

Multitarget Network Strategies to Influence Memory and Forgetting: The Ras/Mapk Pathway as a Novel Option

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Abstract: The Ras/mitogen activated protein kinase (MAPK) pathway has key importance in development, cell differentiation and senescence, tumorigenesis, learning and memory. The clinical manifestations associated with this highly conserved pathway are called RASopathies. Phenotypic features are diverse and overlapping, but cognitive impairment is a common symptom. Here, we propose an approach based on molecular networks that link learning, memory and forgetting to the RASopathies and various neurodegenerative and neurodevelopmental diseases such as Alzheimer's disease, Parkinson's disease and autism spectrum disorders. We demonstrate the cross-talks of the molecular pathways in RASopathies and memory and the role of compartmentalization in these processes. The approved drugs are also overviewed, and *C. elegans* is proposed as a viable model system for experimental exploration and compound target prediction.



Keywords: Learning, memory, molecular networks, neurodegenerative disorders, Ras/MAPK, RASopathies.

1. INTRODUCTION

The Ras/mitogen activated protein kinase (MAPK) pathway is an evolutionary conserved signaling pathway that has been associated with development, cell differentiation and senescence, tumorigenesis, learning and memory. Being one of the most studied pathways [1], the sheer number of experimental results requires systems level approaches [2] to tackle the complexity of the dataset.

Molecular networks include gene regulatory and gene co-expression networks, protein-protein interaction networks, protein co-phosphorylation networks, metabolic and signaling networks. A common theme is that the multivariate equilibrium of reactions and pathways can be meaningfully simplified to visualizable and understandable models. This is especially useful, where not only single interactions, but the co-dependent system of multiple reactions and interactions has to be considered during pharmaceutical lead design, exploration of mechanism of action and toxicity prediction. All the above mentioned networks are well established tools for specific fields (genetic studies, proteomics, phosphoproteomics, metabolomics, respectively), but the combination of metabolic and signaling networks may represent the interactions of arbitrary molecules (DNA, RNA, proteins, 'even' anorganic molecules) to form biologically meaningful, canonical pathways. This is an additional level of organized knowledge above simple interactions. These networks can also explain complete signaling cascades and include all relevant molecule types (enzymes, transporters,

ion channels and ion levels, receptors, just to name a few) that can be targeted in pharmaceutical exploration in medicinal chemistry.

In this review we focus on results in *H. sapiens* because animal and cell culture models have been widely covered elsewhere [3-8].

Section 2 outlines a schematic network representation of the Ras/MAPK pathway and its cross-talks to pathways associated with learning and memory. Section 3 provides insights regarding the compartmentalization of the Ras/MAPK pathway. Section 4 details the related pathological conditions, section 5 proposes novel pharmacological strategies, and section 6 suggests *C. elegans* as a model system for the research of the Ras/MAPK pathway, learning and memory. Lastly, section 7 summarizes the novelties of this review.

2. THE MOLECULAR NETWORK OF Ras/MAPK, IP₃/DAG/PKC, cAMP/PKA, Ras/PI₃K PATHWAYS AND THE VARIOUS FORMS OF Ca²⁺ SIGNALING

Signaling pathways are often bridged by cross-talks that allow the orchestrated regulation of multiple processes. Such biological complexity is beyond intuitive understanding, but network science provides well established methods to represent, simplify and elucidate complex systems. Molecular networks consist of nodes and edges: nodes can be arbitrary molecules such as proteins, metabolites, RNA, etc., and edges are physical, biochemical or functional interactions among these.

Fig. (1) demonstrates a neuron specific subnetwork of the Ras/MAPK pathway and the most important pathways involved in learning and memory formation.

