Neuner, SM, Garfinkel BP, Wilmott LA, Ignatowska-Jankowska BM, Citri A, Orly J, Lu L, Overall RW, Mulligan MK, Kempermann G et al. 2016 Systems genetics identifies Hp1bp3 as a novel modulator of cognitive aging. Neurobiology of aging. 46:58-67. An individual's genetic makeup plays an important role in determining susceptibility to cognitive aging. Identifying the specific genes that contribute to cognitive aging may aid in early diagnosis of at-risk patients, as well as identify novel therapeutics targets to treat or prevent development of symptoms. Challenges to identifying these specific genes in human studies include complex genetics, difficulty in controlling environmental factors, and limited access to human brain tissue. Here, we identify Hp1bp3 as a novel modulator of cognitive aging using a genetically diverse population of mice and confirm that HP1BP3 protein levels are significantly reduced in the hippocampi of cognitively impaired elderly humans relative to cognitively intact controls. Deletion of functional Hp1bp3 in mice recapitulates memory deficits characteristic of aged impaired mice and humans, further supporting the idea that Hp1bp3 and associated molecular networks are modulators of cognitive aging. Overall, our results suggest Hp1bp3 may serve as a potential target against cognitive aging and demonstrate the utility of genetically diverse animal models for the study of complex human disease.

Atlan, G, Terem A, Peretz-Rivlin N, Groysman M, Citri A. 2016 Mapping synaptic cortico-claustral connectivity in the mouse. The Journal of comparative neurology. The claustrum is an intriguing brain structure, featuring the highest connectivity per regional volume in the brain. It is a thin and elongated structure enclosed between the striatum and the insular cortex, with widespread reciprocal connections with the sensory modalities and prefrontal cortices. Retinotopic and somatotopic organizations have been described in the claustrum, and anatomical studies in cats, monkeys, and rats have demonstrated topographic organization of cortico-claustral connections. In this study, we mapped the projections from cortical modalities (visual, auditory, somatosensory, motor and olfactory), and prefrontal regions (anterior cingulate cortex and orbitofrontal cortex) to the claustrum in mice. Utilizing expression of a virally-encoded synaptic anterograde tracer, AAV-SynaptoTag, followed by 3-dimensional reconstruction of the cortical projections, we performed a comprehensive study of the organization of these projections within the mouse claustrum. Our results clearly demonstrate a dorsoventral laminar organization of projections from the sensory cortices to the claustrum, whereas frontal inputs are more extensive and overlap with the inputs from the sensory cortices. In addition, we find evidence in support of a core/shell organization of the claustrum. We propose that the overlap between the frontal inputs and the inputs from the sensory modalities may underlie executive regulation of the communication between the claustrum and the cortical modalities. This article is protected by copyright. All rights reserved.
The claustrum is a mysterious thin sheet of neurons lying between the insular cortex and the striatum. It is reciprocally connected with almost all cortical areas, including motor, somatosensory, visual, auditory, limbic, associative, and prefrontal cortices. In addition, it receives neuromodulatory input from subcortical structures. A decade ago, Sir Francis Crick and Christof Koch published an influential review proposing the claustrum as the 'seat of consciousness', spurring a revival of interest in the claustrum. We review the literature on the claustrum, emphasizing recent discoveries, and develop a detailed hypothesis describing a role for the claustrum in the segregation of attention.

A major challenge in neuronal stem cell biology lies in characterization of lineage-specific reprogrammed human neuronal cells, a process that necessitates the use of an assay sensitive to the single-cell level. Single-cell gene profiling can provide definitive evidence regarding the conversion of one cell type into another at a high level of resolution. The protocol we describe uses Fluidigm Biomark dynamic arrays for high-throughput expression profiling from single neuronal cells, assaying up to 96 independent samples with up to 96 quantitative PCR (qPCR) probes (equivalent to 9,216 reactions) in a single experiment, which can be completed within 2-3 d. The protocol enables simple and cost-effective profiling of several hundred transcripts from a single cell, and it could have numerous utilities.

