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Spine Remodeling and Synaptic Modification

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Abstract The majority of excitatory communication occurs at dendritic spines, and spine modifications accompany synaptic modifications under both physiological and pathological conditions. Although it is increasingly clear that spine remodeling is required for synaptic modification, the exact functions and underlying molecular mechanisms remain unclear. Here, we review recent progress on this topic and discuss the functions of spine remodeling in a broad sense to include both alterations in spine size and actin dynamics. We propose that these two aspects of actin remodeling have distinct contributions to synaptic modification.

Keywords Dendritic spines · Long-term potentiation · Long-term depression · Synaptic plasticity · Imaging · Actin

Introduction

Spines are the major sites of excitatory connections between neurons in the brain [1]. Spines consist of a head and are connected to the neuron by a spine neck. Typically, they are categorized into mushroom, thin, and stubby types [2–5]. Excitation conveyed from presynaptic terminals leads to transmission of information to the postsynaptic neuron. Modification of spines has been observed under various physiological and pathological conditions, and it is an integral part of the remodeling of neuronal connections. Since spine remodeling occurs with the induction of synaptic modification in a fairly reproducible and well-controlled manner, the function and underlying molecular mechanism of spine remodeling have been most extensively studied in the context of synaptic plasticity. In this review, we will focus on recent studies on spine remodeling in the context of long-term potentiation (LTP) and long-term depression (LTD). These two forms of synaptic modifications refer to the long-lasting increase or decrease in synaptic strength, respectively, and are widely used as model paradigms for the investigation of cellular and molecular basis of synaptic plasticity.

An important component of spines is the postsynaptic density (PSD), which forms the platform to host receptors, channels, scaffolding proteins, and signaling systems that enable synaptic transmission and postsynaptic biochemical processes. Among these are glutamate receptors (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor [AMPA], *N*-methyl-D-aspartate [NMDA], and metabotropic subtypes), voltage-gated Ca^{2+} channels, PSD-95, Shank, and calcium/calmodulin-dependent kinase II (CaMKII). Spines also contain smooth endoplasmic reticulum, polyribosomes, and mitochondria, which provide functions ranging from buffering intracellular Ca^{2+} to local protein synthesis. The structure and function of spines appear to be coordinated nicely since synapse size (PSD area) and spine size (spine volume) are proportional to each other [6–9]. The number of synaptic AMPA receptors (AMPARs) and the number of docked synaptic vesicles are also proportional to the area of PSD [10], and thus synapse strength is strongly correlated to spine size. This correlation suggests that regulatory mechanisms must exist to keep this balance. It is well established that spines are modified under

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various physiological and pathological conditions, such as development, learning, aging, and neurodegeneration [2, 3, 11]. Modifications of synapses are typically observed under these conditions, further strengthening the link between functional and structural remodeling at synapses.

Spine remodeling occurs with the induction of synaptic modifications, such as LTP or LTD. Starting from early works on spine remodeling associated with synaptic plasticity, it has been proposed repeatedly that structural modification is important to support persistent synaptic modification, although the exact contribution of spine remodeling remains unclear. This question is especially important and pressing given the universally agreed importance of synaptic modification in many vital functions and malfunctions of the central nervous system, including neural development, learning and memory functions, and neurodegeneration. The most obvious changes are alterations in spine head dimensions, but other less visible processes, such as alterations in the dynamic movement of actin cytoskeleton, also occur. In this review, we define spine remodeling to include both changes in spine dimension and actin dynamics, and we will try to establish that these two different processes carry out distinct functions. It could be argued that this distinction is arbitrary, but we consider it to be at least useful to guide our thinking and future investigation of the underlying molecular mechanisms.

Basics of Actin Dynamics/Spine Morphing

Spines are enriched with actin and the shape and size of spines are controlled by actin cytoskeleton [12]. Actin exists in two states in neurons: monomeric G-actin and filamentous F-actin. The assembly (polymerization) and disassembly (depolymerization) of F-actin can occur rapidly due to the weak noncovalent interactions of G-actin. At steady state, polymerization takes place preferentially at the barbed end of F-actin, while depolymerization occurs at the opposite pointed end. The difference in polymerization rates between the two ends leads to a net turnover of the actin filaments. The dynamics of actin turnover are regulated by actin-binding proteins. A number of toxins have been widely used to study and manipulate the functions of actins. By sequestering G-actin, latrunculins (A and B) inhibit actin polymerization at low concentrations and promotes actin depolymerization at high concentrations. Cytochalasins (B and D) bind to the barbed end of F-actin to prevent the addition of G-actin to inhibit polymerization. Jasplakinolide, on the other hand, stabilizes and/or promotes actin polymerization by binding to F-actin.

Based on their turnover rate, two actin pools have been identified in spines: one at the base of spines and is very stable (turnover time constant is tens of minutes) and the other at the tip of spines and highly dynamic (turnover time constant is tens of seconds) [13, 14]. The dynamics of actin is measured using fluorescence recovery after photobleaching (FRAP). After bleaching the fluorescence of GFP-actin with strong laser illumination, time course of fluorescence recovery in the photobleached area/spines reflects the rate that bleached GFP-actin is replaced by nonbleached GFP-actin and, hence, actin dynamics [13]. Recently, photoactivatable GFP-actin (PAGFP-actin) has been used to examine actin dynamics [14]. The fluorescence of the activated PAGFP-actins decays due to their replacement by non-activated PAGFP-actins as actin turnover occurs and, hence, the rate of this decay allows quantification of actin dynamics. The distinct turnover rates of actins led to the proposal that actin filaments in spines are of two groups: a stable pool that maintains the size and shape of spines and a dynamic pool that controls the dynamic movement of spines. Stable actin filaments are important to maintain glutamate receptors and PSD components (such as GKAP and Shank) [15–17]. Dynamic changes in actin cytoskeleton are mediated by addition and removal of G-actins. At steady state and a given cellular G-actin concentration, the difference in polymerization rates at the barbed and pointed ends results in a net loss of G-actin at the pointed end and a simultaneous gain of G-actin at the barbed end. This leads to a net flow of newly added G-actin through the filament and this process is termed actin treadmilling. Actin treadmilling results in a dynamic turnover of actin filaments without altering the length of F-actin. Macroscopically, this dynamic movement of actin is exhibited as motility or "dancing" of spines, seen both in vitro and in vivo [18–21]. For measuring spine motility, variations in spine shape or area covered by a particular spine in the two-dimensional image projected from three-dimensional *z*-stack images are calculated. This measurement is done on the spine head, and the larger the variation, the higher the motility. Turnover of dynamic actin or spine morphing can be inhibited by drugs that block actin polymerization such as latrunculins and cytochalasins [13, 14, 18, 19] or that stabilize actin filaments such as jasplakinolide [13]. These rapid changes in spine size and shape do not lead to permanent alterations in either parameter [18, 19]. Spine morphing is more prominent during early neuronal development and is progressively reduced with maturation [20, 21]. Spine morphing is also more prominent in the dissociated neuronal culture, likely due to the reduced glial contact. However, spine motility has been reported in acute slices [19], and there is some indication that changes in spine size/shape also occurs in the adult animals in vivo on the timescale of months [22]. Spine morphing is not related to the age or size of synapses in culture [13], suggesting that they may serve more general functions. The function of

