REVIEW

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Dendritic arbor dynamics and stability in health and disease

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Dendritogenesis, a process of dendritic arbor development, is essential for the formation of functional neuronal networks, and in mammals, it begins in early life and continues into adulthood. It is a highly dynamic process in which dendritic branches form and regress until mature connectivity is achieved. Thereafter, dendritic branches are considered stable and do not undergo substantial rearrangements, although several exceptions have been described in the literature. After this long period of relative stability, significant changes in dendritic branching occur when the brain begins to age. Several neurological diseases, occurring both during development and in adulthood, have severe effects on the morphology of dendritic arbors, often associated with intellectual dysfunction. The molecular mechanisms of dendritogenesis are fairly well described. In contrast, knowledge of the molecular mechanisms of dendritic arbor stabilization and pathology-induced instability is still quite incomplete, and several important questions remain unanswered. We describe the dynamic changes during development and adulthood and in different pathologies. Whenever possible, we also provide details on the molecular mechanisms behind dendritic dynamics and stability.

Key words: dendritogenesis, dendritic arbor stability, neurodevelopment, brain aging, neurological disorders

INTRODUCTION

Throughout the animal kingdom, the formation of dendritic arbors (dendritogenesis) is a fundamental component of the complex processes of neuronal development and the formation of functional neuronal networks that underlie the proper functioning of cells of the nervous system. In the vertebrate/mammalian nervous system, which is the focus of this review, dendritogenesis begins during embryonic development after neurons migrating from neurogenic niches have reached their destinations and continues for some time during postnatal development. This dynamic phase of development is particularly vulnerable because many neurodevelopmental disorders result in suboptimal progression of dendrite formation. Once dendritic branches have assumed the shape characteristic of a particular neuronal class, the overall morphology of dendritic branches remains stable for several months or even years, depending on the lifespan of the given species. However, the morphology of dendritic branches can still change during adulthood. These are either fine-tuning changes, e.g., minimal elongations/shrinkages of existing branches triggered by the circadian clock (Ikeno et al., 2013); an enriched environment (Hickmott and Ethell, 2006); or learning (Greenough et al., 1985), or more extensive additions or removals of dendritic spines as in the case of spiny neurons (Knott and Holtmaat, 2008; Holtmaat et al., 2013). It should be noted, however, that mature dendritic arbors may change substantially in certain physiological situations (e.g., lactation, hibernation) to rapidly adapt their functions or metabolism (Stern and Armstrong, 1998; Magariños et al., 2006; von der Ohe et al., 2006). In addition, various nervous system diseases and trauma lead to increased dynamics of adult dendritic branches, often resulting in simplification of neuronal morphology and deteri-

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oration of neuronal connectivity. Finally, the stability of dendritic branches becomes fragile during the physiological aging of the nervous system (Dickstein et al., 2007).

From a molecular perspective, the mechanisms of dendritogenesis are quite well studied and understood, both in vertebrates as well as in invertebrates such as *Drosophila melanogaster* (Landgraf and Thor, 2006; Urbanska et al., 2008; Corty et al., 2009; Jan and Jan, 2010; Lin et al., 2020; Tempes et al., 2020; Lefebvre, 2021; Nourbakhsh and Yadav, 2021). More than 90% of studies on the dynamics of dendritic branches focus exclusively on the development of the nervous system. Hundreds of proteins with diverse cellular functions – from regulating gene expression to regulating the cytoskeleton involved in dendritic growth have already been identified (Landgraf and Thor, 2006; Urbanska et al., 2008; Corty et al., 2009; Jan and Jan, 2010; Lin et al., 2020; Tempes et al., 2020; Lefebvre, 2021; Nourbakhsh and Yadav, 2021). Consequently, how dendritic arbors are affected in neurodevelopmental disorders is also rapidly being deciphered (Kulkarni and Firestein, 2012; Copf, 2016; Martínez-Cerdeño, 2017). In contrast, much less is known about the mechanisms underlying the stability of mature dendritic arbors in vertebrates, despite numerous observations from invertebrates (Williams and Truman, 2005; Urbanska et al., 2008; Jan and Jan, 2010; Kanamori et al., 2015). The existing literature shows that we have very incomplete answers to several fundamental questions. For example, are dendritic arbors of all neuron types equally stable across the lifespan? Are the same or different molecules involved in stability in adulthood as in growth and stabilization during development? Is stabilization an active or passive process, i.e., simple growth inhibition? In this review, we will discuss physiological and disease-related examples of dendritic arbor dynamics and stabilization during the lifespan of the nervous system and the known molecular mechanisms. We also attempt, whenever possible, to address the questions posed above.

Physiological dendritic arbor dynamics through the neuronal lifespan

Development

During development or adult neurogenesis, newly born neurons migrate from sites of neurogenesis to target areas (Hatten, 1999; Kriegstein, 2005). After reaching their destination, the cells form protrusions that specialize into axons and dendrites (Niell et al., 2004). Originally, the process of dendritic tree formation was thought to be a continuous growth and branching of neuronal protrusions. However, research conducted nearly 30 years ago showed that this is not a linear process but a highly dynamic one, in which not only newly formed branches are added and elongated, but some of them also disappear (Dailey and Smith, 1996). Thus, dendritic arbor changes during development are far more dynamic and significant than originally thought.

The molecular mechanism of dendritogenesis has been extensively studied over the years (Urbanska et al., 2008; Jan and Jan, 2010; Lin et al., 2020; Tempes et al., 2020; Lefebvre, 2021; Nourbakhsh and Yadav, 2021); thus, in this review, we will only briefly discuss the major external and internal players in this process. The control of neuronal development in vertebrates by external factors, independent of the nature of the signal, can be reduced to the scheme shown in Fig. 1A. Binding of these factors (e.g., brain-derived neurotrophic factor [BDNF], glutamate, neurotrophin-4/5) to the corresponding receptors in the cell membrane of developing dendrites leads to a change in the activity of the latter and to modulation of intracellular signal transduction pathways involving calcium ions, kinases, phosphatases, and small guanine nucleotide-binding proteins (GTPases) (McAllister et al., 1995; Urbanska et al., 2008; Jan and Jan, 2010; Lin et al., 2020; Tempes et al., 2020; Lefebvre, 2021; Nourbakhsh and Yadav, 2021). Through their effector proteins, global and local changes in cellular processes required for the growth, stabilization, or elimination of individual dendrites occur. These processes include cytoskeletal dynamics (microtubules and microfilaments), microtubular transport, endocytosis and exocytosis, protein synthesis and degradation, and transcription (Urbanska et al., 2008; Jan and Jan, 2010; Lin et al., 2020; Tempes et al., 2020; Lefebvre, 2021; Nourbakhsh and Yadav, 2021).

Usually, a particular extrinsic factor causes simultaneous and coordinated modulation of all processes required for normal dendritic tree morphology. A detailed example of such a sequence of events is the induction of hippocampal dendritic tree growth by BDNF involving the Ras-PI3K/MAPK-Akt-mTOR pathway (Jaworski et al., 2005; Kumar et al., 2005). BDNF binds to tropomyosin-related kinase B (TrkB) and triggers activation of the small GTPase Ras, followed by extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) (Huang and Reichardt, 2003). Studies by other teams and by us have shown that all of these proteins are critical for dendritogenesis and require the activity of another protein kinase, the mammalian target

of rapamycin (mTOR) (Jaworski et al., 2005; Kumar et al., 2005). mTOR is a kinase found in two protein complexes, mTOR complex (mTORC) 1 and mTORC2, which are responsible, among other things, for controlling the balance between anabolic and catabolic processes (mTORC1) and microfilament dynamics, respectively (Malik et al., 2013). Urbanska et al. (2012), Thomanetz et al. (2013), and Skalecka et al. (2016) have shown that both mTOR complexes are involved in the control of dendritogenesis of different types of neurons. During dendritogenesis, mTORC1 was found to control translation (e.g., of the GluA2 subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA]-type glutamate receptor [Koscielny et al., 2018]), regulation of microtubule-microfilament interactions (Swiech et al., 2011), or transcription (e.g., of the extracellular matrix protein CCN family member 1 [Cyr61] [Malik et al., 2013]). In contrast, actin dynamics (Thomanetz et al., 2013), control of RNA-binding protein transport along microtubules (Urbanska et al., 2017), and positive regulation of mTORC1 (Urbanska et al., 2012) were found to be effector processes supporting dendrite growth downstream of mTORC2.

In addition to the kinases described above, there are several others that control dendritic arbor growth, and a detailed description of their contribution is beyond the scope of this review. However, one family of kinases that deserves mention is the family of Ca^{2+}/calmodulin-dependent protein kinases (CamK), specifically CaMKI and CaMKIV, which link the developmental dynamics of dendritic growth to neuronal activity and cellular Ca^{2+} concentration (Redmond et al., 2002; Aizawa et al., 2004; Wayman et al., 2006; Wu et al., 2007). Neuronal depolarization leads to a massive Ca^{2+} influx, mainly through voltage-gated calcium channels. This results in rapid expansion of dendritic trees of cortical and hippocampal neurons cultured *in vitro*. The expansion depends on the activation of CamKI and CamKIV and changes in transcription controlled by the transcription factor cAMP response element-binding protein (CREB) and chromatin-modifying enzymes, e.g., calcium- responsive transactivator and 53 kDa BRG1-associated factor A (Redmond et al., 2002; Wayman et al., 2006). Most striking was the transcriptional upregulation of BDNF and the protein Wnt-2, which are known to have a growth-promoting effect on dendrites, and several regulators of actin dynamics, e.g., gelsolin, ephexin-1, and Rac GTPase-activating protein 1 (RacGAP1) downregulation (Wu et al., 2007).

Ephexin-1 and RacGAP1 are positive and negative regulators of the small GTPase Ras-related C3 botulinum toxin substrate 1 (Rac1), which is one of the three central regulators of actin dynamics along with cell division control protein 42 (Cdc42) and Ras homolog family member A (RhoA). Rac1, Cdc42, and Rho were among the first proteins shown to play a critical role in shaping dendritic arbors both *in vitro* and *in vivo* in response to trophic factors and neuronal activity (Li et al., 2002; Nakayama et al., 2000; Threadgill et al., 1997). The general principle appears to be that loss of Rac1 and an increase in RhoA activity result in the simplification of dendritic arbors (Li et al., 2002; Nakayama et al., 2000; Threadgill et al., 1997; for review Urbanska et al., 2008). In addition to actin filaments, the cytoskeleton consists of intermediate filaments and microtubules. It has been demonstrated that the process of microtubule polymerization, which alters the morphology of dendrites, contributes to the formation of the correct shape of dendritic branches (Delandre et al., 2016). Microtubules are bound by a diverse group of microtubule-associated proteins (MAPs).