Somatic cell nuclear transfer, cell fusion, or expression of lineage-specific factors have been shown to induce cell-fate changes in diverse somatic cell types. We recently observed that forced expression of a combination of three transcription factors, Brn2 (also known as Pou3f2), Ascl1 and Myt1l, can efficiently convert mouse fibroblasts into functional induced neuronal (iN) cells. Here we show that the same three factors can generate functional neurons from human pluripotent stem cells as early as 6 days after transgene activation. When combined with the basic helix-loop-helix transcription factor NeuroD1, these factors could also convert fetal and postnatal human fibroblasts into iN cells showing typical neuronal morphologies and expressing multiple neuronal markers, even after downregulation of the exogenous transcription factors. Importantly, the vast majority of human iN cells were able to generate action potentials and many matured to receive synaptic contacts when co-cultured with primary mouse cortical neurons. Our data demonstrate that non-neural human somatic cells, as well as pluripotent stem cells, can be converted directly into neurons by lineage-determining transcription factors. These methods may facilitate robust generation of patient-specific human neurons for in vitro disease modelling or future...
applications in regenerative medicine.

2010

Citri, A, Bhattacharyya S, Ma C, Morishita W, Fang S, Rizo J, Malenka RC. 2010 Calcium binding to PICK1 is essential for the intracellular retention of AMPA receptors underlying long-term depression [40]. J Neurosci. 30:16437-52. Abstract [41]

NMDA receptor (NMDAR)-dependent long-term depression (LTD) in the hippocampus is mediated primarily by the calcium-dependent removal of AMPA receptors (AMPARs) from the postsynaptic density. The AMPAR-binding, PDZ (PSD-95/Dlg/ZO1) and BAR (Bin/amphiphysin/Rvs) domain-containing protein PICK1 has been implicated in the regulation of AMPAR trafficking underlying several forms of synaptic plasticity. Using a strategy involving small hairpin RNA-mediated knockdown of PICK1 and its replacement with recombinant PICK1, we performed a detailed structure-function analysis of the role of PICK1 in hippocampal synaptic plasticity and the underlying NMDAR-induced AMPAR trafficking. We found that PICK1 is not necessary for maintenance of the basal synaptic complement of AMPARs or expression of either metabotropic glutamate receptor-dependent LTD or NMDAR-dependent LTP. Rather, PICK1 function is specific to NMDAR-dependent LTD and the underlying AMPAR trafficking. Furthermore, although PICK1 does not regulate the initial phase of NMDAR-induced AMPAR endocytosis, it is required for intracellular retention of internalized AMPARs. Detailed biophysical analysis of an N-terminal acidic motif indicated that it is involved in intramolecular electrostatic interactions that are disrupted by calcium. Mutations that interfered with the calcium-induced structural changes in PICK1 precluded LTD and the underlying NMDAR-induced intracellular retention of AMPARs. These findings support a model whereby calcium-induced modification of PICK1 structure is critical for its function in the retention of internalized AMPARs that underlies the expression of hippocampal NMDAR-dependent LTD.

2009


Long-term depression (LTD) in CA1 pyramidal neurons can be induced by activation of either N-methyl-D-aspartate receptors (NMDARs) or metabotropic glutamate receptors (mGluRs), both of which elicit changes in synaptic efficacy through alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor (AMPAR) endocytosis. To address the role of the ubiquitin-proteasome system in regulating AMPAR endocytosis during these forms of LTD, we examined the effects of pharmacological inhibitors of proteasomal degradation and protein ubiquitination on endocytosis of glutamate receptor 1 (GluR1) - containing AMPARs in dissociated rat hippocampal cultures as well as LTD of excitatory synaptic responses in acute rat hippocampal slices. Our findings suggest that the contribution of the ubiquitin-proteasome system to NMDAR-induced vs. mGluR-induced AMPAR endocytosis and the consequent LTD differs significantly. NMDAR-induced AMPAR endocytosis and LTD occur independently of proteasome function but appear to depend, at least in part, on ubiquitination. In contrast, mGluR-induced AMPAR endocytosis and LTD are enhanced by inhibition of proteasomal degradation, as well as by the inhibitor of
protein ubiquitination. Furthermore, the decay of mGluR-induced membrane depolarization and Erk activation is delayed following inhibition of either ubiquitination or proteasomal degradation. These results suggest that, although NMDAR-dependent LTD may utilize ubiquitin as a signal for AMPAR endocytosis, mGluR-induced signaling and LTD are limited by a feedback mechanism that involves the ubiquitin-proteasome system.