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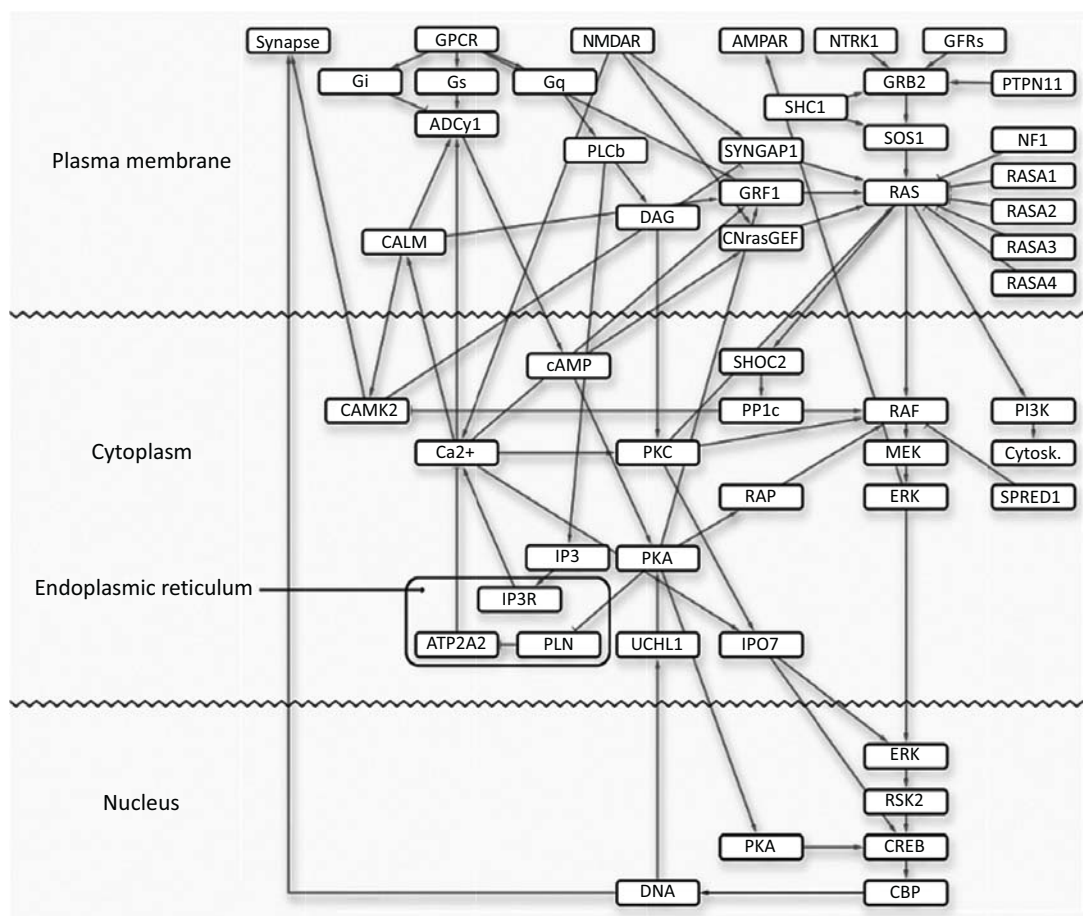


Fig. (1). Schematic network representation of Ras/MAPK, IP₃/DAG/PKC, cAMP/PKA, RAS/PI₃K pathways, Ca²⁺ signaling and their interactions in neurons.

The network of the figure was manually assembled from publications (see the references in the text) and the KEGG pathway database (Release 71.0, July 1, 2014) [9]. Canonical names of the nodes with their abbreviations are listed in the text, 'Cytosk.' refers to cytoskeletal changes, 'Synapse' refers to synthesis of synaptic proteins. The network contains simplifications to enhance lucidity. Arrow-headed lines denote activation while bar-headed lines represent inhibition. Network visualization was performed using Cytoscape 3.0 [10] and GIMP 2.8 (<http://gimp.org>).

Receptor tyrosine kinases (RTK) can activate RAS through the signaling complex containing growth factor receptor bound protein 2 (GRB2), SHC-transforming protein 1 (SHC1) and son of sevenless homolog 1 (SOS1), which leads to the phosphorylation of the Raf kinase (RAF), the mitogen-activated protein kinase kinase 1 (MEK) and the extracellular regulated kinase I/II (ERK 1/2). ERK translocates to the nucleus to modulate gene expression through 90 kDa ribosomal protein S6 kinase (RSK2) and the cyclic AMP-dependent transcription factor (CREB) 1 and 2.