MAPs have several functions, such as controlling microtubule dynamics, integrity, spacing, and microtubular transport. Indeed, proteins belonging to each functional category have been shown to regulate the shape of the dendritic arbor during development (e.g., CAP-Gly domain-containing linker protein 1 [CLIP-170], end-binding protein 3 [EB3], microtubule-associated protein 1B and 2 [MAP1, MAP2], motor proteins—dynein and dynactin subunits, and many kinesins [Harada et al., 2002; Sweet et al., 2011; Swiech et al., 2011; Tempes et al., 2020; Teng et al., 2001]). This exemplifies an essential role of long-distance cellular transport in supplying necessary building blocks for dendrite formation, such as organelles, proteins, and mRNA. However, it should not be forgotten that microtubular transport in axons plays a role in controlling dendritic arbor morphology. It has been demonstrated that disruption of the retrograde transport of TrkB, beta-secretase 1, or Plexin A in axons leads to severe impairment of dendritic trees (Wang et al., 2012; Yamashita et al., 2014; Kononenko et al., 2017). In summary, for this part of the review, the developmental dynamics of dendritic arbors involve the growth of new branches and their stabilization or elimination. These processes involve highly coordinated activities of large protein networks that control almost every aspect of cell function.

Maturity and aging

Already during the very dynamic development of the dendritic tree described above, some dendrites are stabilized and their growth restricted. It is recognized that neuronal activity is essential for den-

drite stabilization, particularly after the first contact between dendritic filopodium and axon, which initially might be stabilized only by mechanical forces (Heiman and Shaham, 2010). Ca^{2+} is one of the major mediators of the stabilization signal (Lohmann et al., 2002). It has been demonstrated that calcium-induced calcium release is a major event contributing to the local stabilization of a given dendritic branch. Among channels that allow Ca^{2+} entry in response to neuronal stimulation are N-methyl-D-aspartic acid (NMDA) type glutamate receptors, which have been shown to be critical for dendritic arbor growth and stability, at least in *Xenopus leavis* (Sin et al., 2002). It is believed that NMDA receptor activity eventually brings AMPA receptors to the synapse, resulting in synapse maturation and dendritic arbor stabilization (Haas et al., 2006). From this point of view, CamKIIα is worth mentioning because it is one of the critical, calcium-dependent kinases involved in synaptic plasticity and AMPA receptor regulation. Like the other proteins in this family, the activity of CamKIIα is regulated by calcium ions. Expression of CamKIIα occurs relatively late in development, at the stage when dendritic trees emerge from a phase of dendritic growth. Interestingly, the pioneering studies of Wu and Cline (1998) showed that overproduction of CaMKIIα in neurons of the *Xenopus leavis* optic tectum during a phase of high dynamics of the dendritic trees leads to their reduction in size and the "freezing" of their morphology. Intriguingly, CamKIIβ protein may be involved in restricting dendritic growth or dendritic branch elimination in the cerebellum, also in a Ca^{2+}-dependent manner. CamKIIβ forms a complex with the channel named short transient receptor potential channel 5, which induces Cdc20-APC E3 ligase, and this pathway restricts dendritic arbor stability (Puram et al., 2011). Another mechanism, acting downstream of neurotransmitters that is likely key to dendritic arbor stabilization is the inhibition of RhoA signaling (Sin et al., 2002), which may act as a destabilizing factor either directly through the control of actin cytoskeleton dynamics (see above) or, for example, by regulating levels of cytosolic PSD-95 interactor (cypin) (Chen and Firestein, 2007). Additional mechanisms described thus far in vertebrates as restricting dendritic growth and promoting the phase of stability are contact inhibition *via* Notch signaling (Sestan et al., 1999) and dendritic distribution of mitochondria (Kimura and Murakami, 2014). In the latter case, the mechanism is unclear. The authors suggested that mitochondria help decrease local Ca^{2+} levels to prevent growth; however, this interpretation is partially contradictory with the idea of the need for local increases in Ca^{2+} for stabilization. On the other hand, mitochondria are found in the proximity of dendritic spines and are needed for their proper functioning and response to synaptic stimulation (Li et al., 2004), which could be a reason for stalling dendritic growth.

While in the early stages of dendritic tree stabilization, there is a strong correlation between the number of synaptic connections and their activity (as discussed above), in later stages, there is probably partial deconsolidation of synaptic and structural plasticity at the level of dendritic spines and dendritic tree stability. This is exemplified by several *in vivo* imaging studies of dendritic spines in adult brain showing high stability of dendritic arbor morphology regardless of the constant turnover of spines (Trachtenberg et al., 2002; Holtmaat et al., 2005; Majewska et al., 2006; Xu et al., 2009; Yang et al., 2009). This seems justified by the need to maintain the overall network of neuronal connections while allowing individual connections to change, both by creating new connections and by removing old ones. However, as described below, strong activation of selected neuronal circuits and their deactivation may lead to more global changes in the number or orientation of dendrites of individual neurons. Fig. 1B shows the main factors affecting dendrite stabilization and physiological and pathological plastic changes of dendrites in mature neurons.

Although the shape of the dendritic tree of most neurons, once achieved, is considered stable even over the years, it should be stressed that our knowledge of this fact usually comes from fixed material, which is inherently not optimal for the analysis of dynamic processes. However, a few examples of long-term *in vivo* imaging of dendritic tree dynamics give us a better sense of dendritic arbor changes in adulthood. Nevertheless, it should be kept in mind that these observations are often limited to a few structures (e.g., olfactory bulbs [OB], upper layers of cortex, rarely hippocampus), neuron types, and even fragments of neuronal dendritic trees (e.g., apical tufts of cortical neurons). One of the very first long-term imaging studies of dendritic arbors *in vivo* was performed by Mizrahi and Katz (2003), who imaged dendrites of mitral and tuft cells of the olfactory bulb in adult mice under basal conditions for several weeks. The unique feature of the dendritic arbors of these cells is that newly generated adult-born cells reaching the olfactory bulb continuously form synapses with them. At the same time, many synapses are lost due to the extinction of older adult-born neurons (~50% of cells reaching OB). In this way, mitral and tuft cell dendrites gain and lose hundreds of synapses daily. Nevertheless, results described by Mizrahi and Katz (2003) showed that the general architecture of these dendritic arbors remained stable for weeks. When the cells

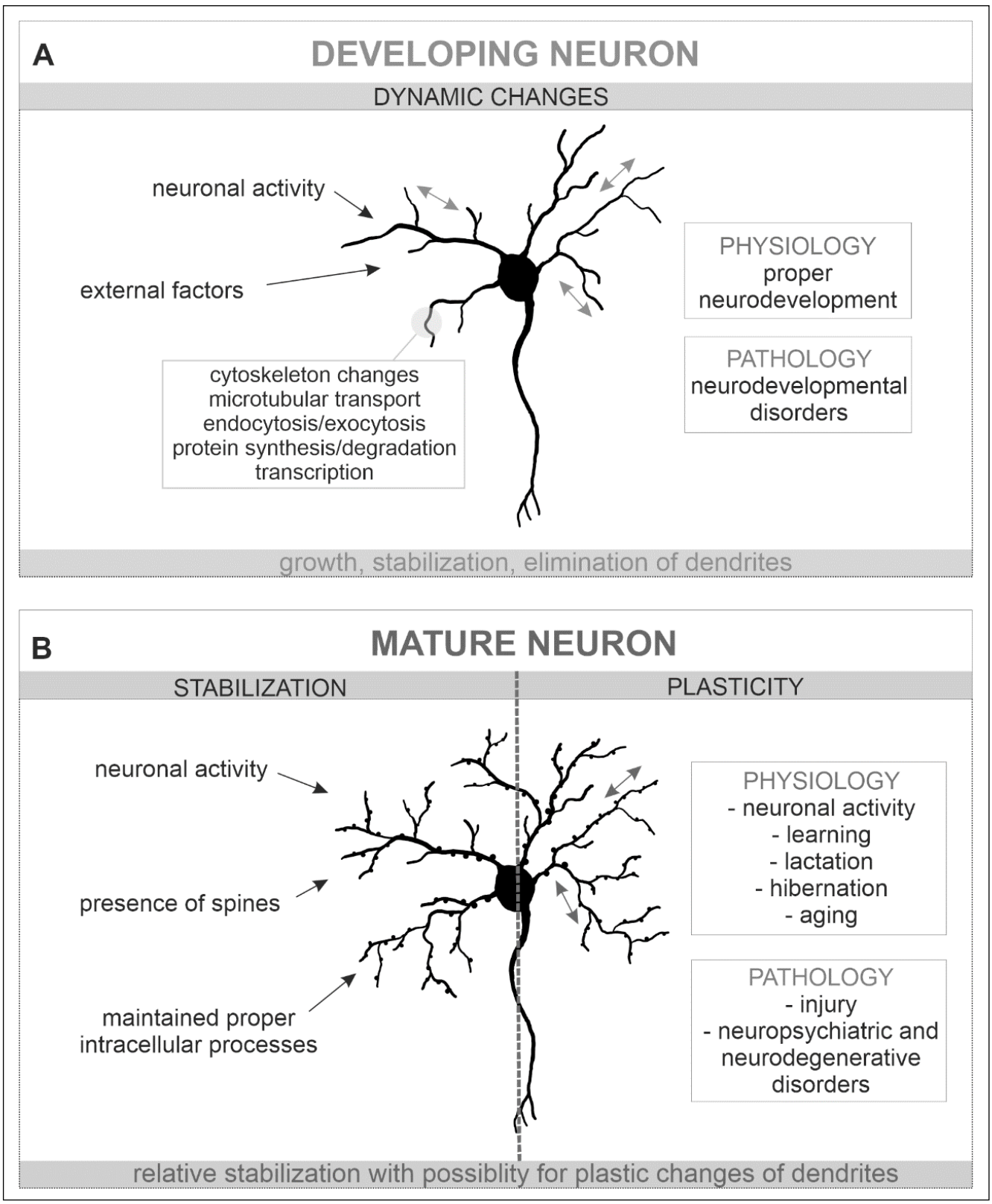

Fig. 1. Growth, stabilization, and plastic changes of the dendritic tree in the development and maturity of the neuron. (A) Diagram depicting the factors and mechanisms of dynamic changes of dendrites at the stage of neuron development. (B) Left: examples of factors supporting the stability of dendritic morphology in a mature neuron; Right: examples of physiological and pathological processes associated with destabilization/plasticity of dendrites in mature neurons.

were imaged at 24-hour intervals, virtually no change was detected. At four-week intervals, subtle dynamics were observed in the shortest, most distant branches. Housing in an enriched environment or learning odors did not change the limited dynamics observed under baseline conditions. It should be noted, however, that when bicuculline, a drug used for disinhibiting the neuronal networks, was administered directly to the olfactory bulb, the dynamics of these most distant branches increased, demonstrating that robust neural network activation can induce some plasticity of dendritic branches. However, experiments performed by Mizrahi (2007) a few years later proved that mature neurons differ in terms of the dynamics of dendritic branches even when the brain structure is the same. Mizrahi (2007) performed long-term imaging of the dendritic arbors of a different group of neurons of the OB, namely adult periglomerular neurons (PGNs) and granular cells (GCs). Because these neurons could be imaged for several days from the day they arrived at OB, Mizrahi made several groundbreaking observations. First, he showed that the dendritic branches of non-spiny and spiny PGNs exhibit different dynamics during development, with the first group being very dynamic. One month after their arrival, OB PGNs and GCs developed a mature morphology, but the dynamics of their arbors' dynamics differed significantly. While PGNs remained dynamic with several daily additions and retractions, especially of distal segments, GC dendrites did not change, and dynamics were restricted to dendritic spines. Differences in the basal dynamics of dendritic arbors of mature neurons of different classes have also been described for the primary visual cortex. Lee et al. (2006) reported that dendrites of layer II/III pyramidal neurons remained virtually unchanged throughout the imaging period (nine weeks). At the same time, dendritic arbors of γ-aminobutyric acid (GABA)-ergic interneurons were quite dynamic, and several imaged branches changed their lengths during a four-week imaging session. The changes involved higher-order dendrites, and each of the imaged nonpyramidal neurons exhibited at least one change. Overall, the authors calculated that up to 14% of the imaged dendrites changed. Most of the changes were lengthening or shrinking, whereas additions or retractions were rare. Length changes ranged from quite subtle, such as 10 μm, to quite large, e.g., >92 μm. A follow-up study revealed that dynamic dendritic arbors are a general feature of cerebral cortex interneurons residing not only in the primary visual cortex but also in secondary visual as well as primary somatosensory cortices (Chen et al., 2011). Also, in this case, the stable neurons were spiny, whereas the dynamic ones were not, or they contained only sparse spines, suggesting that there may be a causal relationship between the overall dynamics of the dendritic branches and the presence of dendritic spines.