actin dynamics is not quite clear, but may facilitate the formation of synapses and trafficking of molecules [23–25].

Plasticity of Spine Dimension and Actin Dynamics

Directionality

Synapses can undergo bidirectional modifications—long-lasting increases (LTP) or decreases (LTD) in strength. It has long been known that spine expansion occurs with the induction of LTP [2, 3], starting from early electron miscopy studies [26–31] and confirmed by recent time-lapse fluorescence imaging studies where the same set of spines are monitored before and after LTP induction (Fig. 1a, b; [32–36], but see [37]). Onset of spine expansion is fast (within 1 min) and long-lasting (hours). Usually, spine size is quantified using spine volume inferred from the intensity of fluorescence inside spine head (either fluorescence of expressed GFP or injected fluorescent dyes). A few studies also showed an increase in spine density and generation of new spines after LTP induction [38–40], although it remains to be clarified whether this increase is selective to developing tissue in culture since it has not been readily observed in studies using acute slice preparation or in the adult animals [33, 41–43]. Recent studies also demonstrated that induction of LTD leads to shrinkage and retraction of spines (Fig. 1b) [43–46]. The onset of spine shrinkage is slower than spine expansion but is also long-lasting. It has further been shown that the same set of spines can undergo either expansion or shrinkage depending on the activity patterns they receive (Fig. 1b) [43]. Thus, similar to synaptic modifications, the size of spines can be regulated bidirectionally.

Activity patterns that induce synaptic modifications, such as LTP and LTD, also induce a long-lasting reduction in the turnover rate of dynamic actin and spine motility [13, 14, 47]. In other words, spines become less motile and do not exhibit extensive changes in their shape after the induction of LTP or LTD. It is important to note that this alteration is not specific to activity patterns. This unidirectional alteration in actin dynamics is in clear contrast to the bidirectional modifications in spine size, suggesting that these two types of spine remodeling may serve distinct functions.

Reversibility

Although most studies showed persistent changes in spine dimension with the induction of LTP or LTD, spine modification can be reversed within a short time window after their occurrence. Kramar et al. [48] provided clear evidence that actin polymerization (which underlies spine expansion, see below) can be reversed by low-frequency synaptic stimulation (LFS) given shortly after LTP induction. Actin polymerization was examined using the fluorescence of rhodamine–phalloidin introduced to the stimulated neurons. Increase in the fluorescence of phalloidin indicates their incorporation to the cytoskeleton and, hence, actin polymerization. Theta-burst stimulation (TBP)-induced LTP is associated with actin polymerization which is stabilized in 15–20 min. Within this 15- to 20-min time window, reversal of actin polymerization can be induced by either LFS or adenosine application, both are known to induce reversal of LTP (or depotentiation). Yang et al. [36] monitored spine size and synaptic response from the same set of spines/synapses before and after LTP induction, using combined patch clamp recording and two-photon time-lapse imaging. They directly showed that LFS reversed spine expansion (Fig. 1b). Both studies found the same time window for reversing spine expansion/actin polymerization and LTP. Furthermore, reversal of LTP and spine expansion share the same pharmacological sensitivity. Hence, an important question to be addressed in future studies is how the reversal of LTP and spine expansion are related to each other, whether induction of one triggers the other or whether they occur in parallel. It is important to distinguish between the reversal of spine expansion and spine shrinkage: (1) they occur on spines of different states—reversal of spine expansion only occurs on spines that expand after LTP induction (not on naïve spines), while shrinkage occurs on naïve spines; (2) different activity patterns required—spine shrinkage requires long (e.g., 15 min) LFS, while reversal of spine expansion requires much shorter (e.g., 5 min) LFS; (3) different intracellular signaling involved—reversal of spine expansion requires activity of protein phosphatase-1 (PP-1) but spine shrinkage does not [36, 43, 49]. Similar to spine expansion, spine shrinkage is also reversible by high-frequency stimulation (HFS) given shortly after LFS (Fig. 1b). It is unknown whether this reversal is time-sensitive, but the reversal of LTD is not. These results show that, similar to synaptic modification, spine modification can be reversed in an activity-dependent manner, and the reversal of spine expansion is also time-dependent. Whether the reduction in actin dynamics associated with LTP/LTD can be reversed by synaptic activity has not been examined. This is an interesting and important question since it will provide valuable insight into the functions of actin dynamics.

Cellular Basis

Initial/Early Phase of Modification

Spine expansion occurs quickly after the induction of LTP and this early expansion shares the upstream signaling mechanisms with LTP, such as opening of NMDA receptor and activation of CaMKII [32, 36, 50]. Spine shrinkage