2008


Experiences, whether they be learning in a classroom, a stressful event, or ingestion of a psychoactive substance, impact the brain by modifying the activity and organization of specific neural circuitry. A major mechanism by which the neural activity generated by an experience modifies brain function is via modifications of synaptic transmission; that is, synaptic plasticity. Here, we review current understanding of the mechanisms of the major forms of synaptic plasticity at excitatory synapses in the mammalian brain. We also provide examples of the possible developmental and behavioral functions of synaptic plasticity and how maladaptive synaptic plasticity may contribute to neuropsychiatric disorders.

2007


Several distinct mutations within the kinase domain of the epidermal growth factor receptor (EGFR) are associated with non-small cell lung cancer, but mechanisms underlying their oncogenic potential are incompletely understood. Although normally ligand-induced kinase activation targets EGFR to Cbl-mediated receptor ubiquitinylation and subsequent degradation in lysosomes, we report that certain EGFR mutants escape this regulation. Defective endocytosis characterizes a deletion mutant of EGFR, as well as a point mutant (L858R-EGFR), whose association with c-Cbl and ubiquitinylation are impaired. Our data raise the possibility that refractoriness of L858R-EGFR to downregulation is due to enhanced heterodimerization with the oncogene product HER2, which leads to persistent stimulation.


Cell migration driven by the epidermal growth factor receptor (EGFR) propels morphogenesis and involves reorganization of the actin cytoskeleton. Although de novo transcription precedes migration, transcript identity remains largely unknown. Through their actin-binding domains, tensins link the cytoskeleton to integrin-based adhesion sites. Here we report that EGF downregulates tensin-3 expression, and concomitantly upregulates cten, a tensin family member that lacks the actin-binding domain. Knockdown of cten or tensin-3, respectively, impairs or enhances mammary cell migration. Furthermore, cten displaces tensin-3 from the cytoplasmic tail of integrin beta1, thereby instigating actin fibre disassembly. In invasive breast cancer, cten expression correlates not only with high EGFR and HER2, but also with metastasis to
lymph nodes. Moreover, treatment of inflammatory breast cancer patients with an EGFR/HER2 dual-specificity kinase inhibitor significantly downregulated cten expression. In conclusion, a transcriptional tensin-3-cten switch may contribute to the metastasis of mammary cancer.


Hsp90 is a highly abundant chaperone whose clientele includes hundreds of cellular proteins, many of which are central players in key signal transduction pathways and the majority of which are protein kinases. In light of the variety of Hsp90 clientele, the mechanism of selectivity of the chaperone toward its client proteins is a major open question. Focusing on human kinases, we have demonstrated that the chaperone recognizes a common surface in the amino-terminal lobe of kinases from diverse families, including two newly identified clients, NFkappaB-inducing kinase and death-associated protein kinase, and the oncoprotein HER2/ErbB-2. Surface electrostatics determine the interaction with the Hsp90 chaperone complex such that introduction of a negative charge within this region disrupts recognition. Compiling information on the Hsp90 dependence of 105 protein kinases, including 16 kinases whose relationship to Hsp90 is first examined in this study, reveals that surface features, rather than a contiguous amino acid sequence, define the capacity of the Hsp90 chaperone machine to recognize client kinases. Analyzing Hsp90 regulation of two major signaling cascades, the mitogen-activated protein kinase and phosphatidylinositol 3-kinase, leads us to propose that the selectivity of the chaperone to specific kinases is functional, namely that Hsp90 controls kinases that function as hubs integrating multiple inputs. These lessons bear significance to pharmacological attempts to target the chaperone in human pathologies, such as cancer.

with Hsp90, inhibits homodimer formation, and reduces its half-life to 4 h. These findings implicate Hsp90 in the stabilization of LIMK1 by promoting homodimer formation and transphosphorylation.


