Review

Neurodevelopmental disorders, immunity, and cancer are connected

Ruth Nussinov,[1,2,*] Chung-Jung Tsai,[1] and Hyunbum Jang[1]

SUMMARY

Immunity could be viewed as the common factor in neurodevelopmental disorders and cancer. The immune and nervous systems coevolve as the embryo develops. Immunity can release cytokines that activate MAPK signaling in neural cells. In specific embryonic brain cell types, dysregulated signaling that results from germline or embryonic mutations can promote changes in chromatin organization and gene accessibility, and thus expression levels of essential genes in neurodevelopment. In cancer, dysregulated signaling can emerge from sporadic somatic mutations during human life. Neurodevelopmental disorders and cancer share similarities. In neurodevelopmental disorders, immunity, and cancer, there appears an almost invariable involvement of small GTPases (e.g., Ras, RhoA, and Rac) and their pathways. TLRs, IL-1, GIT1, and FGFR signaling pathways, all can be dysregulated in neurodevelopmental disorders and cancer. Although there are signaling similarities, decisive differentiating factors are timing windows, and cell type specific perturbation levels, pointing to chromatin reorganization. Finally, we discuss drug discovery.

INTRODUCTION

Cancer is connected to immunity and inflammation. Neurodevelopmental disorders are connected to higher likelihood of cancer [e.g., (Chiang et al., 2015; Crespi, 2011; Dangles et al., 2021; Gangfuss et al., 2022; Morton et al., 2021; Nussinov et al., 2022a; Qi et al., 2016; Rauen, 2013; Zhang et al., 2021b),]. They are also connected to immunity and inflammation [e.g., (Bodnar et al., 2020; Boulanger-Bertolus et al., 2018; Cowan and Petri, 2018; Garay and McAllister, 2010; Jiang et al., 2018; Solek et al., 2018; Sotgiu et al., 2020; Tremblay, 2021; van Eeden et al., 2021),]. Immunity could be viewed as a link between neurodevelopmental disorders and cancer. The literature abounds with publications describing explorations, data, and reviews on the connections of cancer, inflammation, and immunity. Over the last few years, the interest in the connection between cancer and neurodevelopmental disorders has also been soaring (overviewed in (Nussinov et al., 2022a), and references therein) and recently in the connection between neurodevelopmental disorders and immunity as well. Here, we look at these connections and the complex common and distinct nature of their relationships and scenarios.

Signaling pathways in the immune system include the Wnt, Notch, JAK/STAT (Janus kinase/signal transducer and activator of transcription), Hippo (Clara et al., 2020; Pisibon et al., 2021), and the mitogen-activated protein kinase (MAPK) networks. The mammalian MAPKs cascades are key transducing enzymes that transmit signals impacting regulation, neurodevelopment, immunity, and aging (He et al., 2020; Kyosseva, 2016; Lanna et al., 2017; Liu et al., 1996). Dysregulation of their physiological checks and balances leads to uncontrolled growth (Braicu et al., 2019; Dhillon et al., 2007; Santarpia et al., 2012; Yuan et al., 2020). Their associated kinases, phosphatases, and scaffolding proteins control gene expression, cell proliferation, development, and programmed cell death (Chang and Karin, 2001). Stimulated receptor tyrosine kinases (RTKs), a major activating arm of MAPK, toll-like receptors (TLRs), and interleukin receptors (IL-Rs), which activate MAPKs in immune cells (discussed below in the review), transduce signals through active mediators, such as growth factor bound protein 2 (Grb2) and SHP2 (SH2 domain-containing phosphatase 2). The RTKs, e.g., Met receptor tyrosine kinase in autism spectrum disorder (ASD), ERBB4 (erb-b2 receptor tyrosine kinase 4) in ASD and schizophrenia susceptibility (Judson et al., 2011; Norton et al., 2006), and their mediators are also players in neurodevelopmental disorders (Ma and Qiu, 2020; Peng et al., 2013; Tomita et al., 2020), immunity (Crawley et al., 2016), and inflammation (Kaminska, 2005). Proliferation also requires cell growth, a role which can be fulfilled by major pathways such as Ras/phosphoinoside

3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) (Borrie et al., 2017; Papa and Pandolfi, 2019; Wang et al., 2017; White et al., 2020), which like MAPK also feed into the cell cycle at the G1 phase (Nussinov et al., 2016b). Here, we mainly focus on the Ras small GTPase superfamily (e.g., Ras, Rho, Rac, Cdc42, Rab, and Rap), their nucleotide exchange factors (GEFs, e.g., SOS1, Son of Seven-less), GTPase-activating proteins (GAPS), and their upstream regulators, and downstream effectors. As we highlight throughout the review, members of the small GTPase Ras superfamily including their regulators, effectors, and components of their signaling pathways appear to be invariably involved in neurodevelopmental disorders. Indeed, it is so much so that when coming across a possible neurodevelopmental disorder in the literature, we search for the small GTPase or its associated functional components which are involved and so far, unfailingly found them.

Uncovering the connections of cancer, immunity, and neurodevelopmental disorders can help clarify the roles of the microenvironments, location, systemic landscape, and timing. The impact of perturbations of the immune system during neurodevelopment (Estes and McAllister, 2016; Knuesel et al., 2014) emphasize the vital importance of the inter-relationships and their underlying mechanisms. The connections of cancer and the immune and the nervous systems are not surprising (Zengeler and Lukens, 2021). Microglia — resident macrophages of the CNS — are primary actors in active immune defense in the CNS. TLRs, cytokines, inflammasomes, and phagocytic signals are vital to effective immune response (Kumar, 2019). They are also vital to proper brain development (Zengeler and Lukens, 2021).

Germline mutations in small GTPases of the Ras superfamily and proteins associated with their regulation and their signaling, expressed in these cells during development, can lead to neurodevelopmental disorders. Examples include phosphatase and tensin homolog (PTEN) tumor suppressor in ASDs (Amar et al., 2021; Busch et al., 2019; Iakoucheva et al., 2019) and *ARHGAP10*, which encodes Rho GTPase-activating protein (RhoGAP) for RhoA and Cdc42. Dysregulation of the signaling pathway of RhoA was proposed to be associated with schizophrenia. Exonic deletion and a missense variant p.S490P in the RhoGAP domain abolishes the association with the active form of RhoA (Sekiguchi et al., 2020). Cytokine imbalances early in neurodevelopment are associated with autism, schizophrenia, cerebral palsy, and cognitive impairment (Jiang et al., 2018), although molecular details are still unavailable. Cerebral palsy is associated with mutations in Rho GTPase (Jin et al., 2020) and cognitive impairment with Rab (Ginsberg et al., 2011). The structural pathways of the GTPases in regulation, cancer development, and immunotherapy have also illustrated the involvement of signaling via MAPK's Ras/Raf/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) and PI3K's AKT/mTOR pathways (Guven-Maiorov et al., 2014).

Here we provide a new view, intertwining neurodevelopmental disorders and cancer, neurodevelopmental disorders and immunity, and cancer and immunity. At the heart of our suggestion are members of the Ras superfamily of small GTPases and their regulatory proteins and downstream pathways such as the MAPKs. Throughout our review, we exemplify their contributions. We also underscore signaling pathways related to e.g., cytokines, TLRs, fibroblast growth factor receptor (FGFR), all are common dysregulated factors in neurodevelopmental disorders and cancer. TLRs (TLR2 and TLR3) activate RhoA via Src family kinases to nuclear factor kappa B (NF-κB) (Manukyan et al., 2009; Oda and Kitano, 2006), suggesting another common link between neurodevelopmental disorders and cancer.

Though much is still unknown, the role of the immune system in neurodevelopmental disorders is becoming increasingly appreciated [e.g. (Garay and McAllister, 2010; Gottfried and Bambini-Junior, 2018; Mossink et al., 2021; Solek et al., 2018; Zengeler and Lukens, 2021),]. *We suggest that this concept of signaling similarities be construed in the framework of the differences in perturbation levels, which depend on cell type, and timing, with chromatin structure playing a decisive role in both. Chromatin organization and gene accessibility are dominant determinants of gene expression.* That gene expression level is a major determinant can also be seen from the severe autism effects of gene deletions, as in the case of chromosome 16 segment (16p11.2) in autism (Niarchou et al., 2019), which result in scenarios resembling chromatin inaccessibility, except that they are permanent. Gene duplication leads to higher expression levels. These innovative biophysics concepts can map a way forward.