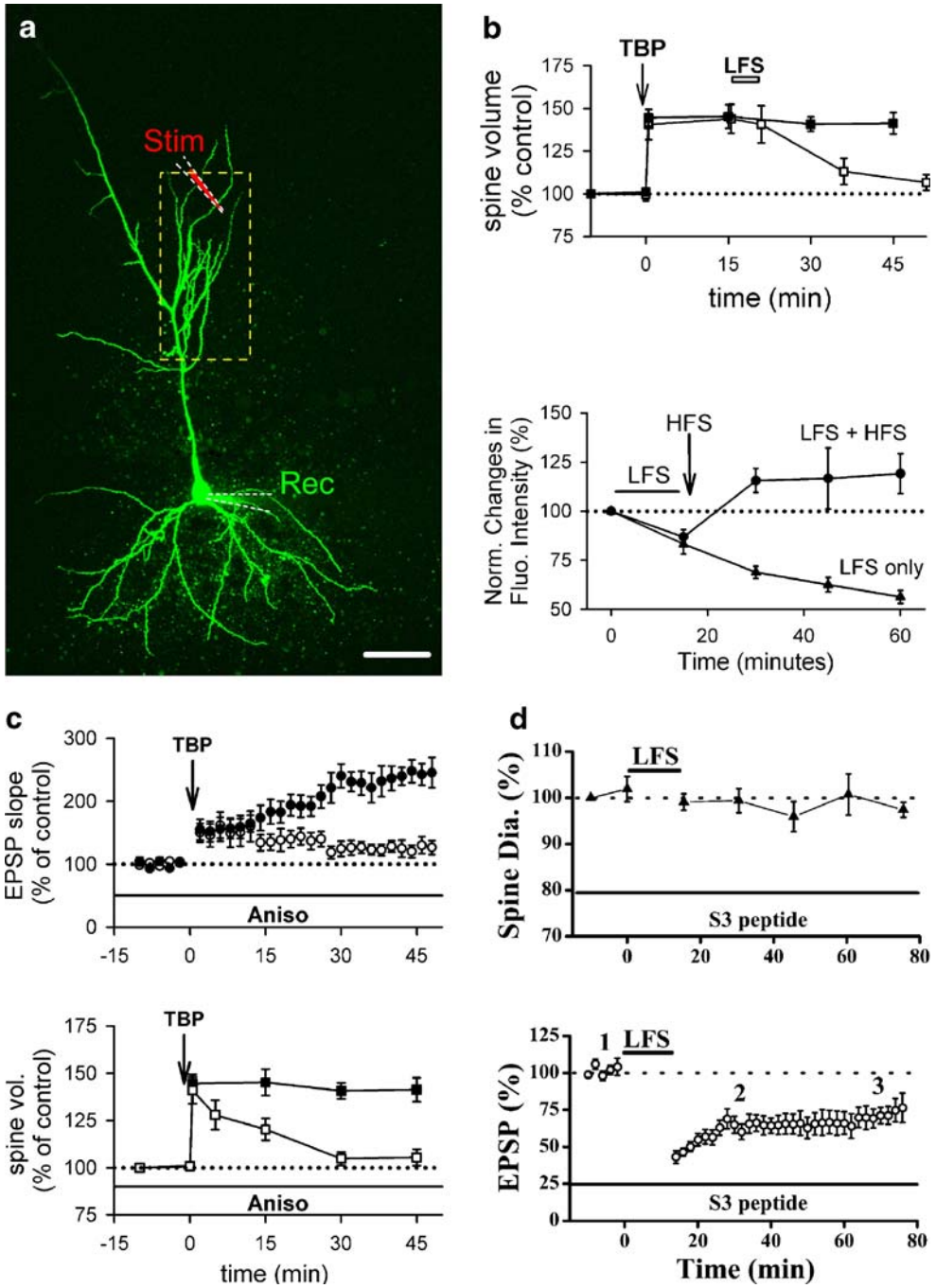

Fig. 1 Modification in spine dimension is reversible and is independently expressed with regard to synaptic plasticity. **a** Both spine dimension and synaptic response can be monitored simultaneously from the same set of spines/synapses using combined two photon time-lapse imaging and patch clamp recording. This image showed such a configuration with the stimulating (*Stim*) and recording electrodes (*Rec*) and the dendritic tree of the recorded neuron. Spines in the *boxed region* are examined at higher magnification using time-lapse imaging. Scale bar, 50 μm. Modified from Yang et al. [36]. **b** Modification in spine dimension is reversible. *Upper* spine expansion readily occurs with the induction of LTP with TBP (*filled symbols*). When LFS is given within a short time window after LTP induction, spine expansion is quickly reversed to baseline (*open symbols*). From Yang et al. [36]. *Lower* after the induction of spine shrinkage by LFS, HFS readily restored spine size to their original values (*circles*). In the absence of HFS, LFS leads to long-lasting reduction in spine size (*triangles*). Modified from Zhou et al. [43]. **c** The initial spine expansion is dissociable from the expression of LTP. This is one of the manipulations that were used to demonstrate the independent expression of initial spine expansion and LTP, blocking protein synthesis with anisomycin (*Aniso*). *Upper* bath application of Aniso blocked LTP (*open symbols*). *Lower* in the same experiments with Aniso application, a transient spine expansion is observed. These results also indicate that interactions between spine expansion and LTP expression are required for the persistent expression of both modifications. In addition, protein synthesis is required for both modifications. From Yang et al. [36]. **d** Dissociation of spine shrinkage and LTD. Postsynaptic loading of the inactive S3 peptide inhibits spine shrinkage (*upper*) but not LTD in the same experiments (*lower*). From Wang et al. [49]

readily occurs after the induction of LFS and shares activation of NMDA receptors, calcineurin (protein phosphatase 2B), and phospholipase C with the expression of LTD [43, 49, 51]. However, distinct downstream signaling mechanisms are employed by synaptic and spine modifications. For LTP, postsynaptic exocytosis, postsynaptic protein kinase A (PKA) activity, interactions between the C-terminal region of GluR1 and its intracellular targets, and protein synthesis are all required for the full expression of LTP, but not for the initial spine expansion (Fig. 1c) [36]. For LTD, activation of protein phosphatase 1 (PP-1) is required for LTD but not for spine shrinkage [43, 49], while inhibiting dephosphorylation of cofilin blocks spine shrinkage but does not affect LTD expression (Fig. 1d) [43, 49]. The above evidence supports a model that modifications of synapses and spines can occur independently.