Calcium signaling plays a central role in synaptic plasticity, learning and memory. Elevations in intracellular calcium level can lead to the activation of Ras in various ways [11-15]. Some of the calcium-dependent signaling

mechanisms act on a short time scale, while others invoke more permanent responses via the facilitation of protein synthesis.

N-methyl-D-aspartate receptors (NMDAR), key elements of long-term potentiation, can induce direct Ca²⁺ influx, while G_q protein-coupled receptors can induce increased intracellular Ca²⁺ levels by the activation of phospholipase C-beta (PLC β). PLC β triggers inositol-(1,4,5)-trisphosphate (IP₃)/diacyl-glycerol (DAG) signaling, and IP₃ releases Ca²⁺ from the endoplasmic reticulum. Both signaling pathways converge on the members of protein kinase C (PKC), a protein family associated with emotional memory and post-traumatic stress disorder [16]. PKC can then activate both Ras and Raf.

Increased intracellular Ca²⁺ levels facilitate the exchange of the Ras-bound GDP to GTP by the Ras-specific guanine nucleotide-releasing factor 1 (GRF1), which leads to activated downstream signaling through Raf.

The propagating Ca²⁺ transient can be re-strengthened from the endoplasmic reticulum by IP₃ receptor-mediated Ca²⁺ release, and upon reaching the nucleus the Ca²⁺ transient can facilitate gene transcription through CREB, a cross-road for multiple pathways including Ras/MAPK [17].

Members of the Kv4 type potassium channel family regulate local membrane depolarization. ERKs can phosphorylate channel components, which leads to stronger depolarization and ultimately to the activation of more NMDARs [18]. This is a rapid, protein synthesis-independent mechanism involving Ca^{2+} , K^+ and Ras/MAPK signaling.

G_s -coupled protein receptors facilitate, while G_i -protein coupled receptors inhibit adenylate cyclase type 1 (ADCY1), the enzyme known for converting adenosine triphosphate to cyclic adenosine monophosphate (cAMP) in neurons. ADCY1 is calcium/calmodulin dependent, therefore it is coupled with the above detailed calcium signaling.

cAMP can regulate the Ras/MAPK pathway either in a PKA-dependent or in a PKA-independent manner [19-20]. During the PKA-dependent process the PKA regulatory subunits bind cAMP, which leads to the opening of the active sites of the catalytic subunits, and the consequent dissociation of the PKA complex. The catalytic subunits can phosphorylate Ras-specific guanine nucleotide-releasing factor 1 (GRF1), upon which GRF1 facilitates the GDP-GTP exchange of Ras. The active PKA catalytic subunits can also translocate to the nucleus to phosphorylate CREB2 and induce the expression of gene cascades.

In the PKA-independent pathway cAMP can bind directly to CNrasGEF, a guanine nucleotide exchange factor that facilitates the GDP-GTP exchange of Ras to increase its downstream activity. The exact details of these processes are not completely explored yet. This is interesting all the more, since the cAMP/PKA pathway is a highly studied signaling pathway in neurons.

PKA inhibits phospholamban (PLN) too, which is a negative regulator of the Ca^{2+} transporting ATPase isoform 2 (ATP2A2) in the membrane of the sarcoplasmic/endoplasmic reticulum. If ATP2A2 is released from PLN inhibition, it transports Ca^{2+} to the endoplasmic reticulum and downregulates the cytoplasmic Ca^{2+} signal.

Ras isoforms are major convergence points of the above mentioned signaling processes (see also Fig. 1). KRas, HRas and NRas are interacting partners of the phosphatidylinositol 4,5-bisphosphate 3-kinase (PI_3K), which contributes to the regulation of the actin cytoskeleton. Glutamate stimulation was shown to alter the dendritic spine volume through Ras [21], and it was found recently that the synaptic actin dynamics play essential role in forgetting too [22].

The large number of cross-talks between the Ras/MAPK, the $\text{IP}_3/\text{DAG}/\text{PKC}$, the cAMP/PKA, the Ras/ PI_3K pathways and the various forms of Ca^{2+} signaling stress the importance of neuron-specific experimental data collection and their representation as molecular networks. The latter are required on two levels: large-scale networks should provide integrated data sources, from which small-scale, high resolution, focused networks can be built. SynSysNet, a synaptic interaction network [23] is a great step forward in that direction.