Signalling through the ERBB/HER receptors is intricately involved in human cancer and already serves as a target for several cancer drugs. Because of its inherent complexity, it is useful to envision ERBB signalling as a bow-tie-configured, evolvable network, which shares modularity, redundancy and control circuits with robust biological and engineered systems. Because network fragility is an inevitable trade-off of robustness, systems-level understanding is expected to generate therapeutic opportunities to intercept aberrant network activation.


Ron, the tyrosine kinase receptor for macrophage-stimulating protein is responsible for proliferation and migration of cells from different tissues. Ron can acquire oncogenic potential by single point mutations in the kinase domain, and dysregulated Ron signaling has been involved in the development of different human cancers. We have previously shown that ligand-activated Ron recruits the negative regulator c-Cbl, which mediates its ubiquitylation and degradation. Here we report that Ron is ubiquitylated also by the U-box E3 ligase C-terminal Hsc70-interacting protein (CHIP), recruited via chaperone intermediates Hsp90 and Hsc70. Gene silencing shows that CHIP activity is necessary to mediate Ron degradation upon cell treatment with Hsp90 inhibitors geldanamycins. The oncogenic Ron(M1254T) receptor escapes from c-Cbl negative regulation but retains a strong association with CHIP. This constitutively active mutant of Ron displays increased sensitivity to geldanamycins, enhanced physical interaction with Hsp90, and more rapid degradation rate. Cell growth and migration, as well as the transforming potential evoked by Ron(M1254T), are abrogated upon Hsp90 inhibition. These data highlight a novel mechanism for Ron degradation and propose Hsp90 antagonists like geldanamycins as suitable pharmacological agents for therapy of cancers where altered Ron signaling is involved.


ErbB2, a member of the EGF receptor family of tyrosine kinases is overexpressed on many tumor cells of epithelial origin and is the molecular target of trastuzumab (Herceptin), the first humanized antibody used in the therapy of solid tumors. Trastuzumab, which is thought to act, at least in part, by downregulating ErbB2 expression is only effective in approximately 30-40% of ErbB2 positive breast tumors. Geldanamycin and its derivative 17-AAG are potential antitumor agents capable of downregulating client proteins of Hsp90, including ErbB2. To investigate the ability of 17-AAG to downregulate ErbB2 in trastuzumab resistant breast cancer cells and the possibility of 17-AAG and trastuzumab potentiating each other's effect, the recently established trastuzumab resistant breast cancer cell line, JIMT-1 was compared to the known trastuzumab sensitive SKBR-3 line. Baseline and stimulus-evoked dimerization and activation levels of ErbB2, and the effects of trastuzumab and 17-AAG alone and in combination on cell proliferation and apoptosis, as well as on ErbB2 expression and phosphorylation have been measured. Baseline activation and amenability to activation and downregulation by trastuzumab was much lower in the
resistant line. However, 17-AAG enhanced ErbB2 homodimerization after 5-10 min of treatment in both cell lines, and decreased proliferation with an IC50 of 70 nM for SKBR-3 and 10nM for JIMT-1. Thus, 17-AAG may be a useful drug in trastuzumab resistant ErbB2 overexpressing tumors. The antiproliferative effect of 17-AAG was positively correlated with phosphorylation and downregulation of ErbB2 and was dominated by apoptosis, although, especially at higher doses, necrosis was also present. Interestingly, IC50 values for ErbB2 downregulation and phosphorylation, in the 30-40 nM range, were not significantly different for the two cell lines. This observation and the negative correlation between resting ErbB2 levels and the antiproliferative effect of 17-AAG may indicate that activation of ErbB2 to some extent could counteract the overall cytostatic effect, especially at higher levels of ErbB2 expression. The usual therapeutic dose of trastuzumab did not change the IC50 of 17-AAG on the proliferation of either cell line, but nevertheless decreased overall ErbB2 phosphorylation and at low doses of 17-AAG further decreased cell growth in the sensitive SKBR-3, thus trastuzumab may be a good combination partner to counteract undesired activating effects of 17-AAG.