Accordingly, the organization of our review initiates with a broad overview of the three connections, starting with immunity. We then highlight biophysics as underlying fundamental biological systems. We end
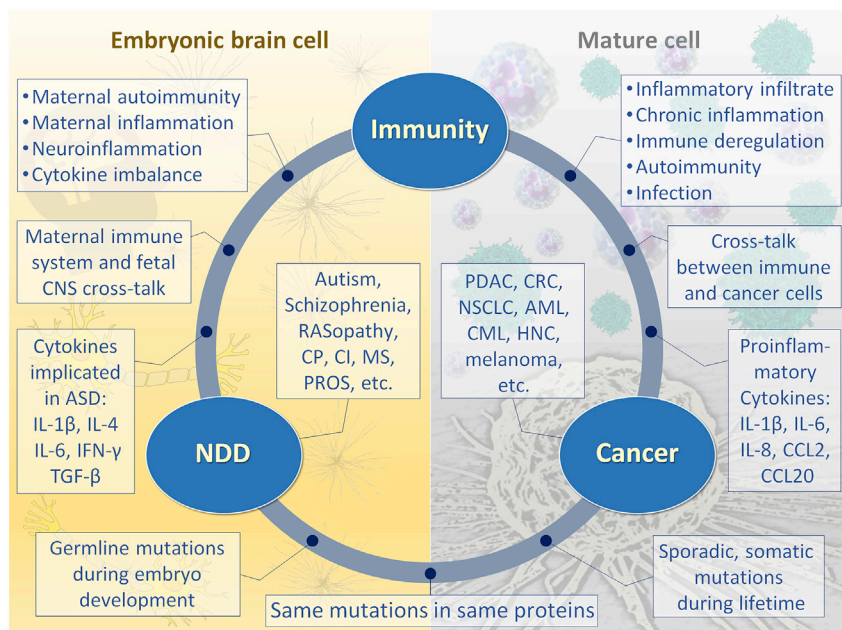
Figure 1. Linkages between cancer, immunity, and neurodevelopmental disorders (NDD)
This figure encapsulates the concept underlying our thesis: immunity could be viewed as the common factor in neurodevelopmental disorders and cancer. Neurodevelopmental disorders and cancer share similarities. However, there are decisive differentiating factors related to the timing window, and cell type specific perturbation levels, pointing to chromatin reorganization. Cancers largely result from sporadic, somatic mutations emerging throughout life, whereas neurodevelopmental disorders result from germline or embryonic mutations during embryo development. Neurodevelopmental disorders are linked to cancer; they can be encoded by the same genes and may also share the same mutations. Both are connected to immunity and inflammation. Abbreviations: CNS, CNS; ASD, autism spectrum disorder; IL-1β/4/6/8, interleukin-1β/4/6/8; IFN-γ, interferon γ; TGF-β, transforming growth factor β; CCL2/20, chemokine ligand 2/20; CP, cerebral palsy; CI, cognitive impairment; MS, multiple sclerosis; PROS, *PIK3CA*-related overgrowth syndrome; PDAC, pancreatic ductal adenocarcinoma; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; HNC, head and neck cancer.

with a broad discussion of cancer, neurodevelopmental disorders, and immunity. The mechanistic connections that the review provides are not only timely. As we discuss in the forthcoming sections, they may also aid drug discovery which is under rapid development and much needed.

THE NATURE OF NEURODEVELOPMENTAL DISORDERS AND CANCER IS SIMILAR. THE DECISIVE DIFFERENCES STEM FROM THE PERTURBATION LEVELS AND THE TIMING. BOTH ARE INFLUENCED BY CHROMATIN ACCESSIBILITY

The immune and nervous systems coevolve as the embryo develops (Zengeler and Lukens, 2021) with connected mechanisms and coordination. The 86 billion neurons and a similar scale of nonneuronal (glia or neuroglia) cells (Azevedo et al., 2009; von Bartheld et al., 2016) fall into distinct cell types. They are differentially located in the brain. This emphasizes that detailed high-resolution studies of the molecules which are involved, their populations in the different cells, and their interactions as the embryo evolves, present staggering challenges. Neurodevelopmental disorders result from dysregulation of neuron differentiation (Song et al., 2019; Zhang et al., 2020). Data for nerve and immune cells of the brain, especially those other than microglia innate immune cells, are lagging. Dysfunction in innate immune signaling pathways has been associated with the phenotypes of specific neurodevelopmental disorders (Chan et al., 2020; Ebstein et al., 2021; Lenz and Nelson, 2018; Mizoguchi and Monji, 2017; Zengeler and Lukens, 2021). These include mental syndromes, such as retardation and autism, and physical presentations, such as facial malformations in RASopathies, double vision in multiple sclerosis, and motor disability as in cerebral palsy (Figure 1). The innate immune system engages microglia leading to neuroinflammation, underlying neurodevelopmental disorders and neurodegenerative diseases (Neuron-line, 2019).

Immunity is also connected to cancer via inflammation (Mantovani et al., 2008). The connections of neurodevelopmental disorders and cancer are similar, with multiple shared proteins and pathways. Their different outcomes, neurodevelopmental disorders, or cancer, relate to the levels of the perturbations, which are influenced by the cell type and the microenvironment, and the timing window in embryonic development. Embryonic chromatin organization differs across developmental stages, and across cell types. The extremely large number of cell types, neural and nonneural, which are expressed at different developmental stages, lead to large perturbations in the genome (and protein) expression levels that influence signaling. Thus, even though the pathways are highly similar, the extent of their signaling can be expected to fluctuate with the cell states. The perturbation in expression levels is determined by the dynamic chromatin remodeling, thus accessibility, which changes during development (Mossink et al., 2021; Nussinov et al., 2021b). This may influence phenotypic presentations, which may differentially overlap, as for example, across RASophathies and ASDs, making their classification difficult. Mutations in neurodevelopmental disorders are mostly in the germline or occurring during embryo development, as for example in *PIK3CA*-related overgrowth spectrum (PROS) (Madsen et al., 2018). The genetic components are also difficult to unravel because most may not be Mendelian (dominant, recessive, or X-linked) and may involve allelic variants in several genes (Au et al., 2020; Ebstein et al., 2021; Savatt and Myers, 2021). However, ~40% are monogenic (Brunet et al., 2021; Deciphering Developmental Disorders Study, 2017). Risk factors include perturbing immune-provoking events, primarily maternal autoimmunity. Cancer largely results from sporadic, somatic mutations emerging throughout life. Mutations are often in the same proteins, and often are common to cancer and neurodevelopmental disorders, leading to questions (Nussinov et al., 2022a) such as "how certain oncogenic mutations can promote cancer while others *in the same proteins* — or even *the same mutations* — can provoke other syndromes" and "*why patients, with neurodevelopmental disorders are more prone to cancer.*" These have recently been taken up and are addressed below. We also discuss why neurodevelopmental disorders are related to higher likelihood of cancer.

IMMUNITY AND THE TUMOR MICROENVIRONMENT (TME)

Cancer is a systemic disease (Hiam-Galvez et al., 2021). It elicits changes in the immune system. Immunity is controlled by interactions of cell lineages in different tissues. Insight into cancer immunology requires a grasp of the TME as well as the systemic immune landscape. Data suggest that immunotherapy drives new immune responses beyond the TME. It also corroborates that prolonged inflammation is a hallmark of cancer (Coussens and Werb, 2002). The environment changes, and the immunological relationships of the tumors and their human host, beyond the adjacent microenvironment (Azizi et al., 2018; Gubin et al., 2018; Steele et al., 2020; Tirosh et al., 2016; Wagner et al., 2019; Zilionis et al., 2019), are still unclear, with data relating to immune cell lineages and their communication across the peripheral immune system still scant. Inflammatory immune cells are present in human tumors; however, they are not attacked by the immune response, likely because the cancer cells evolve mechanisms that mimic peripheral immune tolerance (Gonzalez et al., 2018a).

Classically, carcinomas have been divided into metastatic and nonmetastatic tumors (Gonzalez et al., 2018a; Siegel et al., 2016). Accumulating data suggest that metastasis takes place early in tumor formation (Hosseini et al., 2016; Nussinov et al., 2021c). Circulating cancer cells may dodge and slip away from the primary tumors, mutate, and colonize distant organs (Chambers and Werb, 2015; Gonzalez et al., 2018b; Lambert et al., 2017). Primary and metastatic tumors are composed of neoplastic cells and the extracellular matrix (ECM). They also carry mesenchymal support cells, endothelial cells, and infiltrated inflammatory immune cells which influence cancer evolution and its microenvironment including chronic inflammation (Figure 1). Chronic inflammation is a critical hallmark of cancer (Beaugerie et al., 2013; Coussens and Werb, 2002; Hussain et al., 2000) with autoimmunity, immune deregulation, and infections contributing dominantly. However, exactly how immune cells affect tumor development, early transformation, and metastasis are still not entirely clear.