The above live-imaging examples examined basal turnover of dendritic branches in adult neurons. However, even before the era of 2-photon imaging of the live brain, it was known from fixed specimens stained by the Golgi impregnation method that even these stable dendritic arbors changed their morphology in response to experimental conditions such as an enriched environment, modulation of sensory inputs, and learning tasks. For example, in the brains of cats and rats housed in an enriched environment, dendrites were longer, and arbors were more complex in many brain areas (e.g., sensory and motor cortex) when compared to animals housed under standard conditions (Hickmott and Ethell, 2006). Evidence for the link between task learning and remodeling of mature dendritic arbors comes from analyzing the cerebral cortices of animals undergoing sensorimotor learning. For example, the number and length of most terminal branches of apical dendritic arbors of neurons within layer V motor-sensory forelimb cortex was found to be increased in the sensorimotor cortex of rats trained to reach food with the contralateral forepaw (Greenough et al., 1985). On the other hand, several studies have shown that loss of neural stimulation leads to simplification of dendritic arbors (Hickmott and Ethell, 2006; Dunaevsky and Woolley, 2007). However, loss of sensory input does not necessarily lead to simplification of the arbors of deprived cells. For example, deafferentation of selected vibrissae in rats caused reorientation of the dendritic branches of relevant neurons in barrel cortex without an overall loss of dendritic length or complexity (Tailby et al., 2005). In addition to experimentally-induced plasticity, there are examples of substantial rearrangements of dendritic arbor morphology in response to physiological stimuli, particularly during late pregnancy and lactation. This involves two types of neurons within the supraoptic nucleus. For example, the total dendritic length of oxytocin and vasopressin neurons was shown to decrease and increase, respectively, by approximately 40–50% during lactation. The change in total length was not due to dendritic elongation or shrinkage but rather resulted from the addition and retraction of entire dendritic branches (Stern and Armstrong, 1998). The exact reasons for these changes are not known, but it has been speculated that they help increase the synchronized firing of neurons and are required for proper lactation (Dunaevsky and Woolley, 2007).

After a long period of relative structural stability, changes in dendritic branching again become appar-

ent as the brain ages. Unlike development, however, dendrite distortions, shortenings, and retractions are more likely to be observed. Often, these changes appear to correlate with changes in morphology or loss of dendritic spines. All of these changes lead to a general deterioration of neuronal network connectivity, and Scheibel (1979) suggested that the degree of dendritic arbor simplification is not directly reflected by the age of the individual but rather corresponds to the degree of deterioration of cognitive functions. Scheibel (1979) used the Golgi-Cox impregnation method to analyze the cytoarchitecture of the hippocampus and entorhinal cortex of aging human brains and showed that in the case of the pyramidal neurons of the hippocampus, the cells first lose their spines, especially at their basal dendrites, which are eventually lost as well. The apical arbors are more stable, but in the late stages of aging, only the most proximal segments remain. In the case of dentate gyrus granule cells, lacking basal dendritic branches, the apical dendritic arbor progressively deteriorated, losing more distal branches and shrinking the proximal ones. Similar changes have been observed in different areas of the human cerebral cortex, and in the case of spiny neurons, the loss of dendrites was always accompanied by a substantial reduction in dendritic spines (Dickstein et al., 2007). These changes are not specific to humans but have also been observed in nonhuman primates, dogs, and rodents, with some deviations from the general pattern that was brain area-specific (Grill and Riddle, 2002; Dickstein et al., 2007). The Mizrahi group presented an interesting perspective on the simplification of dendritic arbors during aging. Seeking to determine whether dendritic arbor simplification is an intrinsic feature of aging neurons or rather a response to the aging environment, they compared the dendritic dynamics of young and old neurons arriving in the OBs of aging mice. As a result, Livneh and Mizrahi (2011) showed that young and old neurons had similarly simplified dendritic arbors, suggesting that the "old" environment determines the simplification of dendritic branches in OB during aging.

From a molecular perspective, there are two major unanswered questions about the stability and dynamics of mature dendritic arbors. First, what makes them so stable, and second, what must change for the structural plasticity of dendritic trees to be reactivated in response to sensory stimulation or learning? Finally, it is unknown what happens during aging-failure of the stability mechanism or reactivation of plasticity. Unlike development, knowledge of the molecular mechanisms underlying stability and dynamics in aging is almost nonexistent, and it is difficult to paint a comprehensive picture. However, Koleske (2013) made such an attempt in his comprehensive review of the literature, which led to the conclusion that the key to the stability of mature dendritic branches lies in the balance between stability and dynamics of the cytoskeleton, in particular, the microtubules. The other important and not mutually exclusive mechanism involves the stability of dendritic spines and proper neuronal activity patterns. The best-characterized signaling cascades for stabilizing mature dendrites include TrkB, integrins, and Wnt5A (Koleske, 2013; Chen et al., 2017). The activity of these signaling pathways is required to regulate the activity of proteins that regulate RhoA, Rac1, and Cdc42, ensure appropriate modification of microtubule-associated proteins and correct cellular localization and/or expression levels of NMDA and AMPA glutamate receptors (Koleske, 2013; Chen et al., 2017). Thus, loss of TrkB, Wnt5, or selected integrins in mature neurons simplifies the dendritic arbors of cortical and/or hippocampal neurons *in vitro* and *in vivo* (Koleske, 2013; Chen et al., 2017).

Some other cellular processes, such as the proper transport of proteins through the endosomal system or effective proteasomal degradation, are also crucial for dendritic stability (Bobo-Jiménez et al., 2017; Firkowska et al., 2019). The latter case is interesting as it points again to the control of the outcome of RhoA activity as an essential mechanism to ensure stability. Bobo-Jiménez et al. (2017) demonstrated that the presence of Cdc20 homolog 1 (Cdh1), a regulatory subunit of the APC/C ubiquitin E3 ligase, is essential for maintaining low levels of Rho-associated protein kinase 2, a substrate of RhoA, and for maintaining the stability of the dendritic arbor. Thus, several mechanisms underlying dendritic growth during development are later reused to maintain stability. This raises the question of how dendritic growth can be reactivated in mature neurons, for example, in the situations described above. This issue is even less explored than the stability of dendritic arbors. However, our studies show that the additional activity of proteins that strongly affect dendritic branching in young neurons may not be sufficient to reactivate growth in adult cells. For example, one-week overexpression of active PI3K in mature neurons, which is likely one of the strongest drivers of dendritic growth in young neurons reported in the literature to date, was not sufficient to reactivate dendritic growth (Jaworski et al., 2005). It should be noted, however, that although proteins such as PI3K or mTOR cannot further stimulate the growth of mature neurons, they are still required for stability. Our unpublished data clearly showed that knockdown of mTOR or its interactor—Raptor, in mature hippocampal neurons cultured *in vitro,* led to

simplification of the dendritic arbor (Fig. 2). Interestingly, during development, these proteins control the growth of new branches, but not the stability of existing ones (Urbanska et al., 2012), suggesting that their function changes in mature neurons.

There are more examples of molecules whose decrease or increase can trigger dendritic plasticity in adults. An interesting example is the schizophrenia-related protein Reelin. Surface expression of Reelin increases in cultured hippocampal neurons

