enable faster mounting of a defensive response upon re-exposure to an antigen. In both the adaptive and innate immune system, cells implement molecular memory via changes in transcriptional and epigenetic interaction patterns. In adaptive immunity, activated immune cells express memory [91] and modify chromatin accessibility of certain genes via DNA methylation and histone modifications to transfer certain genes to a primed state [92,93] (e.g. IFN-gamma promoter demethylation in memory T-cells [94]), enabling faster reaction upon re-stimulation with the antigen in question. Additionally, non-coding RNAs are involved in immune memory [95]. Similarly, in trained immunity of the innate immune system, memory phenomena occur [96], including implementation of natural killer cell memory via differential changes in chromatin accessibility [93]. In fibroblasts and macrophages, IFN-beta stimulation leads to the establishment of a transcriptional memory and accelerated and heightened transcriptional responses upon restimulation [97]. Interestingly, there is also a functional overlap in some molecules that are involved in memory formation in the brain and immune system including CREB [98,99], MEF2 [100,101] and DNMTs [102,103].

In skeletal muscle, different memory phenomena have been proposed and described. The first is a type of cell memory in which myonuclei get incorporated to skeletal muscle fibers during hypertrophic growth after exercise and then remain there for extended time periods [104-108]. Upon re-stimulation after atrophy, the muscle grows faster due to the enhanced number of myonuclei present. The second type is a molecular memory with several components, including epigenetic modifications [105,109-112] and stable proteomic changes [113], that mediates differential myocyte responses to future exercise.

In the skin, several types of molecular memory have been described. These include an epigenetic wound healing memory in which stem cells display differential chromatin accessibility after initial injury and heightened regenerative response upon subsequent injury [114] and epigenetic inflammatory memory after wounding and infections [115,116]. The tanning response after UV-exposure can also be seen as a memory phenomenon and tanning and skin pigmentation have been shown to involve epigenetic modifications [117].

In the heart, cardiac memory refers to a changed electrophysiological phenotype after prior activity [118,119] which can persist for weeks. Cardiac memory has been proposed to involve transcription dependent mechanisms [120] which change ion channel incorporation and hence electrical depolarization behavior of cardiac myocytes [121].

In the digestive system, memory is implemented in different ways, including in the enteric nervous system as a synaptic plasticity mechanism termed sustained slow postsynaptic excitation [122] and as epigenetic inflammatory memory in stem cells after injury or infection [123,124].

During development, one of the essential roles of molecular memory is to preserve established cell identities. During cell fate commitment, transcription factor networks are rewired and preserve the resulting cell type [125-127]. Interestingly, erasure of previously established epigenetic memory has also been reported to be a central part of development [128].

Plants were shown to implement memory in various contexts [129-131] with previous work proposing that a forgetting of stress memories might also have beneficial effects [132].

Maladaptive memories in disease

While memory formation is central to physiological function, molecular learning systems can encode maladaptive memories which then drive dysfunction. As we will see below, maladaptive memories are involved in many major human disease entities. As memories are generally modifiable, targeting maladaptive memories via methods such as retraining or memory extinction might be a novel approach to correct disease phenotypes.

In the brain, the concept of maladaptive memory is relatively straightforward. As described above, neurons establish epigenetic modifications during memory formation. In addiction, drug-related memories are formed via epigenetic and transcriptional mechanisms [133,134] and in PTSD, epigenetic modifications are involved in the operations of a harmful memory process [135].

Cancer cells and their precursors can form and hold several types of memory and the formation of cancer memories has been proposed as a fundamental substrate of oncogenesis [136]. Cancers use similar molecular learning mechanisms to the brain (e.g. adaptive transcription and multicellular electrical coupling), and during oncogenesis a learning loop emerges that modifies cancer memories to adapt to environmental stressors including carcinogens, therapeutic interventions and immune system attacks [136].

Mechanical memory in cells has been observed [137-141] which is at least in some contexts implemented via epigenetic changes [142] and has been proposed to be involved in the pathogenesis of fibrosis [137,143]. Cells cultured on stiff substrates retain a mechanical memory after being transferred to softer substrates [137,138]. Interestingly, transcriptomic memory phenotypes can be reversed by preconditioning in appropriate substrates [144] and targeting of mechanical memory in therapeutically injected stem cells in an injury model of fibrosis can enhance therapeutic efficiency [145].