Actin polymerization or depolymerization occurs with activity patterns that induce LTP or LTD, and it underlies spine expansion or shrinkage, respectively [32, 36, 46]. One elegant way of examining the state of actin polymerization in real time is to monitor changes in the fluorescence associated with actins using fluorescence resonance energy transfer (FRET [46]). Actins are tagged with different fluorescent proteins (such as CFP and YFP). When G-actins are dominant, there is only one peak in the emitted fluorescence when CFP-actins are illuminated. When polymerization occurs, YFP-actins bind to CFP-actins to form F-actin, and their close spatial proximity causes FRET between CYP and YFP. As a result, an additional peak at longer wavelength (corresponding to YFP) is detected. The ratio of the two peaks is thus used to calculate the state of actin polymerization. Okamoto et al. [46] found that LTP-inducing stimuli led to an increase in the YFP/CFP ratio and, hence, increase in actin polymerization, while LTD-inducing stimuli led to the opposite. These changes in the state of actin polymerization also correlate to changes in the size of spines where FRET was measured. Modification in actin polymerization is mediated by actin-binding proteins. One particular protein, cofilin appears to play a major role in spine expansion and shrinkage. Cofilin is located in dendritic spines and concentrated at the periphery of spines, suggesting that cofilin may regulate the polymerization state of actin during synaptic plasticity [52]. Cofilin increases the rate of dissociation of G-actin from the pointed end of F-actin and has intrinsic F-actin-severing capability [53]. The activity level of cofilin is regulated by its phosphorylation at Ser-3 in that dephosphorylated cofilin is active, binds, and severs actin, while phosphorylated cofilin is inactive [54]. Phosphorylation of cofilin is mediated by LIM kinase, whose activity is further regulated by upstream modulators, such as Rho-associated coiled-coil forming protein kinases (ROCK) and Ras homolog gene family member A (RhoA). Phosphorylated cofilin can be reactivated through dephosphorylation by a family of protein phosphatases Slingshot [55]. Calcium influx during LTP induction leads to phosphorylation of cofilin in the spine heads (hence, reduction in cofilin activity [56]) and actin polymerization, while LTD induction increases cofilin activity and leads to actin depolymerization and spine shrinkage. Inhibiting phosphorylation of cofilin using a short synthetic peptide devoid of phosphatase activity but serving as pseudosubstrates blocks actin polymerization and impairs the expression of long-lasting LTP [57]. On the other hand, spine shrinkage is prevented in neurons loaded with a short synthetic peptide containing phorphorylated Ser-3 to block the dephosphorylation of cofilin [43, 49].

Activity-induced reduction in actin dynamics/spine morphing occurs rapidly and requires an increase in the intracellular [Ca^{2+}] which is mediated by either opening of NMDA receptors or voltage-gated Ca^{2+} channels [58]. In clear contrast to modification of spine size, reduction in actin dynamics still occurs in the absence of key signaling mechanisms that are required for synaptic modifications (such as protein kinases and phosphatases) and does not require protein synthesis [47]. Ackermann and Matus [47] demonstrated that profilin, an actin-binding protein, is involved in the activity-induced reduction of spine morphing. Profilin regulates actin dynamics by binding to G-actin and enhancing ADP–ATP exchange to increase the pool of ATP-actin in cells [59]. Activity patterns inducing either LTP or LTD cause profilin to translocate from dendrites to spines [47]. Profilin also accumulates in large spines after fear conditioning, but the contribution of profilin to fear memory is unclear [60]. A recent study showed that LTP/LTD is not altered in the profilin II knockout mice [61], suggesting that either profilin II has minimal roles in synaptic plasticity or its role can be replaced or compensated by other actin-binding proteins. As discussed above, phosphorylation/dephosphorylation of cofilin is required for the expansion/shrinkage of spines associated with LTP/LTD. Therefore, there is a possibility that distinct actin-binding proteins may be involved in controlling spine size and actin dynamics/spine morphing. Further investigation of this possibility will not only advance our understanding of the molecular basis of actin remodeling but also provide useful tools to selectively manipulate each process to understand their contributions to synaptic plasticity. This notion is consistent with the observation that modification of cofilin activity is transient (~15 min) [56], but the translocation of profilin is long-lasting (>45 min) [47] after the induction of synaptic plasticity.

Persistent Phase of Modification

Spine expansion can last for many hours after its induction (e.g., 23 h [27]). The persistent phase of increase in spine size requires postsynaptic PKA signaling, the C-terminal

region of GluR1, and protein synthesis [34, 36, 62]. After LTP induction, the increase in F-actin polymerization is long-lasting, for example, to at least 5 weeks in vivo [57]. In contrast, phosphorylation of cofilin may be short-lasting, about 15–30 min after LTP induction in hippocampal slices ([56], but see [63]), and this brief period of altered cofilin activity may underlie the time window during which spine modification can be reversed. New F-actin may be added to spines to sustain spine expansion and these new F-actin filaments may be capped or cross-linked to prevent modification before cofilin activity returns to the resting level. Honkura et al. [14] demonstrated the appearance of a new pool of actin filaments after the induction of LTP and this new actin pool may constitute the new F-actins responsible to support spine expansion since its appearance is essential for spine expansion to occur. One important recent advance in our understanding of spine expansion is the demonstration that synaptic presence of new AMPARs is required to sustain spine expansion. Specifically, deletion of the C terminus of GluR1 of AMPARs or blocking its interaction with its intracellular partners impairs long-lasting spine expansion [34, 36]. Furthermore, the C terminus of GluR1 alone is sufficient to stabilize expanded spines but not enough to drive spine expansion [34]. These findings confirm the dissociation between spine modification and synaptic modification, and it also suggests that once AMPARs are present at the synapse, they interact with the cytoskeleton to stabilize spine expansion. It is also likely that newly synthesized proteins are required to stabilize spine expansion (see below), although the identity of these proteins remains unclear. It is unknown how long actin depolymerization and spine shrinkage last under in vivo conditions. How long the reduction in actin dynamics persists after its induction and how persistent the reduction is have not been examined either.

Relationship to Synaptic Modification

A key question in the investigation of spine remodeling is how it is related to or whether it is required for synapse modification. Actin polymerization is required for the expression of LTP [17, 57, 64, 65] and actin depolymerization is required for LTD [49]. But is it change in spine size or actin dynamics? As discussed in previous sections, the initial changes in spine dimension are not coupled to the expression of synaptic modifications since one process can occur normally in the absence of the other, and they may occur with a different onset [66]. In addition, some studies found that LTP could be induced in the absence of spine expansion [33, 37]. Yasumatsu et al. [67] showed that prolonged inhibition of neuronal activity by blocking action potentials (a condition that typically causes an increase in synaptic strength via upregulation of synaptic AMPARs) does not lead to increase in spine size. The dissociation between spine shrinkage and LTD has been extended by Wang et al. [49] in that spine dimension is not altered when synaptic depression is induced by either inhibition of the constitutive trafficking of AMPARs or by insulin application. Furthermore, Sdrulla and Linden [68] demonstrated another aspect of this dissociation in that retraction of spines induced by repetitive depolarization does not induce LTD. This finding further extends the dissociation to GABAergic neurons. On the other hand, as discussed before, persistent expression of LTP and spine expansion requires interaction between these two processes [34, 36]. Put together, modification of spine size may only be required for the expression of certain forms or phases of synaptic modifications.

