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Autore	Antonelli, Roberta
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Sommario	The correct functioning of the central nervous system relies on the rapid and efficient communication between neurons. This occurs at highly specialized functional points of contact called synapses. Synapses are extremely plastic in structure and function, strongly influenced by their own histories of impulse traffic and by signals from nearby cells. Synaptic contacts are fundamental to the development, homeostasis and remodeling of neural circuits. All these events are achieved through different mechanisms operating at both pre- and postsynaptic sites. At the level of the post synaptic density (PSD) compartment, scaffolding molecules and trans-membrane proteins are known to orchestrate proper synapses formation, maturation and rearrangement required to sustain plasticity processes. Protein phosphorylation represents one of the most important mechanisms engaged in affecting the molecular composition of the post-synaptic device. Most studies have focused on the impact of phosphorylation on the gating properties, surface mobility and trafficking of neurotransmitter receptors while much less is known about the effect of post-translational modifications on scaffolding and cell adhesion molecules functionally linked to neurotransmitter receptors. At GABAergic synapses specific phosphorylation events of the scaffolding molecule gephyrin were

shown to alter its multimerization properties, thus producing parallel changes in the number of receptors trapped by the scaffold leading to alterations of synaptic strength. Most of these phosphorylation events occur at serine or threonine residues preceding a proline, underlying a potential role of proline-directed phosphorylation as modulator of synaptic strength. The key player of such signalling cascade is represented by a small enzyme called peptidyl-prolyl isomerase Pin1 (protein interacting with NIMA 1). Pin1, upon recruitment by its substrates in a phosphorylation-dependent manner, catalyzes the cis/tran isomerization of phospho?Ser/Thr?Pro motifs leading to changes in target protein conformation and biological activity. Pin1 is highly expressed in neurons suggesting that it can exert a crucial role in synaptic transmission and plasticity processes at both inhibitory and excitatory synapses. In the first part of my PhD thesis I focused on the impact of Pin1-dependent signalling on GABAergic transmission. I found that the cell adhesion molecule of the neuroligin family enriched at GABAergic synapses, Neuroligin 2 (NL2), undergoes post-phosphorylation prolyl-isomerization modulation of its activity. Using biochemical approaches I found that the unique Pin1 consensus motif present within the cytoplasmic tail of NL2, Serine 714-proline, is indeed phosphorylated in vivo. Proline-directed phosphorylation at Serine 714 of NL2 strongly impacts on NL2 ability to complex with gephyrin. In particular, at this site, post-phosphorylation prolyl-isomerization negatively regulates the ability of NL2 to interact with gephyrin. In line with biochemical results, immunocytochemical analysis reveal that, in the absence of Pin1 expression, NL2/gephyrin complexes are enriched at GABAergic post-synaptic sites and this enrichment is accompanied by an enhanced synaptic recruitment of GABAA receptors (GABAAR). This effect was associated with a concomitant increase in the amplitude, but not in frequency, of spontaneous inhibitory post-synaptic currents (IPSCs). These findings unveil the existence of a new signalling pathway operating at inhibitory GABAergic synapses able to alter the efficacy of GABAergic transmission by modulating NL2/gephyrin interaction. Given the high abundance of Pin1 at excitatory synaptic contacts, in the second part of my PhD thesis I focused on the impact of Pin1-dependent signalling on excitatory glutamatergic transmission. In particular, I started to investigate whether the scaffolding molecule PSD-95, a member of the Disc-Large (DGL)-Membrane-associated guanylate kinase, could be a target of Pin1-dependent signalling cascade. I observed that Pin1, known to reside in post-synaptic structures, is recruited by PSD-95 at specific Serine-Threonine/Proline consensus motifs localized in the linker region connecting PDZ2 to PDZ3 domains. These sites are represented by Treonine287-Proline, Serine290-Proline and Serine295-Proline, and deletion of all of them almost completely abolished Pin1 interaction with PSD-95. Pin1 exerts a negative control on PSD-95 ability to complex with N-Methyl-D-Aspartate receptors (NMDARs). Indeed an enhanced PSD-95/NMDAR complex formation was detected in brain extracts derived from Pin1-/- mice. In electrophysiological experiments, larger NMDA-mediated synaptic currents were detected in CA1 principal cells in hippocampal slices obtained from Pin1-/- mice as compared to controls, an effect that was associated with an enhancement in spine density and size. These data indicate that Pin1 controls the synaptic content of NMDARs via PSD-95 prolyl-isomerization and the expression of dendritic spines, both required for the maintenance of long-term potentiation. Overall, this study highlights the crucial role

	of Pin1-dependent signalling in the functional organization of both inhibitory and excitatory synapses.
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