3. THE ROLE OF SUBCELLULAR COMPARTMENTALIZATION IN THE Ras/MAPK PATHWAY

Molecular events of learning and memory involve a large number of subcellular compartments and extracellular

localizations. This allows enhanced temporal and spatial regulation, creates function-specific microenvironments and enables synapse-specific learning [15, 24-25], but requires the trafficking of signaling molecules, often on long distance from the synapses to the nucleus.

Synaptic NMDARs (see Section 2) and neuronal growth factor receptors (see Section 4), for example, can trigger Ras, which translocates Raf to the plasma membrane [26] and leads to the phosphorylation of MEK. MEK phosphorylates ERK, then dissociates from it, which is required for the nuclear translocation of ERK [27]. ERK 1/2 is thought to enter the nucleus through the nuclear pore complexes with the help of importin-7 (IPO7) or in an importin-7-independent manner [28-30], but more details are needed to fully elucidate the mechanisms of these translocations.

Ca^{2+} influx through voltage-dependent calcium channels and NMDARs can lead to activity-dependent gene expression in neurons [17, 31]: calcium/calmodulin-dependent protein kinase IV mediates rapid nuclear CREB phosphorylation, while calcium/calmodulin-dependent protein kinase II (CAMK2) facilitates the Ras/MAPK pathway and initiates a slower, but more long-lasting CREB activation. CREB is therefore a convergence point for these two gene-regulating pathways [32].

Protein kinase A is a central enzyme in learning- and memory-related processes. The activated catalytic subunit of PKA also translocates to the nucleus by diffusion to facilitate transcription through CREB [33].

Protein synthesis on the other hand is not restricted to perinuclear localizations. RNA trafficking enables spatially restricted, local translation in response to stimulation [34]. mRNAs are transported rapidly and bidirectionally in large granules together with RNA-binding proteins, ribosomes and translational factors [35].

These examples highlight that new experimental methods and much more subcellular localization data are needed to link the translocation mechanisms to behavioral phenotypes in learning and memory formation [8].

4. PATHOLOGICAL CONDITIONS ASSOCIATED WITH THE Ras/MAPK PATHWAY: RASOPATHIES

RASopathies are clinically defined diseases caused by germline mutations in genes that encode proteins of the Ras/MAPK pathway [36, 37]. Known RASopathies are listed in Table 1. Each disorder has a unique set of phenotypic features, but due to the underlying common pathway, many of these are overlapping including characteristic facial features, cardiac defects, cutaneous abnormalities, and a predisposition to malignancies and varying degree of neurocognitive impairment.

Guanine nucleotide exchange factors (GEFs: GRF1, CNrasGEF on Fig. 1) upregulate, GTPase activating proteins (GAPs: NF1, RASA1, RASA2, RASA3, RASA4, SYNGAP1 on Fig. 1) downregulate downstream Ras signaling. Mutations in the genes encoding either GEFs or GAPs both can cause neurocognitive impairment [8] or even enhanced verbal memory at the cost of impaired visual and

Table 1. Pathological conditions associated with the members of the Ras/MAPK pathway: known RASopathies.

Name of the condition	Affected pathway member	Cognitive impairment*	References
Autoimmune lymphoproliferative syndrome	FAS, KRAS, NRAS	No	[36, 38]
Capillary malformation-AV malformation (CM-AVM) syndrome	RASA1	Secondary	[36, 39, 40]
Cardio-facio-cutaneous (CFC) syndrome	BRAF, MAP2K1, MAP2K2, KRAS	Yes	[36, 37, 41, 42]
Coffin-Lowry syndrome **	RSK2	Yes	[43]
Costello syndrome	HRAS	Yes	[37, 44, 45]
Hereditary gingival fibromatosis type I	SOS1	No	[37, 46-48]
Legius syndrome	SPRED1	Yes	[49-52]
LEOPARD syndrome	SHP2, RAF1, BRAF	Yes	[53-57]
Neurofibromatosis type I (Von Recklinghausen disease)	NF1	Yes	[58-63]
Noonan syndrome	PTPN11, SOS1, RAF1, KRAS, NRAS, BRAF	Yes	[64-67]

*Symptoms of RASopathies are diverse and overlapping, therefore the cognitive impairment column denotes only the possibility to develop varying degree of any cognitive symptom, not a mandatory condition.