Park et al. [69, 70] demonstrated that chemical induction of LTP promotes the mobilization of recycling endosomes and vesicles into spines, and blockade of this trafficking abolishes LTP-induced spine formation/growth. These results suggest that insertion of AMPARs and expansion of spines could be coupled through the delivery of recycling endosomes. However, recent studies pointed otherwise. First, the extent of GluR1 delivery does not always occur hand in hand with the bulk flow of endosomal traffic [71]. Second, inhibition of syntaxin-13-mediated exocytosis blocked trafficking of GluR1-containing AMPARs but not expansion of spines [34]. These results suggest that delivery of AMPARs and expansion of spines are mediated by distinct endosomal trafficking routes and, hence, are likely distinct, independent events.

Is actin dynamics required for the expression of synaptic modifications? Inhibiting actin polymerization after the induction of LTP, although does not interfering with established spine expansion, still blocks the expression of persistent LTP (Fig. 2a, b) [36, 64]. Similarly, inhibiting actin depolymerization blocks the long-term depression of both AMPARs and NMDA receptors (Fig. 2c, d; [49], but see [44]). Hence, modifications in actin dynamics may be required for the expression of both LTP and LTD.

Functions of Spine Remodeling

As defined above, spine remodeling includes changes in spine dimension and actin dynamics/spine morphing. In general, the functions of spine remodeling may be characterized into two types: (1) providing the necessary conditions for the expression and consolidation of synaptic modifications and (2) providing specific information regarding synaptic modifications. We hypothesize that the first type of function is likely mediated by alterations in actin dynamics/spine morphing and is likely permissive and the second type of function is likely mediated by alterations

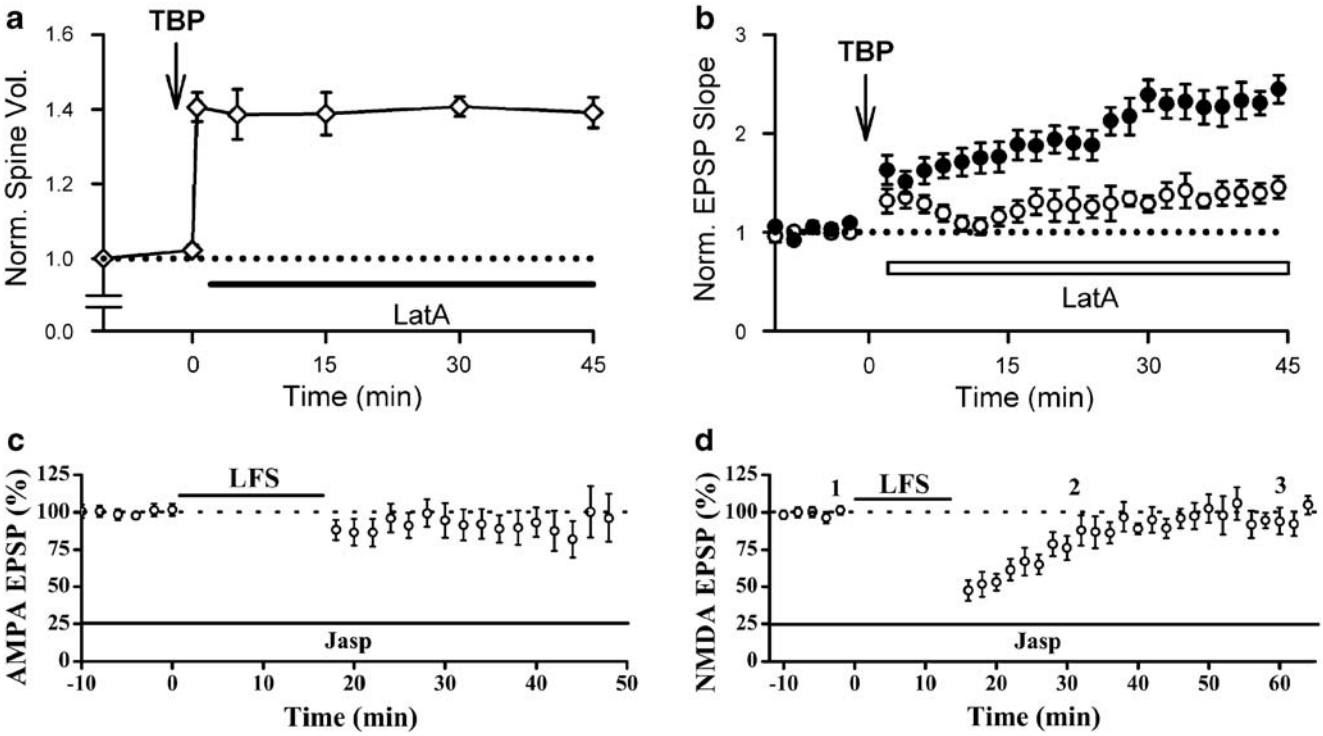

Fig. 2 Actin dynamics are required for the expression of synaptic modifications. **a** Bath application of latrunculin A (*LatA*) which inhibits actin polymerization at the concentration used, shortly after the induction of LTP with TBP, does not affect the established spine expansion. **b** LatA application in the same experiments leads to impairment in the persistent expression of LTP (*open symbols*). From Yang at al. [65]. **c** Postsynaptic loading of jasplakinolide (*Jasp*), which inhibits actin depolymerization, impairs the expression of LTD of AMPAR-mediated synaptic transmission. **d** The same manipulation with Jasp also impaired the expression of LTD of NMDA receptor-mediated synaptic transmission. Modified from Wang et al. [49]

in spine dimension and is likely instructive. Here, changes in spine dimension are more broadly defined as changes in the F-actin, i.e., polymerization and more F-actin with LTP and depolymerization and less F-actin with LTD. Remodeling of synapse requires the participation of many molecules in a highly interactive manner. These molecules need to be at the right place and at the right time for the desired outcome. These molecules can be locally synthesized, transported from other places, or simply accumulate there via diffusion. Hence, spine remodeling may be involved in the trafficking and/or synthesis of these molecules, which may include AMPARs, signaling molecules, and mRNAs. We will discuss the potential functions of spine remodeling according to the processes involved: (1) modifications in anchoring of receptors and signaling molecules, (2) diffusion of receptors and signaling molecules, and (3) synthesis of new proteins.