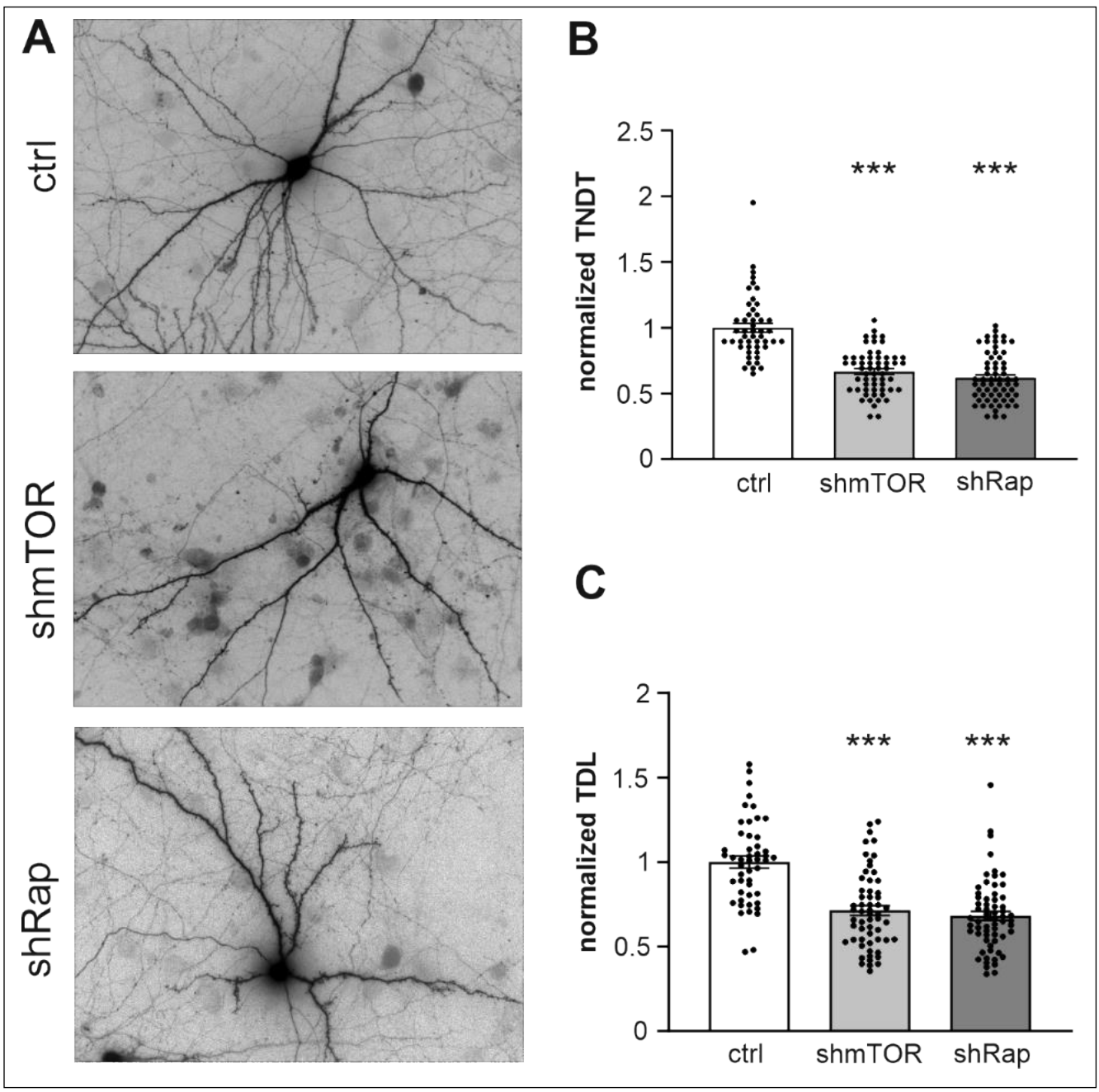

Fig. 2. Loss of mTORC1 in cultured mature neurons leads to simplification of dendritic arbors. (A) Representative micrographs of cultured mature rat neurons, transfected on day *in vitro* 22 (DIV22) with plasmids encoding shRNA against mTOR (shmTOR), or Raptor (shRap) mRNA (Jaworski et al., 2005; Urbanska et al., 2012) and the plasmid encoding GFP for morphology visualization. Cells were fixed 3 days post-transfection. (B) Quantitative analysis of the total number of dendritic tips (TNDT) and total dendrite length (TDL) performed as described in Urbanska et al. (2012). Data are presented as mean ± SEM. Number of independent experiments *N*=3. Number of analyzed cells pSuper (ctrl, 49), shRNA mTOR (58), and shRNA Raptor (63). **p*>0,001, Kruskal-Wallis test followed by Dunn's multiple comparison *post-hoc* test.

as they mature, peaking around day 20 *in vitro* (Ampuero et al., 2017), when dendritic branches are no longer dynamic. However, disruption of Reelin signaling, e.g., by neutralizing antibodies, reactivated dendritic growth in mature neurons. Simultaneously, loss of postsynaptic density protein 95 (PSD95) and mature dendritic spines was observed, again linking dendrite stabilization to mature synapses in spiny neurons. The case of Reelin is particularly interesting because the loss of this protein in developing neurons prevents dendritic growth (Jossin and Goffinet, 2007). Thus, Reelin is an example of a protein that may have opposing functions in regulating the dynamics of dendritic trees, depending on the age of the neurons. Another example of growth reactivation comes from our studies in which we increased dendritogenesis in mature neurons by overexpressing Cyr61, which interacts with integrin receptors (Malik et al., 2013). Further studies are needed to identify additional such proteins. An interesting observation is that the signals that provide stability and dynamics can come from multiple sources. For example, Reelin, which inhibits dendritic plasticity in mature pyramidal cells, is probably secreted by GABAergic neurons (Ampuero et al., 2017).

Pathological instability of dendritic trees

Developmental disorders

The instability of dendritic trees during development is an inherent part of this process, which is required for the proper formation of neuronal circuits. Consequently, many neurodevelopmental disorders or their animal models are associated with a number of changes in dendritic arbor morphology. Particular attention has been paid to the morphology of dendritic arbors in individuals with intellectual disability and/or autism. Initial observations on postmortem brain material from patients revealed reduced dendrites in the prefrontal cortex (Mukaetova-Ladinska et al., 2004) and hippocampus (Raymond et al., 1996). At the same time, increased spine density has been observed in certain areas of the brain of patients with autism spectrum disorder (ASD) (Hutsler and Zhang, 2010). Similar observations were made in autism mouse model strains (e.g., C58/J; Barón-Mendoza et al., 2019). This led to an initial generalization of these symptoms to all ASD types. However, ASD is a very complex group of developmental disorders defined by common clinical criteria, such as atypical development in the areas of socialization, communication, and behavior, rather than by common genetics. Analysis of several mouse models of ASD, particularly so-called "syndromic ASD," i.e., neurodevelopmental disorders with a high penetrance of ASD diagnosis (Geschwind and Levitt, 2007; Levitt and Campbell, 2009), revealed all types of alterations in the shape of dendritic arbors and the number and morphology of dendritic spines. These included reduced or increased dendritic branching with associated changes in spine morphology or lack thereof (Kulkarni and Firestein, 2012). In addition, careful analysis of different brain regions revealed that the absence of the same gene, for example, *Tsc1,* that causes Tuberous Sclerosis Complex (TSC; see below) can lead to an increase, decrease, or no change in dendritic branching depending on the brain region (e.g., striatonigral neurons of the direct pathway [dSPN] *vs.* striatopallidal neurons of the indirect pathway [iSPNs], cerebral cortex *vs.* newborn neurons in olfactory bulb) (Zhang et al., 2014; Benthall et al., 2018; Cox et al., 2018). Although we know much about the mechanisms of dendritic arbor development, our understanding of neurodevelopmental disorders in this context is far from complete, and our interpretations may be biased by available clinical material and fragmentary analysis of existing animal or *in vitro* models.

Nevertheless, we discuss below the best-studied molecular mechanisms underlying dendritic arbor changes in disorders with ASD and intellectual disability (ID), which, given the developmental mechanisms described above, are expected to be generally associated with deregulation of cytoskeletal function, protein synthesis, molecules regulating cell adhesion, and proteins related to synaptic function. Below, we first discuss links between non- syndromic ASD risk genes and dendritic arbor abnormalities and next focus on the most common neurodevelopmental diseases associated with ASD and/or ID (see also Tables 1 and 2). Finally, we describe potential mechanisms underlying dendritic arbor changes in Down syndrome, a disease that combines features of neurodevelopmental and neurodegenerative disorders.

Autism spectrum disorders

ASD include autistic disorder ("classic" autism), Asperger syndrome, and pervasive developmental disorder-not otherwise specified (PDD-NOS). The etiology of ASD is widely studied and very complex. The cause of ASD is a combination of many effects, such as common genetic variants, environmental factors, epigenetic regulation, glial cell abnormalities, and aberrant neurogenesis (Hodges et al., 2020).

There are several examples in the literature linking risk factors for ASD with changes in dendritic arbor complexity. For example, decreased levels of

tyrosine-protein kinase MET (MET) were found in postmortem samples of ASD patients (Campbell et al., 2007), and subsequent animal studies have correlated a non-functional MET pathway as a genetic risk factor for ASD with reduced dendritic tree in the prefrontal cortex and hippocampus (Peng et al., 2016; Heun-Johnson and Levitt, 2018). Studies have shown that MET-induced development of the dendritic tree depends on the activation of the kinase itself and the activation of downstream small GTPase Cdc42 (Peng et al., 2016). Another candidate for the genetic basis of ASD is a thousand-and-one amino acid kinase 2 (TAOK2), a member of the MAP kinase family. Studies have shown that TAOK2 heterozygous and knockout mice have reduced social interactions (similar to ASD models) and reduced basal dendrites due to loss of TAOK2 kinase activity (Richter et al., 2019). The same studies showed that the loss of Taok2 is associated with a reduction in RhoA activity, contributing to the loss of spines. The study also shows that pharmacological RhoA activation rescues spine phenotypes, but whether it restores proper dendritic branching patterns remains unexplored. Mutations within the SH3 and multiple ankyrin repeat domains 3 (*SHANK3*) gene occur in patients with ASD, schizophrenia, or intellectual disability (Durand et al., 2012; Cochoy et al., 2015). Studies conducted using human induced pluripotent stem cells (IPSc) with Shank3 knockdown showed a reduced length and number of dendritic ends (Huang et al., 2019). The observed reduction of the dendritic tree may be related to Shank3's function in growth cone motility *via* an actin-dependent mechanism (Durand et al., 2012). In addition to the above-mentioned proteins, there are a number of other proteins found to be dysfunctional in ASD and ID, resulting in destabilization of neuronal morphology (Lin et al., 2016) (Table 1).

A group of neurodevelopmental diseases is often distinguished, referred to as "syndromic" ASDs, and includes Angelman syndrome (AS), Prader-Willi syndrome (PWS), TSC, fragile X syndrome (FXS), Rett syndrome (RTT), Down syndrome (DS), and PTEN hamartoma tumor syndrome (PHTS). These are neurodevelopmental disorders with a high penetration of ASD diagnosis (Geschwind and Levitt, 2007; Levitt and Campbell, 2009). The coexistence of ASD and other diseases from the group of "syndromic" ASDs is often associated with a pathology in the functioning of a specific gene/protein that can also regulate the formation of normal dendritic arbors and neuronal connections (see Table 2). Interestingly, in the case of some proteins, e.g., Ube3a, SNRP, and DYRK1, their expression seems to be dysregulated in opposite directions in ASD and "syndromic ASD." Yet, the detrimental effect on dendritic branching remains the same. While the exact reason remains unknown, it is likely that these proteins need to be either expressed at a tightly controlled level, or that cross-talk with other misexpressed genes in "syndromic" autism occurs.

Rett syndrome

The neuronal dysfunctions present in Rett syndrome (RTT) involve many areas of the brain and peripheral nervous system. Neuroanatomical research has shown that people with RTT have smaller brains, smaller dendritic trees in pyramidal neurons in certain areas and layers of the cerebral cortex, and a generally disturbed developmental pattern of receptors and neurotransmitters (Armstrong, 2002). Studies have shown that RTT is caused by mutations in the gene encoding for methyl CpG binding protein 2, MeCP2 (Amir et al., 1999). In the mouse model of the A140V MeCP2 mutation, the complexity of the den-

Table 1. ASD-associated proteins influencing dendritic arbors' morphology.

ASD-associated protein	Mechanism	Source
CTTNBP2	F-actin and microtubule cytoskeleton	(Shin et al., 2013; Shih et al., 2014, 2020)
MARK1	microtubule-dependent transport in dendrites	(Maussion et al., 2008)
ELMO1	through Rac1 activation	(Franke et al., 2012; Lanoue et al., 2013; Miryounesi et al., 2019)
Epac2	through crosstalk between Ras and Rap signaling	(Bacchelli et al., 2003; Srivastava et al., 2012)

(CTTNBP2) cortactin-binding protein 2; (MARK1) microtubule affinity regulating kinase 1; (ELMO1) engulfment and cell motility protein 1; (Epac2) exchange protein directly activated by cAMP 2.

Table 2. Syndromic ASD-associated proteins affecting dendritic arbors.