Suppressors of cytokine signaling (SOCS) are Src homology-2-containing proteins originally identified as negative regulators of cytokine signaling. Accumulating evidence indicates a role for SOCS proteins in the regulation of additional signaling pathways including receptor tyrosine kinases. Notably, SOCS36E, the Drosophila ortholog of mammalian SOCS5, was recently implicated as a negative regulator of the Drosophila ortholog of EGFR. In this study, we aimed at characterizing the role of SOCS5 in the negative regulation of EGFR. Here we show that the expression of SOCS5 and its closest homolog SOCS4 is elevated in cells following treatment with EGF, similar to several negative feedback regulators of EGFR
whose expression is up-regulated upon receptor activation. The expression of SOCS5 led to a marked reduction in EGFR expression levels by promoting EGFR degradation. The reduction in EGFR levels and EGF-induced signaling in SOCS5-expressing cells requires both the Src homology-2 and SOCS box domains of SOCS5. Interestingly, EGFR is degraded by SOCS5 prior to EGF treatment in a ligand- and c-Cbl-independent manner. SOCS5 can associate with EGFR and can also bind the ElonginBC protein complex via its SOCS box, which may recruit an E3 ubiquitin ligase to promote EGFR degradation. Thus, we have characterized a novel function for SOCS5 in regulating EGFR and discuss its potential role in controlling EGFR homeostasis.

2004


The tumor suppressor gene 101 (tsg101) regulates vesicular trafficking processes in yeast and mammals. We report a novel protein, Tal (Tsg101-associated ligase), whose RING finger is necessary for multiple monoubiquitylation of Tsg101. Bivalent binding of Tsg101 to a tandem tetrapeptide motif (PTAP) and to a central region of Tal is essential for Tal-mediated ubiquitylation of Tsg101. By studying endocytosis of the epidermal growth factor receptor and egress of the human immunodeficiency virus, we conclude that Tal regulates a Tsg101-associated complex responsible for the sorting of cargo into cytoplasm-containing vesicles that bud at the multivesicular body and at the plasma membrane.


Signal transduction mediated by ErbB/HER receptor tyrosine kinases is crucial for the development and maintenance of epithelial tissues, and aberrant signaling is frequently associated with malignancies of epithelial origin. This review focuses on the roles played by the Hsp90 chaperone machinery in the regulation of signaling through the ErbB/HER network, and discusses potential therapeutic strategies that disrupt chaperone functions. Hsp90 and its associated cochaperones regulate ErbB signal transduction through multiple mechanisms. The chaperone system controls the stability of the nascent forms of both ErbB-1 (EGF-receptor) and ErbB-2/HER2, while regulation of the mature form is restricted to ErbB-2. Regulation by the Hsp90 complex extends to downstream effectors of ErbB signaling, namely Raf-1, Pdk-1 and Akt/PKB. Disrupting the function of Hsp90 results in the degradation of both the receptors and their effectors, thereby inhibiting tumor cell growth. The importance of an Hsp90-recognition motif located within the kinase domain of ErbB-2 is discussed, as well as a direct role for Hsp90 in regulating tyrosine kinase activity. In light of recent observations, we emphasize the ability of specific tyrosine kinase inhibitors to selectively target ErbB-2 to the chaperone-mediated degradation pathway. ErbB-specific drugs are already used to treat cancers, and clinical trials are underway for additional compounds that intercept ErbB signaling, including drugs that target Hsp90. Hence, the dependence of ErbB-2 upon Hsp90 reveals an Achilles heel, which opens a window of opportunity for combating cancers driven by the ErbB/HER signaling network.