Anchoring

Anchoring of AMPARs at the PSD allows them access to glutamate released from the presynaptic terminals and participation in synaptic transmission, and anchoring of signaling molecules allows them to be properly positioned to exhibit optimal effects on their targets. At least part of this anchoring is achieved by linkage to the actin cytoskeleton. For example, AMPARs are linked to the actin cytoskeleton via adaptor proteins such as 4.1N and reversion-induced LIM protein [72, 73]. This anchoring may also be associated with other scaffolding proteins to create "slots" to anchor AMPARs, and it has been suggested that the numbers of slots are increased after LTP induction [74, 75]. Actin cytoskeleton may play an important role by providing the platform to host the necessary scaffolding molecules. This model is supported by the findings that F-actin filaments directly contact PSD components [76, 77] and they are also linked to various scaffold complexes at the PSD [78, 79]. Increased affinity to their anchors and/or increased number of slots allows the newly added AMPARs to be secured at synapses and shift the equilibrium toward movement of AMPARs into synapses from perisynaptic/extrasynaptic regions, as in the case of LTP. This is consistent with the observed reduction of AMPARs in the perisynaptic region and reduced mobility of synaptic AMPARs after chemical induction of LTP [80, 81]. In addition to synaptic AMPARs, perisynaptic AMPARs also appear to be anchored in some way to the actin cytoskeleton, based on the observation that moderate actin depolymerization causes the dispersion of

nonsynaptic AMPARs [15]. This anchoring can also explain the stable presence of perisynaptic receptors for tens of minutes after LTP induction [65], although the mobility of these receptors appears to be high [80]. This anchoring also appears to be weaker than what tethers AMPARs at PSD since perisynaptic AMPARs can be removed by moderate synaptic activity which does not affect synaptic AMPARs [65]. Increased F-actin as a result of actin polymerization may play a major role in this anchoring function. On the other hand, decreased affinity to their anchors induces greater mobility of AMPARs and allows them to diffuse out of the synapse to the perisynaptic/extrasynaptic region for endocytosis [82], as in the case of LTD. AMPARs appear to move to extrasynaptic sites prior to their internalization [83, 84]. LTD is absent in neurons loaded with the actin stabilizer, jasplakinolide (Fig. 2c) [49], and relief of anchoring may be mediated by actin depolymerization which occurs with the induction of LTD [15, 82].

Besides AMPARs, actin polymerization/depolymerization may modify the targeting of key signaling molecules to affect synaptic plasticity. A-kinase anchoring protein (AKAP) is targeted to PSD via F-actin and is a scaffold protein for PKA. Chemical induction of LTD leads to the loss of AKAP from the postsynaptic site, mediated by actin depolymerization [85], and this loss of AKAP results in reduced PKA activity and, hence, favoring the activity of protein phosphatases and expression of LTD [86]. With LTP induction, the accumulation of CaMKII in spines is likely mediated by their binding to F-actin [87]. Thus, changes in the state of actin polymerization affect the targeting of key signaling molecules. This alteration in anchoring of receptors and signaling molecules by actin remodeling appears to be instructive in the sense that it is selective to the directionality of synaptic modification.

Diffusion

Chemical induction of LTD increases the presence of AMPARs at the perisynaptic region, while chemical induction of LTP leads to a reduction of AMPARs at the perisynaptic region [80, 88]. Induction of LTP also promotes the movement of perisynaptic AMPARs to synapses [65, 89]. As discussed above, actin depolymerization associated with LTD induction is likely to cause the dissociation of AMPARs from their anchors and thus increases the portion of mobile AMPARs inside synapses. The combined effects facilitate movement of AMPARs out of synapses [80] and contribute to the enhanced presence of AMPARs at perisynaptic regions. At perisynaptic regions, the movement of AMPARs behaves as Brownian diffusion [80]. It is likely that diffusion of perisynaptic AMPARs is enhanced with the induction of synaptic modification given the observation that diffusion of surface molecules (not anchored or tethered to the membrane) is inversely related to spine motility or morphing [90]. Thus, AMPARs may move more freely and even faster when actin dynamics/spine morphing is reduced with the induction of either LTP or LTD. This enhanced movement facilitates movement of AMPARs toward the endocytotic zone lateral to PSD [91] and leads to increased internalization of AMPARs. On the other hand, more AMPARs are accumulated at the perisynaptic region with the induction of LTP, and enhanced movement of these perisynaptic AMPARs to synapses coupled with greater affinity to anchors and/or greater number of slots increases the chance of these receptors being captured and secured at synapses. After chemical LTP induction, the rate of recovery following photobleaching for tagged AMPARs is reduced [81, 89], suggesting a decrease in the exchange between synaptic and perisynaptic AMPARs, likely due to enhanced trapping of AMPARs at synapses. Hence, enhanced exchange of AMPARs between synaptic and perisynaptic compartments may be facilitated by reduced actin dynamics/spine morphing and may contribute to the expression of synaptic modification, although this alteration by itself does not provide the directionality of synaptic modification. Hence, actin remodeling appears to contribute to the diffusion process in a permissive manner and provides the general conditions to allow synaptic modifications to occur.

In addition to AMPARs, movement of signaling molecules also occurs following the induction of synaptic plasticity. For example, reduction in PKA but increase in PP-1 occurs with the induction of LTD to favor the function of calcineurin and PP-1 over protein kinases, and thus keeping AMPARs dephosphorylated and internalized [86, 92]. Actin filaments are enriched in the spine neck and may act as a barrier keeping large signaling molecules out of the spines [15, 17] and actin depolymerization may be required to remove this barrier. This notion is consistent with the observation that PP-1 is restricted to dendrites under resting condition and LTD induction allows its access to synapses [92]. In addition, a transient actin depolymerization has been reported with the induction of LTP and may remove the diffusion barrier to grant key molecules access to spines to consolidate LTP and spine expansion [93]. This function of actin remodeling also appears to be permissive in that it does not specify the direction of trafficking or the molecules being trafficked.