Disease	Protein level/function	Dendritic complexity	Source
FXS + RTT + ASD	KIAA2022/NEXMIF ↓	↓	(Van Maldergem et al., 2013; Gilbert and Man, 2016; Stamberger et al., 2021)
RTT + AS + ASD	MeCP2 ↓	↓	(Watson et al., 2001; Carney et al., 2003; Jentarra et al., 2010; Nguyenet al., 2012)
FXS + ASD	FMRP ↓	↓	(Thomas et al., 2008; Darnell et al., 2011; Steinberg and Webber, 2013; Jacobs et al., 2016; Utami et al., 2020)
FXS + PWS + ASD	CYFIP1 ↓	↓	(Schenck et al., 2003; Nowicki et al., 2007; De Rubeis et al., 2013; Bardoni and Abekhoukh, 2014; Pathania et al., 2014)
TSC + ASD	TSC ↓	↑	(Tavazoie et al., 2005; Numis et al., 2011; Winden et al., 2019)
PHTS + ASD	PTEN ↓	↑	(Ciaccio et al., 2019; Getz et al., 2022)
AS	Ube3a ↓	↓	(Miao et al., 2013; Khatri et al., 2018; Khatri and Man, 2019)
ASD	Ube3a ↑	↓	
AS + PWS	SNRPN ↓	↑	(Nicholls and Knepper, 2001; White et al., 2007; Li et al., 2016)
ASD	SNRPN ↑	↓	
DS	DYRK1 ↑	↓	(Martinez de Lagran et al., 2012; van Bon et al., 2016; Dang et al., 2018)
ASD	DYRK1 ↓	↑	

↑ or ↓ represents an increase or decrease, respectively; (ASD) autism spectrum disorder; (FXS) fragile X syndrome; (RTT) Rett syndrome; (PWS) Prader-Willi syndrome; (AS) Angelman syndrome; (TSC) Tuberous Sclerosis Complex; (PHTS) PTEN hamartoma tumor syndrome; (DS) Down syndrome; (MeCP2) methyl-CpG binding protein 2; (FMRP) fragile X messenger ribonucleoprotein; (CYFIP1) cytoplasmic FMR1-interacting protein 1; (PTEN) phosphatase and tensin homolog deleted on chromosome ten; (Ube3a) Ubiquitin-protein ligase E3A; (SNRPN) small nuclear ribonucleoprotein polypeptide N; (DYRK1) dual specificity tyrosine-phosphorylation-regulated kinase 1A.

dritic trees of the pyramidal neurons of the somatosensory cortex was reduced (Jentarra et al., 2010).

The correct function and amount of the MeCP2 protein are essential during development and for maintaining normal neuronal connections. MeCP2 seems to act on both transcriptional and post-transcriptional levels. For example, increased expression of insulin-like growth factor binding protein 3 (IGFBP3) is observed both in patients with RTT and in the brains of MeCP2-null mice, and it is associated with delayed maturation of neurons (Itoh et al., 2007). MeCP2 phosphorylation regulates BDNF transcription, suggesting that the absence of MeCP2 or mutations within MeCP2 reduces dendrite complexity (Zhou et al., 2006). Indeed, overexpression of BDNF partially reverses the dendritic atrophy caused by MeCP2 knockdown (Zhou et al., 2006; Nerli et al., 2020). But, the loss of MeCP2 in the adult brain also reduces dendritic trees (Nguyen et al., 2012). However, the observed anatomical changes were accompanied by a decrease in the level of dendritic and synaptic proteins (e.g., CaMKII α/β, GluA2/3[AMPA receptor subunits], GluN2A [NMDA receptor subunit], vesicular glutamate transporter [Vglut], and Synapsin) but not the level of mRNA for these proteins (Nguyen et al., 2012).

Fragile X syndrome

At the molecular level, Fragile X syndrome (FXS) is caused by an expanded CGG repeat (> 200 repeats) in the 5' untranslated portion of the fragile mental retardation 1 gene (*FMR1*). These mutations lead to lower expression or absence of the Fragile X messenger ribonucleoprotein 1 (FMRP) (Hagerman et al., 2010). FMRP is an RNA-binding protein that regulates translation (Bassell and Warren, 2008). Lack of FMRP-mediated translation affects many genes (Gross et al., 2012) essential for neuronal development and function. Imaging studies in patients with FXS showed neuroanatomical differences (reduced white matter volume in different brain regions) that correlated with the degree of ID and with reduced levels of FMRP (Sandoval et al., 2018). The lack of FMRP in rodents impaired the formation of correct synapses and their plasticity (Bassell and Warren, 2008; Dictenberg et al., 2008; De Rubeis and Bagni, 2010). Knockout of *Fmr1* changed the dendritic tree by reducing the growth rate and incorrect pruning of the dendritic ends in mouse neurons (Thomas et al., 2008).

Studies have shown that FMRP, in cooperation with kinesins, participates in the transport of mRNA

(for MAP1b and CAMKIIα) within dendrites, which may be the main reason for the reduction of the dendritic tree in the absence of proper FMRP activity (Dictenberg et al., 2008). Another direct target of FMRP is TAOK2 mRNA. Consequently, abnormalities in the amount of TAOK2 protein described in section 5.1.1 are associated not only with ASD but also with FXS (Darnell et al., 2011). One of the FMRP interactors is cytoplasmic FMRP-interacting protein 1 (CYFIP1), the reduction of which is observed in patients with FXS, ASD, and PWS (Nowicki et al., 2007; Bardoni and Abekhoukh, 2014). Interestingly, decreased levels of Cyfip1 mRNA correlated more strongly with FXS with the Prader-Willi phenotype (PWP) than in the FXS phenotype alone (Nowicki et al., 2007). Studies with neurons cultured *in vitro* have shown that the appropriate Cyfip1 level during development regulates the complexity of the dendritic tree and determines its maintenance (Pathania et al., 2014). Curiously, it was also demonstrated that the presence of astrocytes lacking FMRP in neuronal cultures caused a reduction of dendritic trees in neurons (Jacobs et al., 2016), suggesting that not only problems with FMRP-dependent translation in neurons contribute to the clinical outcome of the disease.

mTORopathies

Mutations in genes of proteins that regulate the function of the aforementioned mTOR kinase lead to severe neurodevelopmental disorders collectively referred to as mTORopathies (Crino, 2011). Mutations in the tuberous sclerosis complex genes—*TSC1* and *TSC2*, phosphatase and tensin homolog (*PTEN*), or neurofibromin (*NF1*)—lead to hyperactivation of mTORC1, resulting in multisystemic developmental disorders that severely affect the nervous system. Symptoms of mTORopathies include brain tumors, macrocephaly or more subtle disorganization of brain tissue cytoarchitecture, epilepsy, ASD, ID, attention deficit hyperactivity disorder (ADHD), and various other neuropsychiatric symptoms (Karalis and Bateup, 2021).

TSC is a multisystem disease caused by mutations in the *TSC1* or *TSC2* genes, which encode hamartin or tuberin, respectively, forming the TSC1-TSC2 complex (Switon et al., 2016). Loss-of-function mutations in these genes result in constitutively active mTORC1 (European Chromosome 16 Tuberous Sclerosis Consortium, 1993; van Slegtenhorst et al., 1997). The characteristic feature of TSC is disorganized cytoarchitecture of the cerebral cortex resulting from impaired differentiation, migration, and maturation of neurons (Mizuguchi and Takashima, 2001). One of the most common changes is cortical tubers, which contain enlarged and dysplastic glial and neuronal cells (Grajkowska et al., 2010). However, dysmorphic neurons are also found outside the tubers, although to a lesser extent (Marcotte et al., 2012). In TSC patient-derived neurons and neurons from mice (from conditional *Tsc*- KO mice or with TSC knockdown), several morphological and functional features reminiscent of changes in patients' brains have been described (Switon et al., 2017; Bassetti et al., 2021). A commonly observed morphological abnormality is increased complexity of the dendritic tree (but see Benthall et al., 2018), the degree of which correlates with the hyperactivity of mTORC1 (Winden et al., 2019). In several cases, dendritic abnormalities could be reversed by the use of mTORC1 inhibitors, like rapamycin. *In vivo* studies have shown that early (but not late) administration of rapamycin inhibited the abnormal growth of the dendritic tree caused by Tsc1-suppression (Cox et al., 2018). However, another study has shown that the increased growth of dendrites in TSC is not exclusively mTOR-dependent but is also associated with increased levels of filamin A (FLNA) (Zhang et al., 2014). FLNA is a key protein for actin cytoskeleton assembly (Vadlamudi et al., 2002), and its overexpression has been shown to cause an abnormal increase in dendrite tree complexity in a mitogen-activated protein kinase (MEK)-extracellular signal-regulated kinases ½ (ERK1/2)-dependent manner (Zhang et al., 2014).

Loss-of-function mutations in *PTEN* lead to multisystem diseases known as PTEN hamartoma tumor syndrome (PHTS) (Pilarski, 2019). Patients with PTEN dysfunction exhibit multiple neuroanatomical alterations such as megacephaly, tumors, and neuropsychiatric symptoms such as epilepsy, ID, and ASD (Ciaccio et al., 2019; Plamper et al., 2020). PTEN inhibits the PI3K-AKT-mTOR pathway, and the loss of its function results in constitutively active mTORC1 (Song et al., 2012). Several studies in mouse models have shown that loss of PTEN function leads to an increase in the number of dendrites (Kwon et al., 2006; Getz et al., 2022). As a result, the overgrowth of dendritic arbors is sensitive to mTOR inhibitors (Tariq et al., 2022). However, mTOR-independent mechanisms may also be involved in pathological dendritic overgrowth. In mouse PTEN-KO neurons, new branch formation was increased, likely due to increased microtubule polymerization in dendritic growth cones. While microtubule polymerization in PTEN-KO cells was insensitive to mTOR inhibition, correction of microtubule dynamics with the use of vinblastine counteracted the dendritic arbor changes (Getz et al., 2022). The authors, therefore, postulated that PTEN controls proper arborization through parallel control of mTORC1 and microtubule polymerization.

Neurofibromatosis 1 (NF1) is a disorder associated with loss of function mutations in *NF1* encoding neurofibromin, which is a GAP for Ras. It leads to macrocephaly and tumor formation in both the central and peripheral nervous systems (Nix et al., 2020). Studies in human cells as well as animals have shown that decreased or absent function of neurofibromin leads to overactivity of mTOR (Johannessen et al., 2005), which could potentially cause excessive dendrite growth. However, other signaling pathways have previously been shown to regulate neuronal morphology in response to loss of neurofibromin (Báez-Flores et al., 2023). For example, in growing neurites, neurofibromin regulates phosphorylation of collapsin response mediator protein-2, CRMP-2, an actin cytoskeleton modulator, by kinases other than mTOR, e.g., cyclin-dependent kinase 5, glycogen synthase kinases 3β (GSK3β), and Rho kinase (Patrakitkomjorn et al., 2008). Loss of neurofibromin increased neurite growth in PC12 cells, suggesting that CMRP-2 and its phosphorylation may be important for dendrite growth, which was later confirmed (Niisato et al., 2013; Jiang et al., 2020). Other studies have also shown that neurofibromin can regulate dendrite growth by reducing the activity of the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA)/Rho/Rho-associated protein kinase (ROCK) pathway (Brown et al., 2012). However, it should be emphasized that no changes in dendritic branching have been demonstrated after the loss of neurofibromin in either human samples or mouse models (Zhu et al., 2001), although it does lead to impaired dendritic spine number and plasticity in response to long-term potentiation (Oliveira and Yasuda, 2014).