IMMUNITY, INFLAMMATION, AND CANCER

Protumorigenic inflammation in the microenvironment (Mantovani et al., 2008) often involves feedforward signaling loop accelerated by tumor development (Grivennikov et al., 2010). In proliferation, intracellular signaling stimulated by oncogenes, such as *RAS*, *MYC*, and their family members, remodel the TME via recruitment of leukocytes, tumor-promoting chemokines, cytokines, and formation of new blood vessels (Soucek et al., 2007; Sparmann and Bar-Sagi, 2004). Dead cells in the tumor center can leak proinflammatory proteins, e.g., interleukin-1 (IL-1) and high-mobility group box 1 (HMGB1) (Vakkila and Lotze, 2004),

which unleash macrophages (Kim et al., 2009). Signaling pathways of oncoproteins, e.g., Ras, Myc, and proto-oncogene tyrosine-protein kinase receptor Ret, can promote proinflammatory cytokines and chemokines, e.g., IL-1β, IL-6, IL-8, C-C motif chemokine ligand 2 (CCL2), and CCL20 (Mantovani et al., 2008) (Figure 1). At high expression levels during embryonic development, the mutant alleles of these oncoproteins, e.g., *MYC* (Vella et al., 2012) and *RET* (Gujral et al., 2006), can also drive neurodevelopmental disorders. Cytokines with a role in the nervous system implicated in ASD include IL-1β, IL-4, IL-6, interferon γ (IFN-γ), and transforming growth factor β (TGF-β) (Goines and Ashwood, 2013).

MAPKs are essential regulators of both the innate and the adaptive immune responses. MAPK activities are regulated by reversible phosphorylation on threonine and tyrosine residues (Arthur and Ley, 2013; Liu et al., 2007). TLRs activate MAPKs in innate immune cells (Figure 2). TLR, IL-1R-associated kinases (IRAKs), and K63-linked polyubiquitylated tumor necrosis factor (TNF) receptor associated factor 6 (TRAF6) form a signaling complex which acts to activate MAPKs in primary macrophages (Arthur and Ley, 2013). In innate immune response, MAPK signaling elicits production of proinflammatory cytokines and chemokines, as well as anti-inflammatory feedback pathways. MAPKs activate downstream kinases important in immunity. One such case is p38α activating MAPK-activated protein kinase 2 (MK2 or MAPKAPK2), which elicits TNF-α. On the other hand, the activation of mitogen- and stress-activated kinases (MSKs) by p38α (or ERK1/2) promotes anti-inflammatory cytokines IL-10 and IL-1 receptor antagonists. In another MAPK-immunity connection, inhibitors of MAPK signaling may act as anti-inflammatory drugs (Arthur and Ley, 2013).

MAPK phosphatases (MKPs) can remove the phosphate groups from threonine and tyrosine and thereby regulate the immune response (Liu et al., 2007). They deactivate MAPKs and exert a feedback control mechanism, which can tune the innate immune responses through the production of inflammatory and anti-inflammatory cytokines. They can also modulate the adaptive immune responses. The expressions of dual-specificity phosphatases (DUSPs), phosphatases controlling innate immune responses, are promoted by MAPK. In a negative loop control, DUSPs inactivate MAPKs signaling (Lang et al., 2006; Lang and Raffi, 2019).

In breast cancer, dysregulation of MAPK because of amplification of *KRAS*, *BRAF*, *RAF1*, and truncations of RasGAP neurofibromin gene (*NF1*) was proposed to be linked to an immune-silent phenotype and treatment resistance (Bedognetti et al., 2017). Preclinical evidence supports the capability of MAPK-pathway inhibition to improve the efficacy of immunotherapy, with B-Raf inhibition targeting melanoma and MEK inhibition suggesting a broad tumor applicability, including neurofibromatosis type 1 (NF1)-associated tumors (Klesse et al., 2020). Other pathways related to the immune-silent phenotype or lack of responsiveness to immunotherapy was proposed to include the Wnt/β-catenin (Spranger et al., 2015) and PI3K/AKT pathways (Peng et al., 2016).

The MAPK network crosslinks the ERK, p38, and c-Jun N-terminal kinase (JNK) pathways. It is a complex key regulator in cancer (Bedognetti et al., 2017; Dhillon et al., 2007). With over 25 proposed binding partners including kinases, scaffold proteins, Ras family activators, and transcription factors, it mediates (Suddason and Gallagher, 2015) and executes diverse functions (Cuevas et al., 2003; Pham et al., 2013; Zhang et al., 2003b). The MAPK pathway also promotes e.g., CD4 (T cell) lineage (Sharp et al., 1997), IL-4 receptor function (Yamashita et al., 1999), production of IL-10, and negatively regulates IL-12 (Arthur and Ley, 2013). Finally, the serine/threonine kinase mTOR functions as a metabolic sensor in the metabolic regulation in innate and adaptive immune cells (Jones and Pearce, 2017). As we discuss in the following sections, this network is not only a hallmark of cancer and important in immunity and inflammation. It is also tightly connected to neurodevelopmental disorders with the same proteins and often the same mutations, playing a role in both cancer and neurodevelopmental disorders.

Finally, immune cells are functionally impaired in many neurodevelopmental disorders, raising the question of whether immune cells actively contribute to cancer growth and spread or just fail to respond to tumor self-antigen.

INNATE IMMUNITY AND INFLAMMATION, AND NEURODEVELOPMENTAL DISORDERS

The immune and nervous systems are interconnected (Zengeler and Lukens, 2021). Cytokines, TLRs, the complement family, and other innate immunity components, as well as acquired immunity-related entities, express and fulfill vital functions in brain development. In addition to microglia, lymphocytes regulate
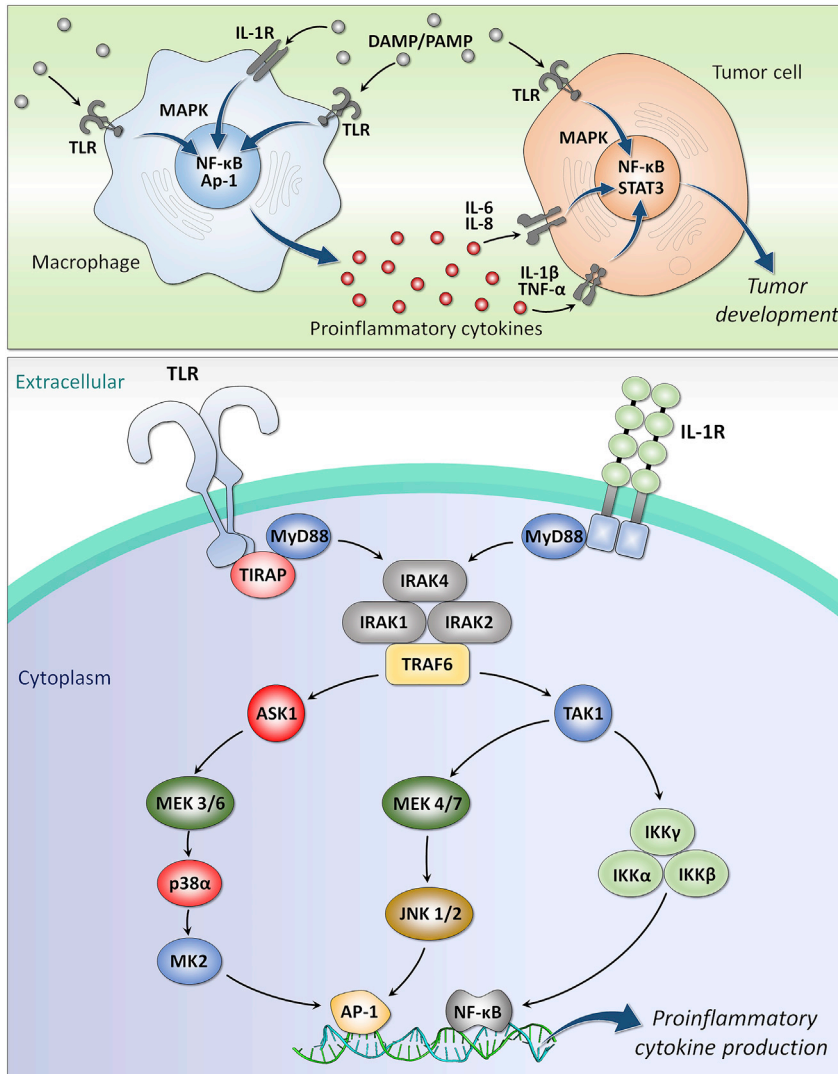
Figure 2. Cross-talk between immune cell and cancer cell