ErbB-2/HER2 is an oncogenic tyrosine kinase that regulates a signalling network by forming ligand-induced heterodimers with several growth factor receptors of the ErbB family. Hsp90 and co-chaperones regulate degradation of ErbB-2 but not other ErbB members. Here, we report that the role of Hsp90 in modulating the ErbB network extends beyond regulation of protein stability. The capacity of ErbB-2 to recruit ligand-bound receptors into active heterodimers is limited by Hsp90, which is dissociated from ErbB-2 following ligand-induced heterodimerization. We show that Hsp90 binds a specific loop within the kinase domain of ErbB-2, thereby restraining heterodimer formation and catalytic function. These results define a role for Hsp90 as a molecular switch regulating the ErbB signalling network by limiting formation of ErbB-2-centred receptor complexes.


Kekkon proteins negatively regulate the epidermal growth factor receptor (EGFR) during oogenesis in Drosophila. Their structural relative in mammals, LRIG1, is a transmembrane protein whose inactivation in rodents promotes skin hyperplasia, suggesting involvement in EGFR regulation. We report upregulation of LRIG1 transcript and protein upon EGF stimulation, and physical association of the encoded protein with the four EGFR orthologs of mammals. Upregulation of LRIG1 is followed by enhanced ubiquitylation and degradation of EGFR. The underlying mechanism involves recruitment of c-Cbl, an E3 ubiquitin ligase that simultaneously ubiquitylates EGFR and LRIG1 and sorts them for degradation. We conclude that LRIG1 evolved in mammals as a feedback negative attenuator of signaling by receptor tyrosine kinases.


ErbB-2/HER2 drives epithelial malignancies by forming heterodimers with growth factor receptors. The primordial invertebrate receptor is sorted to the basolateral epithelial surface by binding of the PDZ domain of Lin-7 to the receptor's tail. We show that all four human ErbBs are basolaterally expressed, even when the tail motif is absent. Mutagenesis of hLin-7 unveiled a second domain, KID, that binds to the kinase region of ErbBs. The PDZ interaction mediates stabilization of ErbB-2 at the basolateral surface. On the other hand, binding of KID is involved in initial delivery to the basolateral surface, and in its absence, unprocessed ErbB-2 molecules are diverted to the apical surface. Hence, distinct domains of Lin-7 regulate receptor delivery to and maintenance at the basolateral surface of epithelia.


ErbB-2 (also called HER2/neu) and ErbB-3 are closely related to the epidermal growth factor receptor (EGFR/ErbB-1), but unlike EGFR, ErbB-2 is a ligandless receptor, whereas ErbB-3 lacks tyrosine kinase activity. Hence, both ErbB-2 and ErbB-3 are active only in the context of ErbB heterodimers, and ErbB-2. ErbB-3 heterodimers, which are driven by neuregulin ligands, are the most prevalent and potent complexes. These stringently controlled heterodimers are repeatedly employed throughout embryonic development and dictate the establishment of several cell lineages through mesenchyme-epithelial
inductive processes and the interactions of neurons with muscle, glia, and Schwann cells. Likewise, the potent combination of signaling pathways engaged by the heterodimers drives an aggressive phenotype of tumors of secretory epithelia, including breast and lung cancers. This review highlights recent structural insights into the mechanism of ligand-induced heterodimer formation, and concentrates on signaling pathways employed by ErbB-2 and ErbB-3 in normal and in malignant cells.

2002


Overexpression of ErbB-2/HER2 is associated with aggressive human malignancies, and therapeutic strategies targeting the oncoprotein are currently in different stages of clinical application. Tyrosine kinase inhibitors (TKIs) that block the nucleotide-binding site of the kinase are especially effective against tumors. Here we report an unexpected activity of TKIs: along with inhibition of tyrosine phosphorylation, they enhance ubiquitylation and accelerate endocytosis and subsequent intracellular destruction of ErbB-2 molecules. Especially potent is an irreversible TKI (CI-1033) that alkylates a cysteine specific to ErbB receptors. The degradative pathway stimulated by TKIs appears to be chaperone mediated, and is common to the heat shock protein 90 (Hsp90) antagonist geldanamycin and a stress-induced mechanism. In agreement with this conclusion, CI-1033 and geldanamycin additively inhibit tumor cell growth. Based upon a model for drug-induced degradation of ErbB-2, we propose a general strategy for selective destruction of oncoproteins by targeting their interaction with molecular chaperones.

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