Down syndrome

Down syndrome (DS) is caused by the triplication of chromosome 21 (Hughes-McCormack et al., 2020). Dysfunction occurs in numerous organs, including brain, resulting in a combination of abnormalities bordering neurodevelopmental and neurodegenerative disorders, leading to ID. Both impaired neurogenesis in the prenatal period and maturation of neuronal connections in early postnatal life have been implicated as causes of ID in DS (Stagni et al., 2018). In addition to the fact that impaired neurogenesis results in a reduced number of cells in the brain, individuals with DS are characterized by reduced neuronal connectivity associated with shorter dendrite length and a reduced number of synapses (Becker et al., 1986, 1991; Bartesaghi, 2022). Research on anatomical and functional neuronal disturbances carried out on human material and on animal models (Bartesaghi, 2022) made it possible to learn about some mechanisms associated with intellectual disability. One of the proteins whose expression is increased in the brains of DS patients is the Down syndrome cell adhesion molecule (DSCAM), which is known to have an inhibitory effect on synaptogenesis and neurite growth (Benavides-Piccione et al., 2004). Experiments on hippocampal neurons using Ts1Cje mice (a mouse model of DS) have shown that NMDA receptor-mediated regulation of DSCAM translation can contribute to dysfunctional changes in dendrite branching in DS patients (Alves-Sampaio et al., 2010). Another protein overexpressed in DS brains is the human minibrain homolog, also known as dual-specificity tyrosine-regulated kinases 1A (MNBH/DYRK1) (Guimera et al., 1999; Dowjat et al., 2007). Overexpression of DYRK1 in mouse cortical neurons impaired dendrite elongation, which also correlated with reduced actin dynamics (Martinez de Lagran et al., 2012). On the other hand, another study has shown that DYRK1 kinase (and its homolog in *Drosophila melanogaster* – MNB) binds to microtubules and is responsible for phosphorylation of β-tubulin, which decreases microtubule polymerization (Ori-McKenney et al., 2016). In *Drosophila*, overexpression of wild-type MNB, but not the kinase-dead version, resulted in the simplification of dendritic arbors of *da* (dendritic arborization) neurons (Ori-McKenney et al., 2016). However, whether this mechanism contributes to the simplification of dendritic branches in mammals is unknown.

Psychiatric diseases

Depression and stress

Depression (Major Depressive Disorder, MDD) is characterized by persistent negative thoughts and emotions that adversely affect motivation, mood, and cognitive capabilities. Brain imaging of patients with MDD has proven that depression is associated with disrupted connections involving many brain structures, like amygdala, thalamus cortex, and hippocampus (Palmer et al., 2015; Hao et al., 2020). Postmortem brain tissue examination of MDD patients has shown reduced dendrites in the prefrontal cortex (Cotter et al., 2002; Drevets et al., 2008; Kang et al., 2012), reduced hippocampal volume (Stockmeier and Rajkowska, 2004; Drevets et al., 2008), increased volume of the lateral nucleus of the amygdala (Rubinow et al., 2016), and diminished arborization of apical dendrites in the subiculum (also observed in patients with schizophrenia [Rosoklija et al., 2000]). Both classical antidepressants (e.g., fluoxetine or paroxetine)

as well as unconventional ones, e.g., psychedelics, increase the dendritic arborization. These effects likely result from the upregulation of pro-dendritic growth signaling pathways such as Akt-mTOR-S6K (ketamine and agmatine [Freitas et al., 2020]) and BDNF (fluoxetine, paroxetine, and sertraline; Seo et al., 2014), as well as pro-neuroplastic mechanisms involving activity-regulated cytoskeleton-associated protein (Arc) and BDNF upregulation (psilocybin and lysergic acid diethylamide [LSD] [Calder and Hasler, 2023]). Depression is caused by a combination of endogenous and environmental factors (Nabeshima and Kim, 2013). Among the most postulated causes of depression are chronic stress and disturbances in the levels of neurotrophic factors, monoamines, or neurotransmitters, as well as inflammatory processes.

Very often, however, these processes occur together, and it is difficult to single out just one of them. All these processes can lead to the disruption of the brain connectivity mentioned above, including a reduction in the complexity of the dendritic trees or the number of dendritic spines.

Chronic stress is one of the most cited causes of depression. Indeed, people with MDD have an overactive hypothalamic-pituitary-adrenal (HPA) axis with elevated cortisol levels (Young et al., 1991). Many animal models are based on inducing symptoms reflective of depression by exposure to prolonged stressors, including immobilization, the presence of an intruder, deprivation, isolation, or change in environment (Willner, 2016; Atrooz et al., 2021). In rodents, such chronic stress causes a reduction in the dendritic arbors in similar brain regions as depression in humans, e.g., dendritic atrophy of *Cornu Ammonis 3* (CA3) and pyramidal neurons of the hippocampus (Vyas et al., 2002; Drevets et al., 2008). However, the stress-induced reduction of dendritic arborization may vary between models because the effect greatly depends on the intensity and duration of stress (summarized by Qiao et al. [2016]). Interesting correlations between MDD, stress, reduction of the dendritic tree, and regulation of gene expression have been noted. For example, increased expression of the transcriptional repressor GATA-binding factor 1 (GATA1) was observed in postmortem prefrontal cortex samples from MDD patients. Studies in rats showed that overexpression of GATA1 resulted in reduced dendritic arbors and depressive behavior (Kang et al., 2012; Choi et al., 2014). On the other hand, gene expression profiling revealed decreased expression of nuclear pore glycoprotein p62 (*NUP62*) in the prefrontal cortex of individuals with MDD. NUP62 is a protein involved in nuclear transport and regulation of chromatin structure. These two functions have a significant impact on gene expression. Studies in rodents exposed to chronic immobility stress provided more detailed insight into the regulation of Nup62 expression and cellular localization. In stressed animals, less Nup62 mRNA was translationally active, resulting in lower Nup62 protein levels in cells. In addition, stress-induced activation of protein tyrosine kinase 2 (Pyk2), the upstream kinase of Nup62, caused redistribution of remanent Nup62 from the nuclear envelope to the cytoplasm. Subsequent experiments in cultured hippocampal neurons showed that knockdown of Nup62 resulted in simplification and shortening of dendritic branches (Kinoshita et al., 2014), suggesting that prolonged stress *via* Pyk2-NUP62 may lead to the dendritic arbor changes observed in MDD patients.

GSK3β is another interesting protein linking stress, depression, and the reduction of the dendritic tree. Studies on post-mortem samples from prefrontal cortex (Karege et al., 2007) and platelets of depressed patients (Diniz et al., 2011) also showed increased GSK3β activity. Increased activity of GSK3β was reported upon chronic stress (Park et al., 2011), and silencing of the GSK3β activity caused antidepressant-like effects in stressed mice (Omata et al., 2011). Mice constitutively and postnatally expressing the active form of GSK3β in neurons had reduced neuropil due to dendritic length reduction (Spittaels et al., 2002). In hippocampal cultures, the increased level of GSK3β also led to the reduction of the dendritic tree, and the inhibition of GSK3β activity stimulated the growth of dendrites (Rui et al., 2013). Interestingly, different classes of antidepressants (like selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], monoamine oxidase inhibitors [MAOIs] or ketamine) show inhibitory effects on GSK3β (summarized in Duda et al. [2020]). GSK3β is a regulator of many proteins involved in the functions of the cytoskeleton and receptor trafficking, thereby regulating the dynamics of dendrites and dendritic spines (Cymerman et al., 2015; Hajka et al., 2021). For example, one of its substrates, Rho GTPase-activating protein 190 (p190RhoGAP), is important for the stability of dendritic trees in mature neurons (Sfakianos et al., 2007). Also, it has been demonstrated that GSK3β-driven phosphorylation of Arc primes it for degradation (Gozdz et al., 2017). Intriguingly, Arc regulates both actin dynamics and synaptic expression of AMPA receptors (Nikolaienko et al., 2018).

The neurotrophic hypothesis of MDD states that a deficiency of growth factors in the brain underlies the development of the disease (Amidfar et al., 2021). Indeed, MDD patients exhibit decreased levels of BDNF in hippocampus and prefrontal cortex (Duman and Monteggia, 2006). In animal models of depres-

sion, stress and corticosterone can decrease BDNF levels in some parts of the brain, e.g., hippocampus and cerebral cortex (Smith et al., 1995; Adachi et al., 2014). On the other hand, treatment with antidepressants (in patients with MDD and animal models of depression) may increase BDNF levels (Dwivedi, 2009; Duman et al., 2021). Studies in rodents show a clear link between BDNF, stress, depressive-like behaviors, and changes in dendritic branching. For example, in rats, chronic stress, on the one hand, leads to reduced BDNF levels in the hippocampus while increasing it in the amygdala. These BDNF expression changes correlated with a decrease or increase in dendritic arbor complexity in the hippocampus and amygdala, respectively (Lakshminarasimhan and Chattarji, 2012). A more causative link between BDNF, dendritic complexity, and depression was proven by selective targeting of a subset of BDNF transcripts with a long 3' untranslated region in the mouse prefrontal cortex, which led to a simplification of the dendritic tree and increased depressive-like behavior (Oh et al., 2019). Studies on rodents have also proven that BDNF is a factor in determining resistance to stress (Taliaz et al., 2011; Sweeten et al., 2019). Overexpression of BDNF in the dentate gyrus resulted in a reduction of depressive-like behaviors in mice exposed to chronic mild stress. In addition, reduced levels of corticosterone with increased levels of BDNF were also observed among young (but not adult) stressed mice (Taliaz et al., 2011). Considering the importance of this neurotrophin in dendrite growth (Licznerski and Jonas, 2018), a decrease in BDNF is considered one of the main factors for dendrite instability in depression.

Like the neurotrophic hypothesis, the monoamine hypothesis of MDD postulates that decreased levels of serotonin, dopamine, or norepinephrine contribute to the onset of the disease (Barchas and Altemus, 1999). In patients and animal models of MDD, various combinations of changes in monoamine levels are observed that may contribute to the pathophysiology of neurons and depression. In general, a decrease in all monoamines is often observed, but there are also patients in whom only one monoamine is lowered (Delgado, 2000; Jiang et al., 2022). Moreover, there are reports correlating polymorphisms in genes encoding monoamine transporters or receptors with MDD (Shao and Zhu, 2020). It should be noted that classical antidepressants target monoamine levels by either inhibiting reuptake (SSRIs, SNRIs) or monoamine oxidase (MAO), an enzyme that inactivates monoamine neurotransmitters by removing the amine group (Sanacora et al., 2004; Ramachandraih et al., 2011). Increased levels of MAO-A, an MAO brain-specific isoform, are observed in MDD patients (Meyer et al., 2006). It was shown that MAO-A is required for rapid stress-induced dendritic remodeling, and MAO-A KO mice showed no stress-induced behavioral changes or reduction in dendritic arbors (Godar et al., 2015).