Recent studies showed that myosin V plays a prominent role in delivering AMPARs to synapses in the context of LTP. Specifically, myosin Va is required for the insertion of AMPARs to spines during LTP [94], while myosin Vb plays an essential role in the delivery of endosomes to spines and local exocytosis (including AMPARs) during LTP [71]. In addition, myosin Va has been shown to facilitate the accumulation of mRNA/protein complex in the spines [95]. The trafficking carried out by myosin V is

directional from dendrites towards spine head and, hence, likely play an instructive role in synaptic modifications. Two important questions remain to be resolved as why two different myosin V isoforms are involved in the LTP expression and whether a similar process occurs in the expression of LTD. Are AMPARs with different subunit compositions being trafficked by myosin Va and Vb or are different forms of LTP involved? In addition, it remains to be tested whether this trafficking of myosin requires actin remodeling in that either myosin V travels along the newly added F-actin to gain access to the spines or changes in actin dynamics facilitate the movement of myosin-based cargos. Thus, myosin may represent a dynamic link between spine remodeling and synaptic plasticity.

Synthesis of New Proteins

Protein synthesis is required to sustain LTP and spine expansion [36, 62, 96], and synthesis of new proteins requires actin polymerization. For example, synthesis of PKMζ, an atypical isoform of protein kinase C, is required for the long-lasting expression of LTP and long-term memory in an actin polymerization-dependent manner [97, 98]. The polymerized F-actin could serve as a platform for translocation to occur. Actin polymerization could also serve to transport mRNA to spines where polyribosomes are present for local synthesis [95, 99–101]. There is no direct evidence that proteins are synthesized inside the spine head, but dendritic synthesis of proteins has been demonstrated [102, 103]. Thus, trafficking of newly synthesized proteins into the spine head may play an important role in the stabilization of synaptic modification (Fig. 3). Alternatively, rather than being directly involved in protein synthesis, interaction between polymerized actin and newly synthesized proteins may be critical to sustain LTP and spine expansion. Although long-lasting LTD also requires protein synthesis [104], it is unknown whether actin may play a role. In addition, it is unknown whether long-lasting spine shrinkage requires protein synthesis.

It is quite likely that alteration in actin dynamics plays a permissive rather than instructive role in the expression of synaptic modification. In other words, changes in actin dynamics/spine morphing may be required to place synapses in a “plastic” state but does not provide the directionality of synaptic modification (Fig. 3).

Key Questions Remained

Modifications of Spine Dimension and PSD Dimension

Although persistent alterations in spine dimension have been observed with LTP/LTD induction in most studies, transient [33] and no expansion of spines [37] after LTP have been reported. Thus, it remains to be clarified as whether modifications in spine dimension is required for the expression of synaptic plasticity. We propose that persistent modification in spine dimensions is only required for long-lasting alterations in synaptic strength which is defined as changes that last more than a few hours and require protein synthesis. This proposal is based on the observations that: (1) persistent spine expansion requires protein synthesis [36, 62], (2) spine expansion becomes transient when signaling events required for protein synthesis dependent LTP are inhibited [36], (3) actin polymerization is required for late phase LTP but not the early phase [57, 64]. Early phase LTP is defined as the LTP observed within 60 min after induction. In that regard, Yang et al. [36] also found that the protein synthesis-independent component of LTP was not affected by inhibition of actin polymerization. (4) The initial phase of LTD (1–2 h) is not affected by blockade of cofilin-mediated actin depolymerization and occurs normally in the absence of spine shrinkage [43, 49]. It remains to be tested whether long-lasting LTD required spine shrinkage. On the other hand, short-lasting changes in spine dimension could be induced by stimuli that only induce short-lasting synaptic modifications [33].

Why do persistent modifications in spine dimension only occur with strong stimuli that induce long-lasting synaptic modifications? We suggest that this is due to the persistent remodeling of PSD induced by these stimuli. Increase in PSD length occurs with LTP and the opposite may occur with LTD. Persistent PSD remodeling is required to sustain synaptic modification, by securely anchoring new scaffolds, glutamate receptors, and signaling molecules in the case of LTP (Fig. 3) or ensuring stable removal of the above components in the case of LTD. This suggestion is supported by the recent findings of Steiner et al. [105] that spine expansion becomes transient when trafficking of PSD-95 is inhibited. Although studies using electron microscopy have demonstrated changes in PSDs after LTP induction, it is unclear whether such process already takes place in the enlarged spines observed using time-lapse imaging. It is important to emphasize that increased/decreased spine volume does not necessarily reflect bigger/smaller synapses or PSDs. Recent time-lapse imaging experiments demonstrated that PSD molecules, such as PSD-95, are much more dynamic than previously thought [81, 106]. The challenge for future studies is to monitor changes in PSD, glutamate receptors, and spine dimensions in the same set of spines before and after the induction of synaptic plasticity in order to understand the relative timing of these changes and relationship between them.