In the TME, an innate immune cell such as macrophage leads to production of proinflammatory cytokines that can promote cancer (*top panel*). Tumor-associated antigens, which act as pathogen-associated molecular pattern (PAMP) or damage-associated molecular pattern (DAMP), can activate TLR or IL-1R in macrophage (Korneev et al., 2017; Sarode et al., 2020). After activation, TLR recruits MyD88 through an adapter protein, TIRAP (or MAL, MyD88 adaptor-like), activating the IRAKs/TRAF6 signaling (*bottom panel*). IL-1R can directly recruit MyD88 without the adapter protein. The IRAKs/TRAF6 complex promotes the activation of ASK1 (apoptosis signal-regulating kinase 1, a.k.a, MAP3K5) or TAK1 (TGF-β-activated kinase 1), leading to the activation of transcription factors, NF-κB, and AP-1 (activator protein 1). These transcription factors target the genes to produce the proinflammatory cytokines such as IL-1β, IL-6, IL-8, and TNF-α. Both ASK1 and TAK1 activate the MAPK signaling pathway targeting AP-1. TAK1 also activates the IKK (IκB kinase) complex composed of IKKα, IKKβ, and IKKγ (a.k.a. NEMO, NF-κB essential modulator) leading to the activation of NF-κB. AP-1 and NF-κB are also known to contribute to tumor developments including cell cycle regulation, growth, survival, chemokine, and adhesion molecule production for cell migration and apoptosis.

cognition and act in the neuronal circuits (Morimoto and Nakajima, 2019). The cytokines mediate diverse processes (Borsini et al., 2015; Carpentier and Palmer, 2009; Deverman and Patterson, 2009; Zengeler and Lukens, 2021). The IL-1 family of cytokines includes inflammatory IL-1α, IL-1β, and IL-33. The structural pathway of IL-1 initiated signaling was constructed, including some mapped mutations, revealing mechanisms of oncogenic mutations (Acuner Ozbabacan et al., 2014). More broadly, the constructed structural pathways of cytokines illuminate their roles in regulation of cancer development and immunotherapy (Guven-Maiorov et al., 2014). IL-1α and IL-1β interact with IL-1R1 (interleukin-1 receptor type 1), triggering
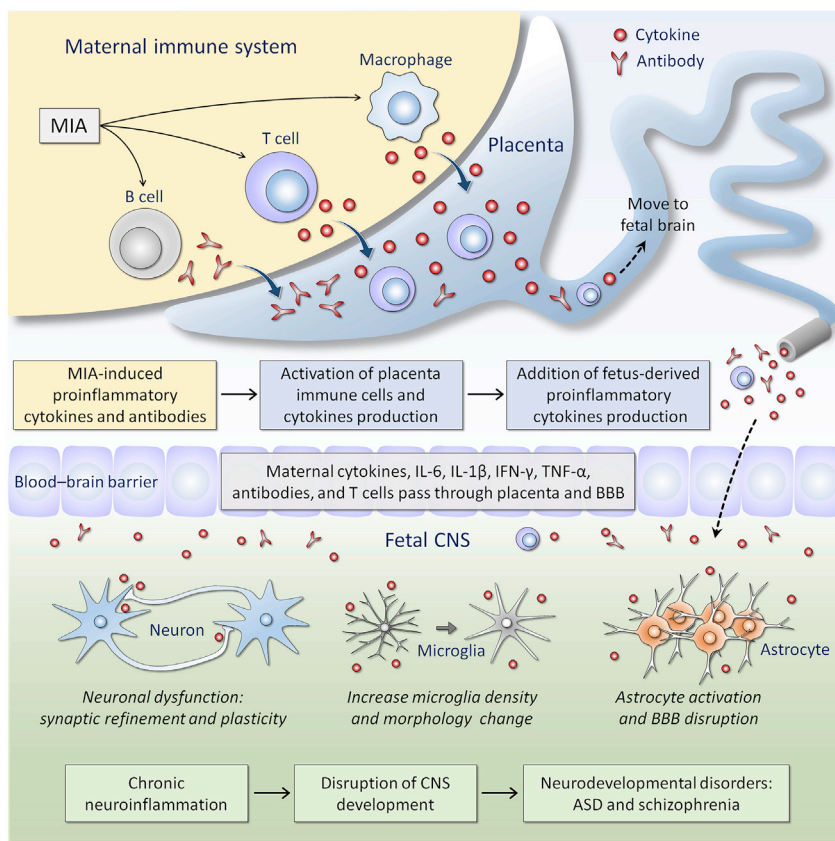
Figure 3. Maternal immunity and neuroinflammation of fetal brain

Abnormal maternal immune responses because of genetic autoimmune diseases or infections during pregnancy induce maternal immune activation (MIA). In response to MIA, maternal immune cells, such as macrophage, T cell, and B cell, release proinflammatory cytokines (IL-6, IL-1β, IFN-γ, and TNF-α) and antibodies. These maternal cytokines, antibodies, and even T cells cross the placenta and activate fetal immune cells, enhancing the production of fetus-derived proinflammatory cytokines. This leads to an increase in the levels of proinflammatory cytokines and immunological markers that can cross the blood-brain barrier (BBB) to the central nervous system (CNS) of the fetal brain. The alterations in the cytokine levels of CNS affect fetal brain development, inducing chronic neuroinflammation that leads to neurodevelopmental disorders such as autism spectrum disorder (ASD) and schizophrenia.

myeloid differentiation primary response 88 (MyD88)-dependent, MAPK, and nuclear factor κB (NF-κB) signaling pathways (Borsini et al., 2015; Carpentier and Palmer, 2009; Deverman and Patterson, 2009; Zeng-eler and Lukens, 2021) (Figure 2). The brain is currently viewed as immune-controlled with molecules associated with the immune system acting in brain development. It contains $\sim 10^{11}$ neural cells that are classified into hundreds of different neuronal subtypes, which may partly explain the distinct phenotypes of the neurodevelopmental disorders and their partial overlaps. The cell type-specific chromatin structures and accessibility of the regulatory regions of the involved genes dictate altered gene expression patterns as brain cells evolve (Suliman-Lavie et al., 2020).

Maternal immune activation (MIA) is a significant risk factor for neurodevelopmental disorders, such as autism (Enstrom et al., 2009), schizophrenia, and cerebral palsy (Figure 3). Elevated IFN-γ cytokines were observed to modify the expression of genes associated with schizophrenia and autism in the offspring brain (Warre-Cornish et al., 2020). Recently a cohort study associated maternal autoimmune diseases with increased attention-deficit/hyperactivity neurodevelopmental disorder (ADHD) among children, suggesting a possible shared genetic vulnerability or a role for MIA (Hughes et al., 2018). A Swedish population-wide familial co-aggregation study indicated that the connection between ADHD and autoimmune diseases relates to shared genetic risk factors, rather than MIA (Hegvik et al., 2021). Maternal autoimmunity and inflammation have also been associated with childhood involuntary movements and sounds, and
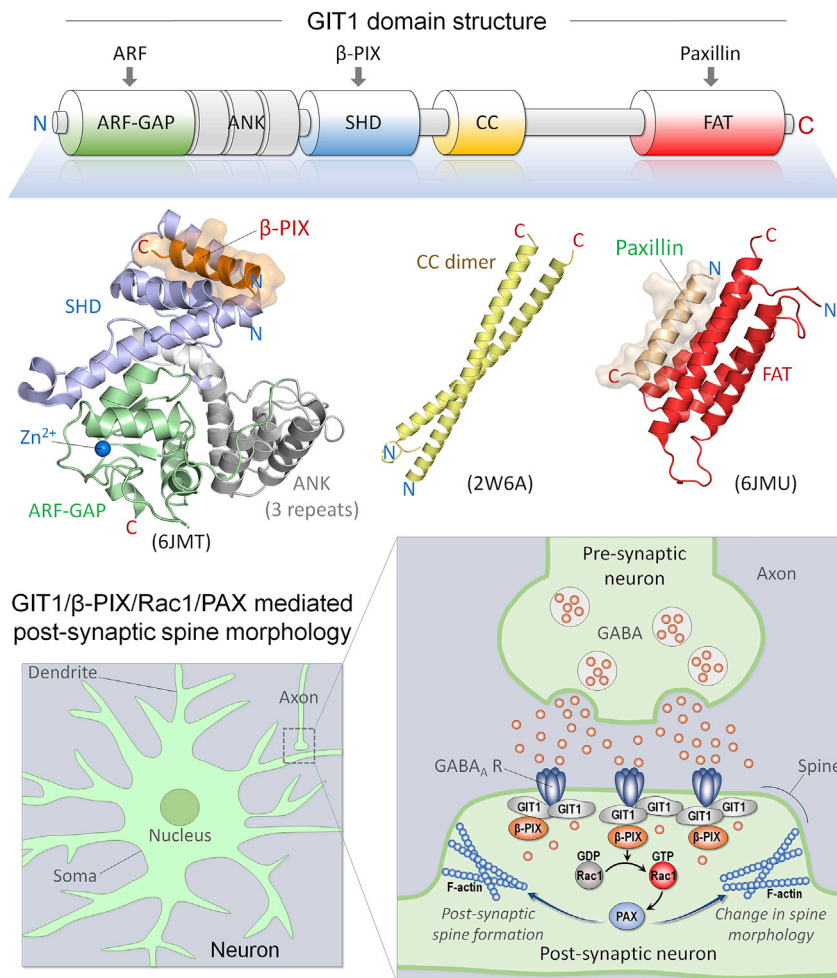
Figure 4. GIT1 domain structure and its function in synapse formation