In addition to the neurotrophic and monoamine hypotheses, there is also a hypothesis linking an imbalance between excitation and inhibition (E/I) in neuronal networks to the occurrence of depression. E/I abnormalities are caused by altered levels of neurotransmitters and their receptors (Krystal et al., 2002; Duric et al., 2013; Palmer et al., 2015; Wang et al., 2021), and those discussed in the context of depression include glutamate (an excitatory neurotransmitter), GABA (inhibitory neurotransmitter), serotonin, and dopamine (Wang et al., 2021). However, researchers have focused primarily on glutamate and GABA, and decreased levels of both neurotransmitters (Hasler et al., 2007) and their receptors (Sanacora et al., 2004; Feyissa et al., 2009) have been observed in various brain regions in patients with MDD. For example, glutamatergic adaptation to stress stimuli has been shown to be impaired in the medial prefrontal cortex (Cooper et al., 2021). Similar abnormalities have also been observed in stress-based rodent models of depression for both glutamatergic (Treccani et al., 2016; Elhussiny et al., 2021) and GABAergic neurotransmission (Banasr et al., 2017). Several studies have demonstrated a direct link between impaired glutamate and GABA transmission under stress and changes in dendritic tree morphology. Interestingly, it has been demonstrated that changes in the E/I balance caused by certain drugs (e.g., those targeting glutamate and GABA receptors) can produce an antidepressant effect through the following adaptive changes in neural network functioning (Krystal et al., 2002). For example, inhibition of the NMDA receptor (by CGP 43487) reversed the reduction in hippocampal apical dendrites in stressed mice (Magariños and McEwen, 1995). This observation was also confirmed with another NMDA receptor inhibitor, ketamine. One of the proposed explanations for the antidepressant effect of ketamine (and other NMDA receptor inhibitors) is its action on GABAergic neurons to restore E/I balance in depression-like brain states (Ren et al., 2016). On the other hand, ketamine increases the activity of mTORC1, which has been shown to be decreased in depression (Li et al., 2010). Generally reduced levels of activity (inhibitory and excitatory) and alterations in receptors (as seen in MDD patients) may contribute significantly to dendritic tree remodeling (Parrish et al., 2007; Redmond, 2008; Tailby et al., 2005) and the complex dependencies are still being explored.

Finally, inflammation is another factor that has been associated with MDD and prolonged stress. In-

creases in cytokines and other pro-inflammatory factors are observed in patients with MDD (Zorrilla et al., 2001; Raison et al., 2006; Osimo et al., 2020). Many studies have shown that stress leads to increased levels of corticosterone (after activation of the HPA axis), which can cross the blood-brain barrier and stimulate microglia to trigger a pro-inflammatory response in the brain (Frank et al., 2012; Grippo and Scotti, 2013). Moreover, pro-inflammatory agents have been shown to stimulate the HPA axis and enhance the stress response (Harbuz et al., 2003; Raison et al., 2010). One of these pro-inflammatory factors released by active microglia and increased in the brains of MDD patients (Himmerich et al., 2008) and mice after chronic stress (Delpech et al., 2015) is tumor necrosis factor-alpha (TNF-α). Therefore, TNF-α antagonists are being tested to treat depression (Uzzan and Azab, 2021). Similar observations have been made for interleukin 1β (IL -1β) in both MDD patients (Levine et al., 1999) and stressed animals (Nguyen et al., 1998). Interestingly, in the context of depression, both TNF-α and IL-1β have been reported to increase serotonin uptake (Zhu et al., 2006). They can also induce dendrite remodeling. Administration of TNF-α to neuronal cultures or stimulation of glial cells to produce TNF-α led to simplification of the dendritic tree through a Rho-dependent mechanism (Neumann et al., 2002). Evidence linking IL -1β to the reduction of dendritic tree complexity is more indirect. For example, IL-1β (*via* the IL1 receptor) has been linked to the downregulation of BDNF mRNA induced by isolation stress in mice (Barrientos et al., 2003). Moreover, another study has shown that knockout of interleukin-1 receptor accessory protein like 1 (IL1RAPL1), which is essential for IL1 receptor function, caused an increase in the number of dendrites (Montani et al., 2017).

Schizophrenia

Schizophrenia is a long-term mental health condition significantly impacting a patient's everyday life. Three types of symptoms may be associated with schizophrenia. The so-called positive symptoms include a distorted perception of reality (e.g., hallucinations) and resulting actions. Another group, which includes lack of motivation and anhedonia, is called negative symptoms. The third group of symptoms concerns cognitive functions such as memory or attention deficits. Several brain imaging studies and post-mortem studies have noted a significant reduction in the volume of certain brain areas, including the temporal lobe and thalamus (for a review, see Harrison [1999]). In line with these observations, several studies have reported changes in the dendritic arbors of cortical neurons in the brains of schizophrenic patients (for a review, see Moyer et al. [2015]). A reduced length of basal dendrites and a reduced number of dendrites were found in layers 3 and 5 of prefrontal cortical areas and anterior cingulate cortex (Moyer et al., 2015). Curiously, neurons in layer 3 of the visual cortex were not affected (Moyer et al., 2015).

It is difficult to determine the molecular drivers of schizophrenia-related changes because the etiology of schizophrenia is complex and not easily recapitulated in animal studies. The interaction of genes and environment is thought to play an important role in the development of the disorder. SNPs, mutations, or expression levels of dozens of genes have been suggested to predispose to schizophrenia, with *DISC1*, *DTNBP1*, *RELN*, and *AKT3* being primary examples. Therefore, most data on changes in dendritic arbors come from *in vitro* culture studies or transgenic animals with deregulated expression of schizophrenia susceptibility genes. For example, overexpression of the disrupted in schizophrenia 1 protein DISC1-Boymaw fusion protein in cultured neurons, resulting from a chromosomal translocation found in a family severely affected by schizophrenia, has been shown to lead to simplification of dendritic arbors. The direct cause of dendritic arbor simplification was a loss of mitochondrial motility and dynamics (Norkett et al., 2016).

Another schizophrenia susceptibility gene is *RELN* encoding Reelin, the loss of which in cultured neurons resulted in the loss of dendritic branches due to downregulation of mTORC1 signaling (Jossin and Goffinet, 2007). However, it should be emphasized that disruption of cortical migration of neurons is the most prominent phenotype of *in vivo* loss of Reelin.

The third known schizophrenia susceptibility gene, *DTNBP1*, encodes dysbindin-1, part of the BLOC-1 complex involved in vesicular transport, e.g., of lysosomes or synaptic vesicles (Mullin et al., 2011). Several studies reported a decrease in dysbindin-1 levels in schizophrenia (Wang et al., 2017; Jun et al., 2022). Knockdown of dysbindin-1 led to simplification of dendritic arbors of cultured neurons (Fei et al., 2022). Interestingly, Akt and Disc1 appear to be necessary for the proper function and stability of this protein, respectively, linking different signaling pathways that contribute to schizophrenia (Fei et al., 2022). However, it should be noted that studies have been published that showed increased levels of dysbindin-1 in individuals with schizophrenia and its inverse correlation with basal dendrite length in deep layer III pyramidal cells in the dorsolateral prefrontal cortex (DLPFC) (Konopaske et al., 2014, 2015, 2018). Considering less-known genetic factors thought to

influence the dendritic arbor in schizophrenia, a missense mutation in the Kalirin gene (*KALRN*) was identified in patients (Kushima et al., 2012). In a mouse model, introduction of such mutation in *Kalrn* led to overactivation of RhoA, which promoted dendritic simplification (Grubisha et al., 2021). Another gene associated with schizophrenia and dendritic branching is *BDNF*. It has been shown that individuals experiencing their first episode of schizophrenia have lower blood BDNF levels than healthy individuals (Singh et al., 2020). However, the causal relationship has yet to be experimentally demonstrated. Another mechanism proposed for dendritic simplification in schizophrenia that is not directly related to susceptibility genes is the pruning of dendrites by local apoptosis (Parellada and Gassó, 2021). Glutamate excess can trigger synaptic apoptosis, leading to a loss of synapses and dendrites but not neuronal trunks. This explains why the loss of cortical volume in schizophrenia occurs without the loss of neuronal cells (Bennett, 2011). For example, activation of NMDA receptors by caspase-3 can trigger local apoptosis and prune dendritic spines and branches (Williams et al., 2006; Ertürk et al., 2014).

Eating disorders

Eating disorders are characterized by abnormal eating behavior and are not fully understood, but they likely result from an interaction of genetic, environmental, and psychological factors, like the other neuropsychiatric disorders mentioned earlier. There is not much data directly linking eating disorders to dendritic arbor remodeling. Interesting examples include the consequences of excessive food intake leading to obesity. The worldwide obesity epidemic is largely attributed to increased sugar consumption, which is considered to be the fundamental and most important factor. In a rodent model, long-term sucrose consumption was found to reduce dendritic length and branching in brain regions that modulate the reward circuit, including the main neurons of the basolateral amygdala and the middle spiny neurons of the nucleus accumbens (Klenowski et al., 2016; Shariff et al., 2017). Relatedly, other studies examined how stress and diet interact to affect brain morphology and memory processing. Baran and coworkers (2005) showed that, in rats, neither stress from three weeks of crowding and predator exposure nor a high-fat diet alone reduced dendritic branching and spine density. However, in rats receiving both stress and a high-fat diet, there was a reduction in the length and number of branch points of apical dendrites of CA3 neurons. These results suggest that there is a synergistic effect between a high-fat diet and stress that negatively affects the dendrites of CA3 neurons (Baran et al., 2005). There are no data on the molecular aspects underlying these changes. However, research suggests that continuous consumption of high-fat diets has depressive effects (Sharma and Fulton, 2013). Therefore, it is tempting to speculate that similar mechanisms may be at play in obesity-related changes in dendritic branches as in depression.