In autoimmunity, an autoimmune memory in the adaptive immune system has been proposed [146] and T cell memory is involved in autoimmune disease progression [147]. Trained immunity via epigenetic reprogramming of the innate immune system has been proposed to contribute to autoimmune disease pathology [148].

Metabolic memory describes a phenomenon in which after an initial period of pathological metabolic state and subsequent return to healthy conditions (e.g. initial hyperglycemia followed by normoglycemia) patients still deteriorate even though the supposed disease cause is removed [149]. In diabetes for instance, metabolic memory via epigenetic changes has been proposed to contribute to diabetic nephropathy [150,151]. In obesity, adipocytes establish a transcriptional obesogenic memory which leads to heightened rebound weight gain and transcriptional deregulation after the continuing of high-fat feeding [152].

In post viral syndromes, epigenetic memory mechanisms might be a defining feature. Severe COVID19 causes alterations in transcriptional activity and innate immune phenotypes in circulating hematopoietic stem and progenitor cells for up to one year after infection [153]. Blockade of IL-6R signaling during the acute infection phase attenuated this maladaptive memory phenomenon.

Maladaptive memories have been proposed as a substrate to hold altered identities in maladapted organ systems across a variety of diseases [154]. I hypothesize here that every disease with an environmental component might be caused at least partially by maladaptive molecular memory formation. Finding maladaptive memory configurations might hence be a valuable goal in understanding drivers of a given disease.

Synthetic molecular memories and learning circuits

With our increasing abilities to manipulate the molecular content inside of cells, it might possible to create synthetic learning circuits and incept into organisms synthetic molecular memories. For instance, previous work has explored synthetic nucleic acid based signaling cascades that could instantiate neural networks within a neuron [41]. One of the goals of vaccination is the creation of therapeutic immunological memories and vaccination against SARS-CoV2 establishes a lasting epigenetic memory in immune cells [155]. Perhaps molecular transfer technologies can make it possible to directly incept the relevant molecular memory engrams into cells, for instance via RNA transfer [156], thus enabling memory synthesis via molecular synthesis. With regard to the brain and the RNA transfer experiments discussed above, it could be possible to encode behavioral programs in easily transferable nucleic acid sequences and to thus incept brain memories via molecular transfer. Memories are generally acquired, modified and extinguished through learning which suggests that it might be possible to train cells and tissues to lose their maladaptive memories via therapeutic paradigms such as the application of integration pressure [154].

Memories as conceptual tools to explain biological phenotypes

We usually want a simple conceptual framework to explain observables in living systems. One very fruitful but also limited approach in the past has been to map genotypes to phenotypes. For instance, many current models of oncogenesis aim to explain malignant phenotypes by referring to single or a few genomic mutations or epigenetic modifications. However, as I have previously argued, the concept of cancer memory can be more powerful in explaining malignant phenotypes [136]. In line with a definition of memory in the brain where a memory involves changes at multiple levels including molecular alterations (e.g. epigenetic marks and transcription of single genes), molecular networks (e.g. memory transcriptomes), cellular alterations (e.g. synaptic plasticity) and cell networks (e.g. memory network engrams), malignancy in cancer could be analyzed at multiple levels as cancer memories, making cancer memory a simple and effective concept to capture the multi-level and environmentally modifiable determinants of a malignant phenotype. Since molecular memories are important drivers of adaptation processes across the whole organism, it would be useful to develop general approaches for the study and modification of molecular engrams. These could elucidate molecular drivers of certain phenotypes in health and enable therapeutic targeting of maladaptive memories in disease.

Conclusions

Biological organisms from single cells to human beings encode molecular memories in the course of adaptation, in many cases instantiating a molecular learning system. Molecular engrams encoded in epigenetic, transcriptional and RNA-based modifications are involved in physiological processes in the brain, immune system, skeletal muscle and skin among others, as well as during

organismal development. Organisms can form and hold maladaptive memories in different tissues leading to diseases including cancer, autoimmunity, addiction, PTSD, fibrosis, obesity, diabetes and post-viral syndromes, giving rise to the notion that these diseases could perhaps be characterized as learning disorders in cells and tissues. Molecular memories can be powerful conceptual tools to explain environmentally modifiable phenotypes and their manipulation could lead to novel therapeutic approaches such as training paradigms to extinguish maladaptive memories and the inception of synthetic therapeutic memories.

Contributions

TL conceived and wrote the manuscript.

Conflicts of interest

The author declares no conflict of interest.

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