GIT1 contains an N-terminal GTPase-activating domain for ARF (ARF-GAP), three repeats of Ankyrin (ANK) domain, a Spa2-homology domain (SHD), a coiled-coil (CC) domain, and a C-terminal focal adhesion targeting (FAT) domain. The ARF-GAP domain contains a zinc-finger-like motif regulating the ARF family of small GTPases. The main binding partner for SHD is β-PIX (ARHGEF7, a GEF for Rho GTPases such as Rac1 and Cdc42). The crystal structure depicts a helix of β-PIX GBD (GIT-bind domain) binding to SHD of GIT1 (PDB: 6JMT, mouse). The crystal structure of the CC domain of GIT1 representing a parallel CC dimer (PDB: 2W6A, rat). The CC domain is responsible for dimerization of GIT1, mediating oligomerization of GIT1 and β-PIX. The crystal structure of the FAT domain is complex with paxillin (PDB: 6JMU, mouse). The FAT domain is also called PBS (paxillin-binding site). GIT1 is important for synapse formation, regulating spine density and synaptic plasticity. At the postsynaptic neuron, subcellular localization of GIT1/β-PIX scaffold regulates synaptic stability of neurotransmitter gamma-aminobutyric acid receptor A (GABA$_A$ R) cluster that mediates inhibitory synaptic transmission. The exchange factor β-PIX activates locally coordinating Rac1 (or Cdc42). The active Rac1 (or Cdc42) activates the serine/threonine kinase PAK, leading to F-actin polymerization and stabilization, in turn promoting spine formation and stabilization. Dysfunction of GIT1 by mutations or gene deletion is associated with neurodevelopmental disorders such as microencephaly and cognitive deficit observed in schizophrenia.

obsessive-compulsive disorder, with transcriptomic data showing common enriched innate immune pathways (Jones et al., 2021).

Neurodevelopmental disorders can also involve mutations in ADP-ribosylation factor (ARF) GTPase-activating protein GIT1 (GIT1), a signaling adaptor, which interacts with RhoA guanine nucleotide exchange factors, especially factor-7 (ARHGEF7, also called β-PIX), which regulate postsynaptic spine morphology and density that support learning and memory (Figure 4). GIT1 is also associated with microencephaly, a neurodevelopmental phenotype (Hong and Mah, 2015; Manresa-Arraut et al., 2018). In addition, GIT1 is

involved in breast tumor growth by regulating Notch signaling (Zhang et al., 2022). PAK-interacting exchange factor (PIX) proteins act for Rac1 and Cdc42 small GTPases in the Ras superfamily. Maternal multiple sclerosis is not a risk factor for neurodevelopmental disorders in offspring (Carta et al., 2021), but other autoimmune conditions can be. In multiple sclerosis, 60% of patients carry somatic variants, arising during a developmentally late-embryonic stage (Van Horebeek et al., 2019). Neurodevelopmental disorders such as ASDs, cognitive impairment, cerebral palsy, epilepsy, and schizophrenia were associated with inflammation during development (Deverman and Patterson, 2009; Jiang et al., 2018).

THE CONNECTIONS BETWEEN NEURODEVELOPMENTAL DISORDERS AND CANCER

Neurodevelopmental disorders are associated with specific cell types at specific locations and certain developmental time windows during the brain evolution. The locations of the cells are linked to their function (Bhaduri et al., 2021; Neuroscience News and Research, 2021). Cells in the prefrontal cortex are associated with cognition, in the back they are linked to vision. The respective genes are expressed early. Expression patterns of cells in-between these areas are delayed, likely linked to the identities of the gained interactions (Curry and Glasgow, 2021; Luo et al., 2021; Rubenstein, 2011; Szczupak et al., 2021). As examples of locations and function, in early and mid-fetal development, ASD risk genes in prefrontal and primary motor cortices, striatum, cerebellum, and medial dorsal nucleus of the thalamus express at high levels (Nussinov et al., 2022a). Connective tissue dysplasia is common in patients with NF1 microdeletions and include CNS cancers in the brain or spinal cord, astrocyte cells that support nerve cells, peripheral nerve sheath tumors, and more (Mensink et al., 2006). Cerebral Palsy affects the motor area of the brain's outer layer that directs muscle movement. It is caused by abnormalities in the brain that disrupt the brain's ability to control movement and posture. Structural and functional changes are in the connective tissue in the gastrocnemius muscle, a superficial two-headed muscle that is in the back part of the lower leg (Pingel et al., 2021). Nuclear receptor subfamily two group F member 1 (NR2F1) cortical transcription factor and B-cell lymphoma/leukemia 11A (BCL11A), which is required for neuronal morphogenesis and sensory circuit formation in dorsal spinal cord development (John et al., 2012) and interacts with NR2F1, provide an example on the molecular level. Both are associated with neurodevelopmental disorders (Bhaduri et al., 2021; Rubenstein, 2011). In forebrain patterning, FGF/FGFR signaling (Figure 5) from a rostral source was proposed to influence the adjacent neuroepithelium by regulating the expression of transcription factors (Garel and Rubenstein, 2004; Grove and Fukuchi-Shimogori, 2003; Hoch et al., 2009; Mason, 2007; O'Leary et al., 2007; O'Leary and Sahara, 2008; Rash and Grove, 2006; Rubenstein, 2011; Sur and Rubenstein, 2005) in telencephalon patterning and neurogenesis (Gutin et al., 2006; Hebert et al., 2003; Sansom et al., 2005; Thomson et al., 2009). This RTK-stimulated signaling regulates cellular lineage commitment, differentiation, proliferation, and apoptosis, which is crucial in embryonic development and in adult homeostasis, providing another example (Xie et al., 2020). FGF/FGFR signaling pathways include Ras/Raf/MEK/ERK, PI3K/AKT/mTOR, JAK/STAT, and phospholipase Cγ (PLCγ)/PKC (Xie et al., 2020).