Neurodegenerative diseases

Alzheimer's disease

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative diseases. Brain samples from AD patients' brains show a significant reduction in both synapses and dendritic trees (Flood, 1991; Anderton et al., 1998). One of the factors that distinguishes AD from natural brain aging or dementia is an increased level of amyloid-beta (Aβ) peptide fragments derived from the amyloid precursor protein (APP). Both familial forms of Alzheimer's disease (fAD) and later-onset forms with unknown etiology (sporadic AD) result in the production of excess Aβ. Amyloid β-peptides form soluble aggregates called Aβ-derived diffusible ligands (ADDLs) and insoluble aggregates called amyloid plaques (APs) (Haass and Selkoe, 2007). A mouse model of AD, characterized by the presence of diffusible ligands ADDLs but not insoluble APs, showed shortened dendrites and reduced branching (Alpár et al., 2006; Price et al., 2014). Regarding the molecular mechanisms downstream of ADDLs, further studies have shown that ADDLs stimulate the activity of several kinases (microtubule affinity regulating kinase [MARK1], p70S6 kinase [p70S6K], BR serine/threonine kinase [BRSK], and proto-oncogene tyrosine-protein kinase Fyn [FYN]), which subsequently phosphorylate the microtubule-associated protein tau (Tau) (Zempel et al., 2010). The hyperphosphorylated Tau is transported to the dendrites, where it leads to microtubule accumulation and consequent dystrophic thickening of the dendrites (Wu et al., 2010; Zempel et al., 2010; Larson et al., 2012). Furthermore, it led to enhanced stability and resistance to dynamic changes in dendritic microtubules (Hoover et al., 2010; Ittner et al., 2010; Golovyashkina et al., 2015). However, not only mislocalized Tau causes dendritic dystrophy in AD due to disruption of the microtubule network. Increased cofilin levels have been observed in AD patients and in animal models of AD (Kang and Woo, 2019). Studies have shown that the administration of ADDLs caused aggregation of cofilin

into insoluble aggregates called Hirano bodies, which disrupted the microtubule network (Zhao et al., 2006). But, microtubules are not the only element of the cytoskeleton affected in AD. Administration of ADDLs led to a decrease in the level and activity of p21-activated kinase (PAK), which in turn decreased the level of the F-actin-stabilizing spine protein Drebrin, changing the morphology of dendritic spines towards less mature ones (Lacor et al., 2007). Such a decrease in effective signal inputs to the neuron may also be responsible for the process of destabilization of the connections with a reduction of dendritic branches (Lin and Koleske, 2010).

Parkinson's disease

Parkinson's disease (PD) is another frequent neurodegenerative disease. The picture of PD is characterized by aggregation of α-synuclein (α-Syn) in cellular inclusions, leading to the formation of Lewy bodies, mitochondrial dysfunction, and progressive loss of nigrostriatal dopaminergic neurons and basal ganglia dysfunction (Tsukita et al., 2019). In addition to motor system symptoms, PD patients exhibit dementia, cognitive deficits, sleep-wake disturbances, and depression (Barone et al., 2009). Because most studies of PD focus on the loss of neurons rather than the disruption of their morphology, there are not many reports of changes in dendritic branching in patients' brains. However, Patt et al. (1991), who analyzed brains in 9 PD cases, observed shortening of dendrites, loss of dendritic spines, and a variety of dendritic varicosities. These pathologies affected the melanin-containing pars compacta neurons, leading to the hypothesis that selective loss of connectivity between striatal neurons and dopaminergic neurons of the substantia nigra could result in a loss of balance between inhibition and disinhibition of the latter (Evans, 2022).

In animal models, loss of dendritic branches by dopaminergic neurons has been demonstrated both in an alpha-synuclein seeding model (Paumier et al., 2015) and in genetically modified mice. For example, the dendritic branches of dopaminergic neurons were damaged in a mouse model with a leucine-rich repeat kinase 2, LRRK2 (R1441G) mutation (Li et al., 2009). LRRK2 is a protein kinase with myriad cellular substrates, and PD-related mutations increase its activity (Araki et al., 2018). Therefore, determining the molecular processes downstream of LRRK2 in PD pathology is a major challenge. These processes include lysosomal stress, impaired autophagy, and accumulation of Tau (Araki et al., 2018), which all may cause dendritic pathology. Another gene mutated in the rare cases of PD is *VPS35*, encoding an essential component (vacuolar protein sorting ortholog 35, VPS35) of the retromer complex required for proper protein sorting, lysosomal function, and mitophagy (Tang et al., 2015a; 2015b; 2020). Mice with a loss of Vps35 showed simplification of dendritic branches and loss of dendritic spines. However, it should be noted that these studies focused on hippocampal and cortical neurons and not on dopaminergic neurons. Another factor in PD could be mitochondrial dysfunction; *PINK1* is an additional gene mutated in PD. It encodes PTEN-induced kinase 1 (Pink1), but in the case of *PINK1*, mutations usually result in decreased kinase activity. Pink1 has been shown to regulate the length of dendrites of dopaminergic neurons, and this function depended on its contribution to the regulation of mitochondrial transport along microtubules (Das Banerjee et al., 2017).

Other neuropathological conditions

Epilepsy

Epilepsy is a multifaceted neurological disorder that often co-occurs with other disorders and is characterized by recurrent seizures. The mechanism underlying epileptic seizures is excessive neuronal activity within the cerebral cortex (Goldberg and Coulter, 2013). The causes of epileptic seizures are diverse and can be classified as structural, genetic (977 genes are associated with epilepsy), infectious, metabolic, immunological, injury-related, and unknown (Shorvon, 2011). A meta-analysis of magnetic resonance imaging (MRI) data from more than 2,000 epilepsy patients revealed numerous abnormalities. The most common abnormalities in the different types of epilepsy included sclerosis in the hippocampus and decreased gray matter volume in the cortex (Whelan et al., 2018). Analyses of brain samples from epileptogenic areas of over 9,000 patients revealed many dysmorphic neurons, including those with abnormal dendrite morphology (Blumcke et al., 2017). Studies performed on tissues from patients with treatment-resistant epilepsy showed altered dendrite thickness and disrupted organization of basal and apical dendrites, depending on the type of epilepsy (Rossini et al., 2021). Other studies have shown that changes occur not only at the site of epileptic seizure onset. A reduced number and swelling of dendritic branches (in the third layer of the cortex) correlated positively with the number of epileptic seizures, even though the fragment of cortex was far from the original site of epileptogenic activity (Multani et al., 1994).

There is still debate as to whether epilepsy causes changes in dendritic trees or whether these changes cause epilepsy (Wong and Guo, 2013; Rossini et al., 2021). The main argument for the hypothesis that dendritic changes cause epilepsy is the coincidence of epilepsy with various neurodevelopmental diseases with dendritic pathophysiology discussed in the previous chapters. A prevalence of epilepsy is observed in DS (8–14%), FXS (10–20%), ASD (5–46%), RTT (48%), and TSC (60–90%) (Shimizu et al., 2022). On the other hand, there are animal models of epilepsy triggered by chemical/electrical stimulation or head/brain injury (Wang et al., 2022) that tend to support the opposite view that seizures precede and cause dendritic changes. In the model of early-onset epilepsy, induction of seizures (lasting one week) by administration of tetanus toxin to the rat hippocampus resulted in a significant reduction in the diameter of apical and basal dendrites and a reduced number of dendrites (Jiang et al., 1998). Analysis of the consequences of seizures *in vivo* in mice after kainic acid administration revealed dendrite beading in the hippocampus and cortex after seizure induction. The morphological changes were found to depend on a change in Ca^{2+} concentration, leading to activation of cofilin and acute depolymerization of F-actin (Zeng et al., 2007). Thus, the experiments and clinical observations do not provide a clear answer as to whether abnormalities within dendrites contribute to the occurrence of epilepsy or are its consequence (Wong and Guo, 2013).

Stroke and brain injury

Conditions such as stroke or brain injury cause both pathological and plastic changes to restore connectivity of the dendritic tree in the affected area of the brain (Harris et al., 2022). At the site of injury or stroke, hypoxia or hemorrhage, mass neuronal death, and inflammation induction occur, affecting the function and morphology of neurons in this and related areas (Slujitoru et al., 2012; Kuriakose and Xiao, 2020). Both localized and more distant effects of stroke or injury (associated with dendritic abnormalities) are associated with neuronal connection breakdown and excitotoxicity through massive cell death (Hossmann, 2006). Excitotoxicity (glutamate-mediated neuronal overexcitation) is mediated by calcium-permeable NMDA receptors (Lai et al., 2014; Belov Kirdajova et al., 2020), which leads to a morphological reduction in dendritic tree complexity or beading of dendrites (Gao et al., 2011; Ratliff et al., 2020) or, in the case of significant overstimulation, cell death (Baracaldo-Santamaría et al., 2022). To avoid the latter, neuronal cells reduce the dendritic trees, which is observed in animal models of stroke. One of the candidates linking excessive (but not lethal) activation of NMDA receptors to retraction of dendritic branches is RhoA. Excessive stimulation of synaptic NMDA receptors in dendritic spines activates RhoA, which diffuses into dendrites (Murakoshi et al., 2011). The proposed mechanism for NMDA receptor-dependent retraction of dendrites is activation of the RhoA-Rock pathway in the dendrite (Quassollo et al., 2015). In a mouse model of ischemic stroke, a significant increase in dendritic tree remodeling dynamics was observed within two weeks of stroke. In single neurons surrounding the affected area, both dendrite retractions (at the site of impact) and extensions (away from the site of impact) were observed. These two processes balance each other so that the overall length of dendritic branches doesn't change (Brown et al., 2010). Other studies have shown that the dendritic branches of distant neurons connected to the peri-infarct area (in the other hemisphere) are also affected after stroke. In such areas, reduced dendritic complexity of apical dendritic branches has been observed (Merino-Serrais et al., 2023).

Despite the reduction in dendrites in stroke and brain injury, compensatory effects have also been reported. Survivors of stroke or brain injury show improvement in previously damaged functions after months/years, thanks to the formation of new axonal projections, migration of newborn neurons (Carmichael, 2006), and dynamic growth of apical dendrites (Brown et al., 2007). Molecular studies have shown that one of the key proteins for dendrite recovery after stroke is cordon-bleu (Cobl) (Ji et al., 2021). This protein is responsible for actin polymerization and is critical for dendritic branch growth (Ahuja et al., 2007; Haag et al., 2012). Excitotoxicity, excessive NMDA receptor activation, and Ca^{2+} overload associated with ischemic stroke lead to Cobl degradation, contributing to the reduction in dendritic branching. However, Cobl protein levels recover two to four days after stroke (the dendritic repair window in mouse models of stroke). At the same time, dendritic trees in wild-type mice grew again during this period. This contrasted with Cobl knockout mice, in which no regrowth of dendritic branches was observed (Ji et al., 2021).

CONCLUSIONS

Most previous studies on the dynamics and molecular mechanisms regulating the morphology of dendritic trees have focused on the early life stage of neurons. What happens after the phase of dendritogenesis

has been considered rather uninteresting, mainly because changes at the morphological level have usually not been observed. However, the fact that dendritic trees are impaired in numerous diseases of the mature brain suggests that the process of long-term stabilization of dendrites is very active at the molecular level and that its deciphering is important for a deep understanding of the major neuropathological changes and brain aging. At the same time, the few live imaging studies of mature dendritic trees suggest that their long-term stability may not be a feature that is equally evident across different classes of neurons, with studies to date indicating significant differences between spiny and aspiny neurons. Further progress in understanding the mechanisms that regulate the long-term stability of dendritic trees will, therefore, in our view, require systematic functional screening studies that will provide a more comprehensive list of key proteins for this phenomenon. On the other hand, it will be necessary to describe the dynamics of dendritic arbors in the mature nervous system for as many different types of neurons as possible. Perhaps the molecular data obtained from screening can be used to determine the signatures of stable and dynamic cells, which, in the age of single-cell sequencing, would allow pre-selection of the most interesting cells for *in vivo* imaging experiments. At the same time, single-cell sequencing data from pathological brains could help identify populations that exhibit dendritic tree instability associated with a particular neuropathological condition.

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