**Coffin-Lowry syndrome is not reckoned among RASopathies, but it is related to the 90 kDa ribosomal protein S6 kinase 1, a target of ERK.

working memory [68-69], suggesting that a fine balance and tight regulation of the Ras/MAPK pathway is necessary for healthy cognition.

How can some RASopathies show neurocognitive impairment, while others, involving the very same gene(s), do not? For example, mutation in the *SOS1* gene has been found both in Noonan syndrome and hereditary gingival fibromatosis type 1, but only patients with Noonan syndrome have learning difficulties. Tissue specificity of the protein isoforms is a possible explanation: the KRAS mutation in cardio-facio-cutaneous syndrome is expected to be less tissue specific compared to the B and T-lymphocyte specificity in autoimmune lymphoproliferative syndrome. The interacting partners of affected proteins can vary among tissues and subcellular compartments as well, causing differences in regulation, which further emphasizes the need for network-based approaches.

Such interactions of the Ras/MAPK pathway show cross-talks with other neurodegenerative diseases (see Fig. 1). The cognitive and memory dysfunction in Alzheimer's disease is thought to be caused by amyloid-beta plaques and tau protein tangles. ERK negatively regulates the expression of beta-secretase, a precursor enzyme of amyloid-beta plaques [70]. Tau is hyperphosphorylated in the tangles, and ERK and MEK have been shown to phosphorylate tau [71].

Alpha-synuclein, ubiquitin carboxyl-terminal hydrolase L1 (UCHL1) [72] and Leucine-rich repeat kinase 2 (LRRK2) are proteins encoded by 3 of the 9 genes associated with Parkinson's Disease. Increased alpha-synuclein level is suggested as a consequence of Ras/MAPK dysfunction [73]. UCHL1 cross-talks with the Ras/MAPK pathway [6, 74]. LRRK2 also has a Ras/GTPase superfamily-like domain

[75], although no relation with the Ras/MAPK pathway has been revealed. 3,4-dihydroxyphenyl-L-alanine (L-DOPA) is the most effective and commonly used treatment in Parkinson's disease. It can cause L-DOPA induced dyskinesia through protein kinase A targets [76], among which there are members of the Ras/MAPK pathway (see Section 2).

High affinity nerve growth factor receptor (NTRK) 1 and 2 are receptors of the brain-derived neurotrophic factor (BDNF), which regulates directly the growth factor receptor-bound protein 2 (GRB2). BDNF is linked to learning and memory [77], autism [78] and depression models [79-80]. Autism traits are also associated with RASopathies [81].

The network and the pathological conditions were manually assembled from publications (see the references in the text of Section 2, 4, and 5), network insertion of drugs was manually curated using the DrugBank database (release 4.0, 1st January 2014) [82]. Rectangles in the middle of the figure mark signaling proteins of the Ras/MAPK pathway, ellipses on the right mark Ras-dependent pathological conditions (RASopathies), while octagons on the left indicate drugs affecting Ras/MAPK-dependent signaling. Arrow-headed lines denote activation while bar-headed lines represent inhibition. Network visualization was performed using Cytoscape 3.0 [10] and GIMP 2.8 (<http://gimp.org>).

5. NETWORK-BASED COMPOUND DESIGN

Members of the Ras/MAPK pathway were identified as drug targets with the help of their UniProt protein identifiers. The drugs were collected from DrugBank and the result set was filtered to approved drugs and was verified manually from publications.