Small GTPases of the Ras superfamily are key regulators of diverse cellular and developmental events including differentiation, cell division, vesicle transport, nuclear assembly, and control of the cytoskeleton (Lundquist, 2006). It is thus not surprising that dysregulation of members of this superfamily, their regulators, effectors, and signaling pathways are associated not only with cancer, but invariably also with diverse neurodevelopmental disorders (Figure 6). Hamartin and tuberin tumor suppressor genes, *TSC1* and *TSC2*, encode tuberous sclerosis complex 1 (TSC1) and TSC2, respectively. The GTPase-activating proteins TSC1 and TSC2 inhibit Rheb (Ras homolog enriched in brain) protein, thus acting as tumor suppressors. Their coiled-coil domains form an intracellular complex that regulates Rheb, whose signaling promotes activation of mTOR kinase, stimulating cell growth (Jin et al., 2017; Rosset et al., 2017). TSC also increases the rates of autism (25–50%), epilepsy, and mental retardation (Wiznitzer, 2004). Additional examples include Rho GTPases in palsy (Jin et al., 2020) and in intellectual disability (ID) (Zamboni et al., 2018). Rho GTPases link extracellular cues to the neuronal responses required for the construction of neuronal networks, as well as for synaptic function and plasticity. Rac3 has been linked to neuronal development (de Curtis, 2019) as discussed before for Rac1. Rit2 (Ras-like without CAAX 2) has been linked to schizophrenia, bipolar disorder, and autism in addition to cancer (The Human Protein Atlas, 2021). Mutations in the GTP/GDP-binding region of RalA, a Ras-like small GTPase, cause ID and developmental delay (Hiatt et al., 2018). Indeed, Rho GTPases were proposed as therapeutic targets in Alzheimer's disease (Aguilar et al., 2017), and disrupted in schizophrenia 1 (DISC1) regulates axon guidance through the activation of Trio/Rac/p21-activated kinase (PAK) small GTPases signaling pathway (Chen et al., 2011). In addition, individuals with bipolar disorder experience high risk for lung, colorectal, and breast cancer (Johns Hopkins Medicine, 2012; McGinty
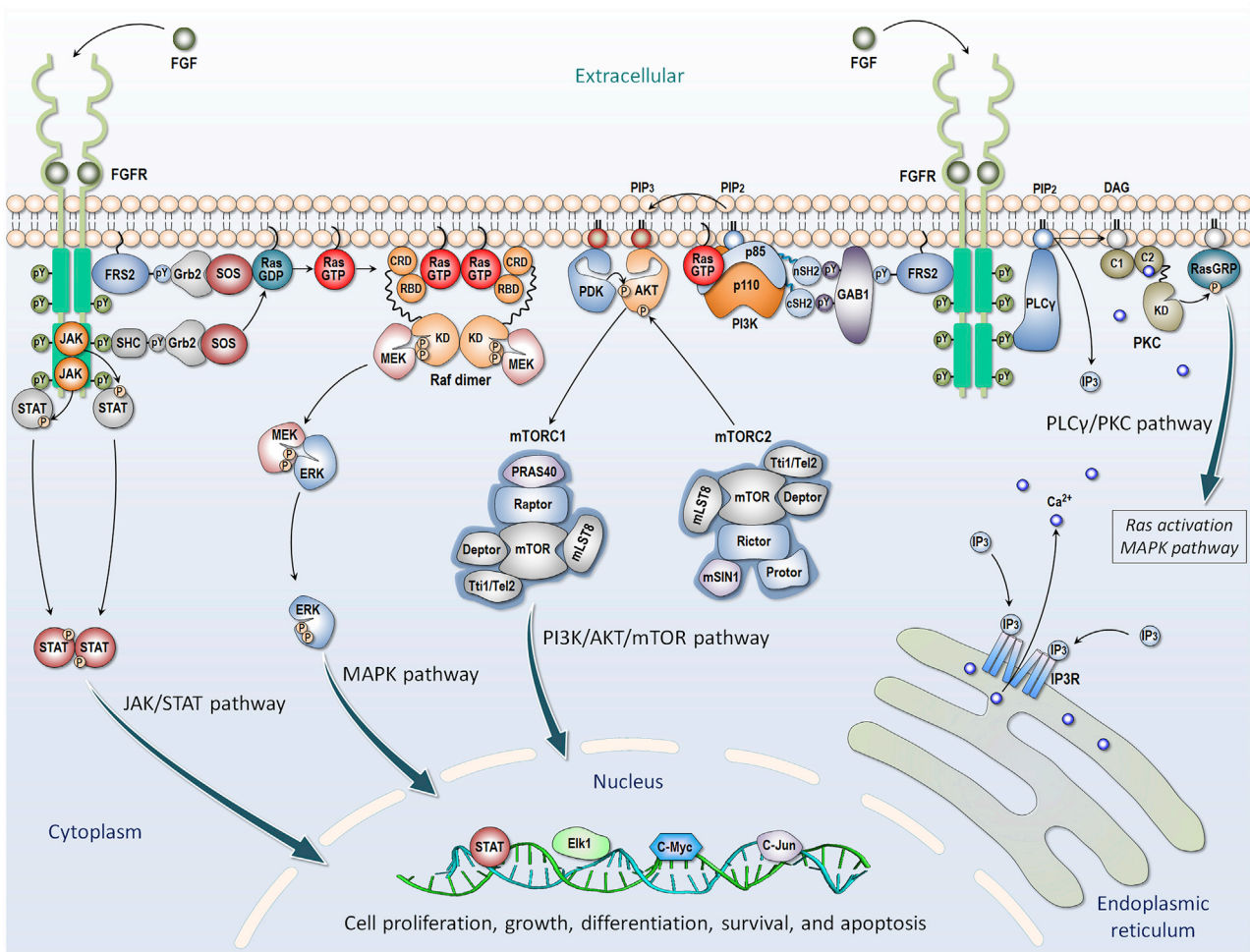
Figure 5. The classical FGF/FGFR signaling pathway

The FGF/FGFR signaling regulates a wide range of cellular functions, including migration, proliferation, differentiation, and survival, as well as development, metabolism, and tissue homeostasis. Human diseases, such as cancer and neurodevelopmental disorders are often observed with dysfunction of the FGF/FGFR signaling. Binding of FGF to the receptor at the extracellular side leads to dimerization and activation of the kinase domain of FGFR in the cytosol. FGFR regulates the downward signaling pathways of Ras/Raf/MEK/ERK, PI3K/AKT/mTOR, JAK/STAT3, and PLCγ/PKC. The active FGFR kinase domain phosphorylates FRS2 (FGFR substrate 2), an adaptor protein bound to the juxtamembrane domain of FGFR. Phosphorylated FRS2 recruits Grb2/SOS and GAB1 (Grb2 associated binding protein 1) to the plasma membrane, activating Ras in the MAPK and PI3K in the PI3K/AKT/mTOR pathways, respectively. Active Ras proteins form a nanocluster, recruiting Raf to the plasma membrane and leading to Raf activation through the dimerization of kinase domains. Active Raf dimers lead to activation of a series of the MAPK kinases. A lipid kinase PI3K phosphorylates signaling lipid phosphatidylinositol 4,5-bisphosphate (PIP$_2$) to phosphatidylinositol 3,4,5-trisphosphate (PIP$_3$) at the plasma membrane. PIP$_3$-bound PDK1 (phosphoinositide-dependent protein kinase 1) and mTOR complex 2 (mTORC2) phosphorylate and activate PIP$_3$-bound AKT. The active AKT regulates the activation of mTORC1 leading to cell growth. In the JAK/STAT pathway, JAK binds FGFR, phosphorylates the receptor's Tyr residues to recruit STAT to the receptor, and then phosphorylates STAT to release it. Two phosphorylated STAT proteins form a dimer, enter the nucleus, and bind to DNA for gene transcription. In the PLCγ/PKC pathway, PLCγ binds to the phosphorylated Tyr residue at the C-terminal tail of FGFR and hydrolyzes PIP$_2$ to produce IP$_3$ (inositol triphosphate) and DAG (diacylglycerol). The released IP$_3$ molecules from the plasma membrane translocate to the ER and bind to the IP$_3$ receptor (IP3R) at the ER membrane, promoting Ca^{2+} release to the cytosol. DAG and Ca^{2+} recruit the C1 and C2 domains of PKC (protein kinase C), respectively, to the plasma membrane and activate the kinase domain of PKC. The active PKC kinase domain phosphorylates and activates DAG-bound RasGRP (Ras guanyl-releasing protein 1, a GEF for Ras) at the plasma membrane. Active RasGRP interacts with Ras and activates Ras/MAPK signaling. FGFR regulates a number of cellular functions from embryogenesis to adult tissue homeostasis, targeting various transcription factors, such as STAT, Elk1, c-Myc, and c-Jun, leading to cell proliferation, growth, differentiation, survival, and apoptosis.

et al., 2012), with those with serious mental illness, such as schizophrenia, bipolar disorder, and disabling depression are 2.6 times more likely to develop cancer than the general population. However, another study did not observe an apparent association between bipolar disorder and cancer in a large epidemiological study of outpatients in a managed care population (Kahan et al., 2018). *ARHGAP10*, which encodes
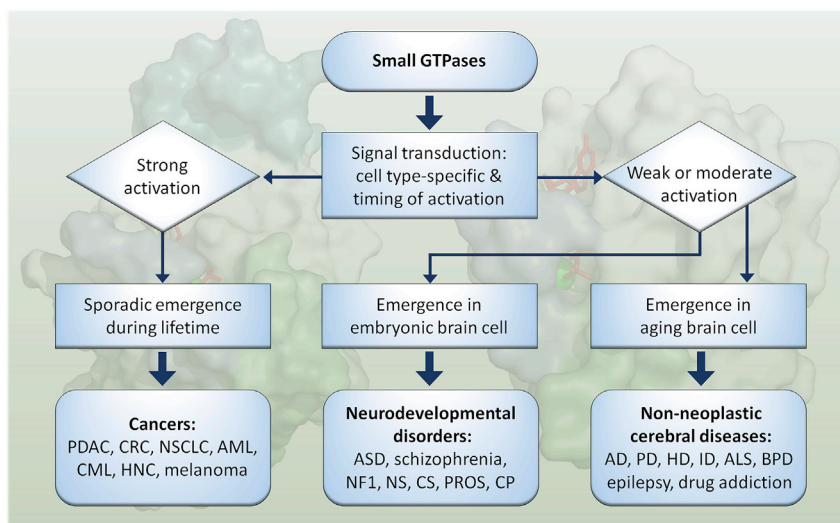
Figure 6. Small GTPases and their associated neurologic and cancer pathologies