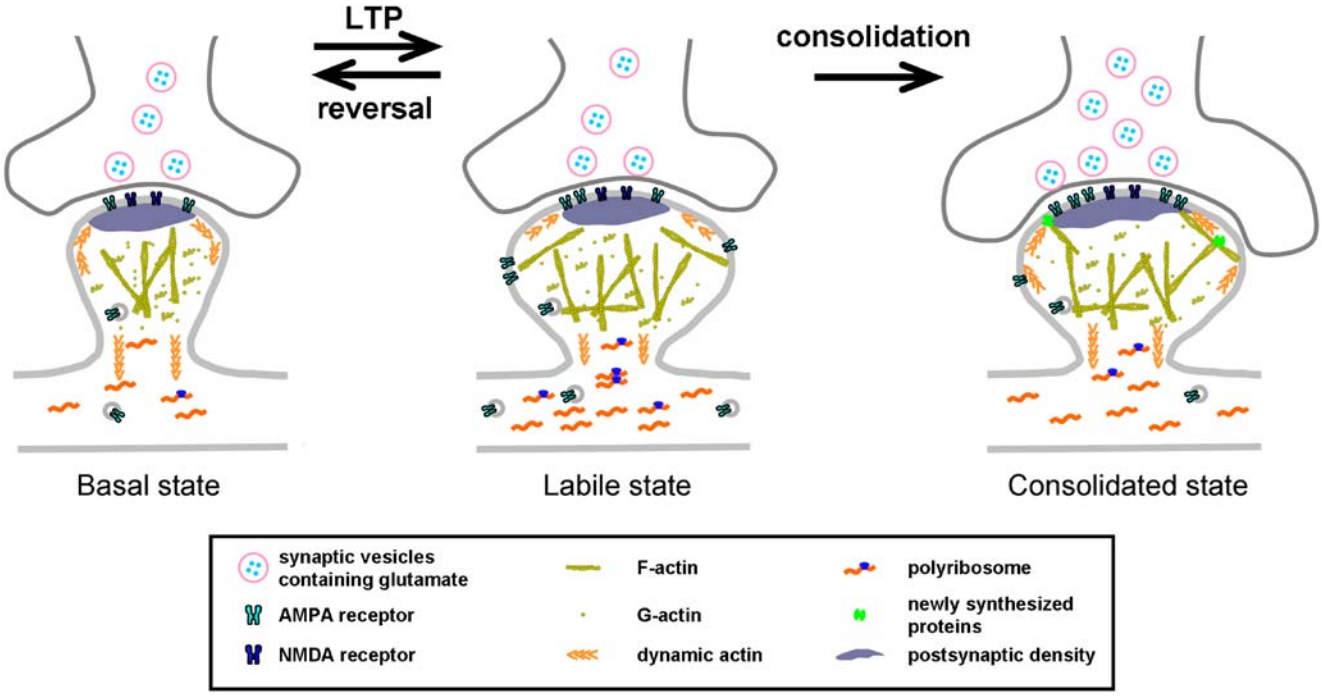

Fig. 3 A proposed model on spine remolding associated with synaptic plasticity. Spine expansion in the context of LTP is used to illustrate the major points. In the short period (10–15 min) after LTP induction, both spines and synapses enter a labile state during which these modifications can be readily reversed to the basal state. Spine remodeling includes both spine expansion (mediated by increased actin polymerization) and enhanced actin dynamics. Increased accumulation of AMPARs at the perisynaptic region occurs, which could have resulted from enhanced delivery of AMPARs to the postsynaptic membrane. Enhanced actin dynamics is proposed to be essential for the trafficking of receptors and signaling molecules into the spine head and PSD in a permissive manner. Increased protein synthesis is also initiated at this stage. No changes in PSD and presynaptic terminals occur at this stage. At the consolidated stage, new AMPARs are anchored at the PSD, and this process can at least partially underlie the expression of LTP. Spine expansion is stabilized by the increased presence of F-actins which are linked/capped by actin-binding proteins. The presence of AMPARs at synapses also appears to contribute to this stabilization. Newly synthesized proteins could participate in all of the above processes. The size of PSD is also increased and plays an important role in stabilizing modifications in AMPARs and actin cytoskeleton. On a more protracted timescale, enlargement of presynaptic terminals occurs with more synaptic vesicles docked at the active zone. Synaptic and spine remodeling is completed at this stage

The Long-Term Consequence of Spine Modifications

Most time-lapse imaging studies are restricted to 1 to 2 h due to technical limitations and, hence, the consequence of long-lasting spine expansion and shrinkage remains to be examined. One possibility is that spine shrinkage may lead to loss of spine and synapse, while spine expansion may lead to splitting of spine and duplication of synapse [107]. Consistent with this notion, cofilin activity is found to be required for spine loss after long incubation with amyloid beta peptide [108]. In addition, spine loss and turnover of presynaptic boutons occur after LTD induction [45, 109], but it remains to be tested whether spine shrinkage contributes to or is required for the observed spine elimination. It has also been shown that loss of synaptic AMPARs is required for amyloid beta peptide-induced spine loss [110], but it is unknown whether this loss of AMPARs is accompanied by or leads to spine shrinkage and in turn results in spine loss.

Presynaptic Modifications

If spine modifications are long-lasting, while the proportion between synapse strength and spine dimension are kept constant, corresponding presynaptic changes ought to occur. How these changes are brought to place and at which timescale they occur remain unclear. What is required is an increase or decrease in presynaptic functions, which could correspond to larger or smaller readily releasable pool of synaptic vesicles (Fig. 3). Induction of LTP leads to an increased probability of releasing glutamate from the presynaptic terminals [111], which appears to be selectively associated with the readily releasable pool [112]. Addition of trans-synaptic modules has been proposed to account for the growth of synapses associated with LTP [75] in which coordinated growth of active zone and PSD enable the proper alignment of presynaptic and postsynaptic compartments. It also remains to be elucidated whether retrograde signals are required to induce such presynaptic changes since the initial signaling and modifications occur at the postsyn-

aptic site. Another issue to be addressed is whether presynaptic modification is initiated only after the stabilization of postsynaptic changes since spine modification and LTP can be reversed within a short window after their induction, while presynaptic changes appear to occur with a significant delay compared to postsynaptic changes [113].

On a longer timescale, alterations in presynaptic functions may lead to changes in morphology, such as enlargement of the presynaptic terminal (in LTP) or a total loss of presynaptic terminal (in LTD; Fig. 3). Induction of LTD increases the turnover of presynaptic boutons and decreases synaptic contacts [109]. Bastrikova et al. [114] showed that LTD induction leads to an increased or even complete separation of presynaptic bouton from the dendritic spine, which is indicative of lessening of synaptic connections or early indication of presynaptic withdrawal. It is interesting that this increased separation does not occur on spines that show shrinkage. Again, whether and/or how changes in spine remodeling may contribute to the long-lasting modifications in the presynaptic terminals awaits further examination.

Conclusion

Recent advances in the imaging and molecular techniques have prompted rapid progress and renewed interests in structural modifications associated with synaptic plasticity. It is becoming increasingly clear that persistent remodeling of the synapse requires structural alternations at the synapse, but the picture is far from complete. A better understanding of the molecules involved and their interactions in these processes will not only allow us to manipulate them with far more precision but also to have far better understanding of the interactions between structure and function and how functional modifications become permanent.

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