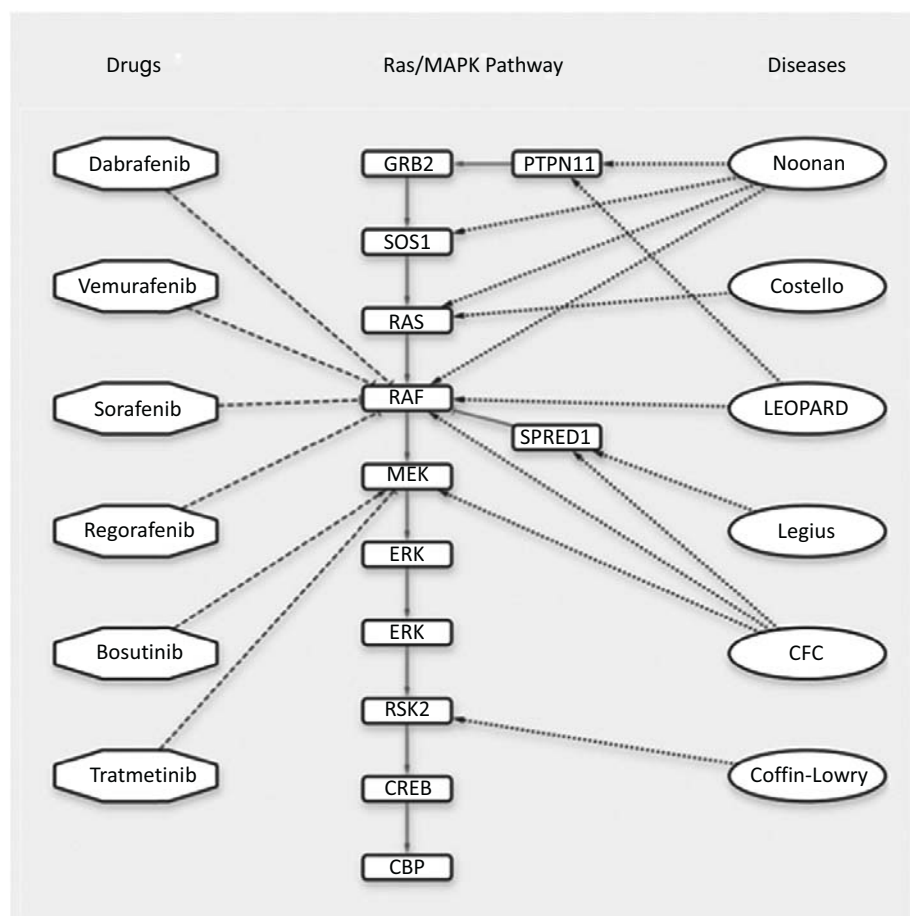


Fig. (2). FDA-approved drugs and the pathological conditions associated with the Ras/MAPK pathway.

Table 2. Approved drugs targeting the proteins of the Ras/MAPK pathway according to the DrugBank database (release 4.0, 1st January 2014 [82]). See also Figure 2.

Drug name	Target protein	Mechanism of action	DrugBank ID
Bosutinib	MEK1, MEK2	Unknown	DB06616
Dabrafenib	BRAF, CRAF	Kinase inhibitor	DB05190
Regorafenib	BRAF, CRAF	Kinase inhibitor	DB08881
Sorafenib	BRAF, CRAF	Kinase inhibitor	DB08553
Trametinib	MEK1, MEK2	Kinase inhibitor	DB08911
Vemurafenib	BRAF, CRAF	Kinase inhibitor	DB00398

The FDA-approved drugs targeting the Ras/MAPK pathway are listed in Table 2. All of them are anticancer compounds, which have two current implications for RASopathies. First, cancer treatment with the above mentioned drugs may lead to RASopathy-like symptoms, and indeed there is a report of vemurafenib treatments, where cutaneous adverse effects were overlapping with the symptoms of RASopathies [83]. Second, a widely experienced adverse effect of anticancer treatment is the long-lasting cognitive dysfunction [84]. Taken together the

following 3 leads (1) the Ras/MAPK pathway is involved in the molecular processes of learning, memory and forgetting [85-89]; (2) the aforementioned anticancer compounds target the members of this pathway, and (3) the adverse effects of the anticancer treatment overlap with the symptoms of RASopathies [83], here we propose that the link between Ras-dependent anti-cancer treatment-induced cognitive dysfunctions and the cognitive impairment observed in RASopathies should be experimentally explored.