Dysregulation of members of the Ras superfamily including the subfamilies of Ras, Rho, Rab, ARF, Rap, Rheb, and Rit are associated with cancer, neurodevelopmental disorders, and nonneoplastic cerebral diseases. Strong activation of these small GTPases resulting from sporadic somatic mutations accumulating throughout life can provoke cancers. During embryonic brain cell development, the same (as in cancer) or different mutations in the same proteins activate the small GTPases, their regulators or nodes in their pathways, leading to neurodevelopmental disorders. The mutations appear to be mostly of moderate strength but can be strong hotpots. During aging, these mutations are associated with non-neoplastic cerebral diseases in the brain. However, they can collaborate with oncogenic mutations emerging during life, rendering individuals with neurodevelopmental disorders more susceptible to cancer. Abbreviations: PDAC, pancreatic ductal adenocarcinoma; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; HNC, head and neck cancer; ASD, autism spectrum disorder; NF1, neurofibro-matosis type 1; NS, Noonan syndrome; CS, Costello syndrome; PROS, PIK3CA-related overgrowth syndrome; CP, ce-rebral palsy; AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease; ID, intellectual disability; ALS, amyotrophic lateral sclerosis; BPD, bipolar disorder.

RhoGAP for RhoA and Cdc42, was identified as a novel gene for schizophrenia risk (Sekiguchi et al., 2020). At the same time, *ARHGAP10* plays a key role in the proliferation, migration and invasion of lung cancer cells (Teng et al., 2017), and expression of *ARHGAP10* correlates with prognosis of prostate cancer (Gong et al., 2019). Rac1 and Cdc42 pathways are pivotal axes in metastatic cancer (Svensmark and Brake-busch, 2019). Human Rac1$^{P29\ S/L}$ is present in melanomas (Mar et al., 2014) where haptotaxis (directionality) and velocity of cells are reduced (King et al., 2016). On the other hand, higher expression levels of Cdc42 in mammary gland epithelial cells increased motility, invasion, and poor prognosis of metastatic breast can-cer. Functional dysregulation of Cdc42 causes diverse developmental phenotypes (Martinelli et al., 2018) and Rac1 has been implicated in ASD and ID (Tian et al., 2018) and glial changes in neurodevelopmental disorders (Wang et al., 2020). For further discussion and data see (Shieh, 2019). The connection between neurodevelopmental disorders and cancer has also been reviewed for pathologies such as RASopathies, including NF1, Noonan syndrome (NS), Costello syndrome (CS), [e.g., (Baltanas et al., 2020, 2021; Bergqvist and Wolkenstein, 2021; Castel et al., 2020; Christou et al., 2022; Gripp et al., 2020; Gross et al., 2020; Inoue et al., 2021; Kessler et al., 2021; Klomp et al., 2021; Leclerc et al., 2021; Lee et al., 2021; Malaquias and Jorge, 2021; Mitri et al., 2021; Prior, 2021; Rauen et al., 2021; Riller and Rieux-Laucat, 2021; Van et al., 2020; Weber and Carroll, 2021),], PROS (Madsen et al., 2018; Martinez-Lopez et al., 2017; Venot et al., 2018; Venot and Canaud, 2017), ASD (Hanly et al., 2021; Liu et al., 2021; Spina Nagy et al., 2021; Tiwari et al., 2021; Valentine et al., 2020; Yehia et al., 2019, 2020), cerebral palsy, and more (Bartels et al., 2020; Curry and Glasgow, 2021; Fahey et al., 2017; Gabriele et al., 2018). All have been linked to the Ras small GTPases superfamily and their signaling components. The activation mechanisms of mutations in cancer have been explored in several proteins, including K-Ras, B-Raf, and PI3Kα (Lu et al., 2016a, 2016b; Maloney et al., 2021; Nussinov et al., 2021d; Zhang et al., 2019; 2021a), as well as a comparison between cancer versus neurodevelopmental dis-order mutations (Smith et al., 2019). Ongoing work exploiting the recent determination of the activation

mechanism of PTEN at the membrane (Jang et al., 2021) aims to elucidate neurodevelopmental mutations in autism versus cancer.

Recently, we asked how *same-gene mutations* can promote both cancer and neurodevelopmental disorders and *why patients with neurodevelopmental disorders are more prone to cancer* (Nussinov et al., 2022a). We proposed that these questions can be understood in terms of four components: first, the expression level of the protein in the type-specific cell; second, the mutation strength; third, the timing of the protein (and mRNA) expression during embryonic development versus in the differentiated state; and fourth, the expression levels of proteins in the pathway through which the signal propagates. Very high expression levels and potent protein activation events result in robust signaling that can drive cancer (Goyal et al., 2017) including stemness (Madsen et al., 2021). Low expression levels and weaker activation (or downregulation) can lead to moderate signal transduction and neurodevelopmental disorders. We associated these to the cell cycle, oncogene-induced senescence (OIS), and premature developmental senescence. Both act by exiting the cell cycle (Nussinov et al., 2022a).

Neurodevelopmental disorders can emerge from germline or embryonic mutations. Their phenotypes are determined by the cell type-specific expression levels of the alternatively spliced isoforms (and their co-expression modules) of the corresponding genes at certain timing windows (Chau et al., 2021; Gandal et al., 2018). These need to be sufficiently high for the signal to go through. Both relate to chromatin structure and accessibility of the respective genes and their regulators, which vary with cell type, developmental stage, and location in the brain, as recently shown for autism (Suliman-Lavie et al., 2020). Thousands of alternatively spliced isoforms are expressed at different levels during brain development, and isoforms of the same gene can have divergent properties and interact with different protein partners (Guglielmi, 2022; Lin et al., 2015; Yang et al., 2016), arguing that isoform-level data are essential (Guglielmi, 2022). The identity of the mutation also influences the signal strength.

WHY INDIVIDUALS WITH NEURODEVELOPMENTAL DISORDERS MAY BE MORE LIKELY TO DEVELOP CANCER?

To explain why individuals with neurodevelopmental disorders may be more likely to develop cancer, we consider these aspects: (i) Cancer and neurodevelopmental disorders involve the same signaling pathways, often the same proteins. (ii) A single mutation is commonly insufficient to promote cancer. Rather, several mutations are involved (Nussinov et al., 2021c; Tomasetti et al., 2015). (iii) An embryo may not survive multiple preexisting strong drivers. However, it may survive one. Thus, preexisting embryonic germline mutations in neurodevelopmental disorders may collaborate with emerging sporadic mutations to drive cancer (Nussinov et al., 2022a). The mutations may emerge in the same protein, or pathway, or different pathways, and/or in chromatin remodelers.

THE RAS GTPASES SUPERFAMILIES ARE FUNDAMENTAL PLAYERS IN IMMUNITY, NEURODEVELOPMENTAL DISORDERS, AND CANCER

Here we highlighted the Ras superfamily of small GTPases, including the subfamilies of Ras, Rho, Rab, ARF, Rap, Rheb, and Rit (Auer et al., 2011; Reichova et al., 2018), as vital players in neuronal development and cell differentiation. In line with our thesis, they are differentially expressed in the nervous system, in neurons and glial cells (Stankiewicz and Linseman, 2014). Their physiological activities are essential for neuronal differentiation and maturation (Bolis et al., 2003; Govek et al., 2005; Heasman and Ridley, 2008; Huang et al., 2017; Martin-Vilchez et al., 2017; Reichova et al., 2018); changes in their signaling strength are expected to contribute to neurodevelopmental disorders. Proper axon growth and synaptic development requires (i) a sufficiently high number of the active molecules, which depends on the expression level of their differentially expressed isoforms and isoform co-expression modules (Chau et al., 2021), and (ii) that their cell-specific populations and that of their regulators be balanced (Hynds, 2015; Martin-Vilchez et al., 2017). Within the Ras GTPase superfamily, Rho GTPases regulate changes in post-synaptic spine morphology and density that support learning and memory (Martin-Vilchez et al., 2017) (Figure 4). The timing of the regulators' actions within the specific cells was proposed to uniquely regulate either early spine precursor formation or maturation and to exhibit stage-specific roles at discrete stages of synaptic development (Ahnert-Hilger et al., 2004; Hodges et al., 2011; Nakayama et al., 2000; Newell-Litwa et al., 2015; Ng et al., 2002; Rex et al., 2009; Tashiro and Yuste, 2004; Zhang and Macara, 2006; Zhang et al., 2003a). A change in their signaling can result in abnormal spine morphology and synaptic development, contributing

to neurodevelopmental disorders (Billuart et al., 1998; Huesa et al., 2010; Nadif Kasri et al., 2009; Petratos et al., 2008). Rho family members are regulators of the cytoskeleton and are critical in ID, cerebral palsy, and can also be involved in cancer. Rac is a subfamily of Rho. The population of the Rac3 isoform is believed to have evolved more recently than Rac1. Increasingly, observations validate its vital function in neuronal development and in cancer, with its specific actions differing from those of Rac1, underscoring the non-redundant roles of the isoforms in the brain (de Curtis, 2019).

POSSIBLE THERAPEUTIC TARGETING STRATEGIES IN NDDS AND CANCER

Considering the similarities of signaling pathways between neurodevelopmental disorders and cancer, with involvement of the same proteins, and sometimes even the same mutations, in principle similar drugs and strategies can be used. NF1 provides a remarkable recent example. After a series of clinical trials, phase II registration trial of the MEK inhibitor selumetinib (ClinicalTrials.gov, 2021; Herrick et al., 2021; Klesse et al., 2020; Osum et al., 2021), resulted in the FDA approval of a therapy for NF1 related inoperable plexiform neurofibromas in children. MEK is a kinase in the MAPK pathway, through which NF1 signals. NF1's mutations involve a genetic disorder characterized by the development of multiple noncancerous, as well as neurofibromatosis, an inherited disorder of the nervous system in which tumors develop on nerves. Selumetinib (AZD6244 hydrogen sulfate) causes plexiform neurofibromas to shrink or slows down their growth. Ongoing efforts target mutations in other RASopathies, such as CS with mutations in Ras (G12S). Here, strategies targeting oncogenic Ras are being tested. However, because the mutation is different, the drug that needs to attach to it differs.

Abilify and Risperdal antipsychotic medications, approved by the FDA for children with autism, provide examples for different types of drugs, which do not relate to cancer. Such drugs include targeting receptors (metabotropic glutamate receptor 5 (mGluR5) antagonists) to improve cognition and behavioral deficits in the fragile X syndrome (Berry-Kravis et al., 2018) and autism (Diaz-Caneja et al., 2021), as well as neuropsychiatric drugs. These are away from our focus here.

BIOPHYSICAL STUDIES ARE VITAL

Biophysics seeks to understand how complex systems, such as the brain and the immune system work. Despite the paucity of data, biophysics is being employed in systems and connections discussed here. Throughout the review we highlighted pathways, signaling, and interactions. These involve structures, affinities, and concentrations. This is biophysics.

As examples, biophysics indicates that mechanistically, physiological activation is unchanged in dysfunction, except that the processes are not regulated. Mutations work by mimicking the wild type, as can be seen in Ras (Nussinov et al., 2021a, 2022b). Biophysics can suggest why mutations in the same protein can lead to differential outcomes, e.g., cancer or neurodevelopmental disorders, as discussed before. The structures of many members of the small GTPases superfamily are available, including their regulators and effectors. These, including their dynamics, allow modeling their interactions to construct their signaling pathways. Examples include the architecture of the Toll/IL-1R homology (TIR) domain signalosome in the TLR4 signaling pathway, where the modeling coupled with experimental data could provide insights into signaling in cancer and inflammation pathways (Guven-Maiorov et al., 2015) and TRAF3, a key node in innate and adaptive immune signaling (Guven-Maiorov et al., 2016). Notably, chromatin structure, its dynamics and modulation, is unraveled by biophysics.

PERSPECTIVE

Neurodevelopmental disorders and cancer frequently share the same pathways and the same proteins, leading us to propose that the nature of neurodevelopmental disorders and cancer is similar. The differences between cancer and neurodevelopmental disorders largely stem from the perturbation levels of gene expression, which we believe relate to cell type, and the timing window of expression in embryonic development. These factors point toward chromatin structure playing key roles. Cell type and timing window may also explain the overlaps and differences among the neurodevelopment disorders phenotypic presentations, such as among the spectrum of ASDs and RASopathies, IDs, and facial deformations. The coevolution of the immune and nervous systems (Zengeler and Lukens, 2021) suggests that immunity may be a common connecting factor between neurodevelopmental disorders and cancer. Multiple pathways of immune-related factors including cytokines, TLRs, FGFR can be dysregulated in neurodevelopmental disorders and in cancer.

Members of the small GTPase superfamily and their signaling components play cardinal roles under physiological conditions, in neurodevelopmental disorders, in cancer, and in immunity. Exactly how is only beginning to be understood. Systems in the human body are not stand-alone. This is especially striking here, because we are dealing with the nervous system and immunity. The rapid increase in the number of publications connecting neurodevelopmental disorders and immunity and inflammation, and those connecting neurodevelopmental disorders and cancer are testament to the peaking interest of the community in unraveling these connections because of their potential in human health.

We believe that for in-depth understanding two key elements are crucial: (i) the cellular structural networks of the protein families, and (ii) the expression levels of each of the proteins that are involved *in the specific cell type during a specific stage in development*. Owing to sparseness of data, such single cell transcriptomics are technically highly challenging; entries are missing, and they are noisy. Structural networks may not be able to distinguish between isoforms whose sequences (thus structures) are highly similar, yet have different functions, as discussed earlier for Rac1 versus Rac3, or K-Ras4B versus e.g., N-Ras or H-Ras, or splice isoform K-Ras4A (Muratcioglu et al., 2017; Nussinov et al., 2016a; Nussinov et al., 2021e), or Rap1A versus Rap1B (Nussinov et al., 2020). Posttranslational modification, degradation, and other forms of regulation are also important factors. Together with single, cell-specific transcriptomics determined for specific cell states and developmental windows, and mutational data, they can however help make strides toward deciphering the enigma of the connections between neurodevelopmental disorders, immunity, and cancer. To do this, we need *measurements of signal strengths and determination of thresholds* in cancer, especially in stemness, and in neurodevelopmental disorders. We expect them to differ. This is the essence of our signaling-by-numbers paradigm, where the *numbers* relate to the *number of active molecules* in specific cells at specific times (Nussinov et al., 2022a). Finally, with similar pathways, and same proteins, similar therapeutic targeting strategies may be used.

CONCLUSION

Cancer involves proliferation, where cell growth and division are out of control. Neurodevelopmental disorders involve dysregulation of differentiation, resulting in altered cell lineage. Unlike cancer, neurodevelopmental disorders are nonlethal. Yet, dysregulated MAPK — a pathway that initiates proliferation in cancer — is a major signaling pathway in both. Because cancer, which is mostly the outcome of sporadic mutations and neurodevelopmental disorders — mostly the outcome of germline mutations — occurs in (largely) different cell types during different developmental stages of the embryo, their chromatin organization and consequently accessibility are likely to differ. Thus, even though the pathways are similar in both processes, the phenotypic outcomes vary.

Immunity has two major functions, to prevent infections and repair cell damage. Both require release of cytokines. In cancer, the immune response can kill the cancer cell or support survival. Neither is involved in neurodevelopmental disorders. Yet, via crosstalk, cytokines may influence the strength and duration of the same signaling pathway in cancer and in neurodevelopmental disorders. Different cell types have different accessible genes, thus the affected proteins in the pathways differ. However, chromatin accessibility can underlie both. Proteins involved in the innate immune system, such as Toll-like receptors, cytokines, inflammasomes, and phagocytic signals, are critical to brain development. Thus, dysfunction of innate immune signaling pathways can be functionally associated with neurodevelopmental disorders, such as ASD and schizophrenia.

AUTHOR CONTRIBUTIONS

R.N. and H.J. conceived and designed the study. R.N. prepared the initial draft, and H.J. edited the manuscript and prepared figures. R.N., C-J.T., and H.J. edited and approved the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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