There are no approved drugs for the causal treatment of RASopathies. The requirements for such compound would include reversibility, capability to cross the blood-brain barrier, and probably the ability to target multiple members or regulators of the involved pathways. Ras itself is difficult to target [90]. This example shows that targeting single, central molecules with many interactors (e.g. signaling hubs, such as Ras) may have a strong effect, but the molecular perturbations may also spread widely due to the large network neighborhood and may cause side effects or toxicity [91].

It has been proposed that multitarget approaches based on molecular network analysis may allow a fine-tuned modulation of the required pathways instead of their complete blockade, and may also overcome drug resistance by downregulating redundant pathways [91-95]. This strategy was recently successfully applied to KRAS [96]. Various combinations of compounds activating serotonin and/or dopamine receptors were also found to moderately enhance the Ras-PI₃K/PKB signaling input in mice [97]. This suggests that combination therapy, e.g. multitarget „cocktail drug treatment” with already approved drugs or new compounds is an option worth exploring. Multi-target-directed drug design strategies are actively explored areas in medicinal chemistry [98].

Network analysis can highlight promising drug targets [91, 99]. For example, even a pilot analysis of the molecular network in (Fig. 1) reveals that Raf has the highest betweenness centrality, a measure often associated with importance in signal transmission [100]. Raf is also the target of the highest number of approved drugs among the members of the Ras/MAPK pathway. In-depth analyses need larger, more detailed, neuron-specific signaling networks that also take into consideration regulators and key players of subcellular translocation as compound targets.

6. C. ELEGANS AS A MODEL SYSTEM FOR Ras/MAPK SIGNALING, LEARNING AND MEMORY

The most common animal model systems for RASopathies include *M. musculus* [36], *D. rerio* [101] and *D. melanogaster* [102]. De novo synapse formation is part of the synaptic plasticity in all these organism, which is an additional level of complexity.

The well explored wiring diagram of the 302 neurons in *C. elegans* [103] does not change in mature animals, synaptic plasticity is therefore restricted to the changes of the synaptic strength. The Ras/MAPK pathway and fundamental molecular processes of learning and memory are both evolutionary conserved and have been found in *C. elegans*. There is a wide range of established molecular biological tools for *C. elegans*, the worm has a short lifespan, and the laboratory conditions of related experiments are also economic. The phenotypic characterization of *C. elegans* orthologues of known human disease genes, proteins or drug targets may lead to a better understanding of the underlying molecular processes [104, 105]. In reverse: mapping of genes, proteins or processes explored in *C. elegans* to their human orthologues may highlight novel targets for experiment design or early compound target discovery in *H. sapiens* [106].

In summary, *C. elegans* is a simple, yet representative model system that may provide valuable insights into the shared molecular properties of RASopathies, various neurodegenerative diseases and their relation to the fundamentals of learning and memory [107].

7. SUMMARY

The Ras/MAPK pathway is an important signal transduction and convergence pathway in the regulation of synaptic proteins, active in both long-term potentiation and in the modulation of dendritic spine volume. Here we presented the Ras/MAPK, IP₃/DAG/PKC, cAMP/PKA, Ras/PI₃K pathways and the various forms of Ca²⁺ signaling as an interconnected network in neurons. This is the first time to our best knowledge that pathways involved in learning and memory are associated with the Ras/MAPK pathway in a focused, network-oriented approach also considering tissue and intracellular compartment-specificity.

Neurodegenerative and neurodevelopmental disorders are diseases with diverse molecular background, therefore the affected molecular networks and biomarker patterns should be identified to understand the systems level pathomechanisms and to achieve definitive diagnostic criteria.

Reviewing Ras/MAPK-related pathological conditions (RASopathies) we proposed the first time that the cognitive dysfunction caused by anticancer drugs targeting the Ras/MAPK pathway might have common molecular roots with RASopathies. Compound design for these conditions is challenging due to the highly regulated and central nature of the Ras/MAPK pathway, thus tissue-specific, network-based, multitarget approaches might be options for *in silico* exploration. Finally, *C. elegans* might be a viable model system for early experimental validation.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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