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Overlapped Pathways of Autism Genes and Cancer Genes are Targeted by Viruses

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Mini Review

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Abstract

Genes of the Ras-MAPK and the PI3K-AKT-mTOR/PTEN pathways demonstrate numerous mutations in whole-exome testing of autistic individuals and in many cancers, and they are also affected in certain genetic syndromes associated with autism such as tuberous sclerosis, neurofibromatosis type 1, Noonan's syndrome, and fragile X Syndrome. These pathways include genes related to cell growth and hence might also serve as viral targets specifically of viruses implicated in autism such as rubella, CMV, EBV, HSV1, HSV2, HHV6, and polyomaviruses. This article shows that these viruses associated with autism affect genes of these two pathways with mutations common to both autism and cancer.

Keywords: Autism; Oncogene; CMV; Herpes; Polyomavirus; Rubella; EBV; HHV6

Abbreviations: **MAPK:** Mitogen-Activated Protein Kinase Cascade; **PI3K:** Phosphoinositide 3-Kinases; **AKT:** a serinethreonine protein kinase; **MTOR:** Mammalian or MechanisticTarget of Rapamycin; **PTEN:** Phosphatase and Tensin Homolog; **CMV:** Cytomegalovirus or Human Herpesvirus 5; **EBV:** Epstein - Barr virus or Human Herpes virus 4; **HSV1:** Herpes Simplex Virus; **HSV2:** Herpes Simplex Virus 2; **HHV6:** Human Herpesvirus 6; **NF1:** Neurofibromatosis type 1; **FXS:** Fragile X Syndrome.

Mini Review

Whole-exam testing of autistic individuals demonstrates that genetic pathways studded with mutations often overlap with those commonly associated with cancer [1-3]. Why genes with mutations in autism overlap with those of oncogenes is somewhat perplexing as cancer has not been associated with autism [4]. This finding may simply have to do with the accessibility of vast databases of cancer genes. Utilizing such databases exposes a possible link of autism to pathways that control cellular growth and development. Many such pathways are highly conserved to regulate the cell life cycle, reduce tumor suppression, and inhibit apoptosis. Two particular pathways, the Ras-MAPK (Ras-Raf-MEK-ERK) and the PI3K-AKT-mTOR/PTEN pathways include such numerous mutations in common in both exome testing of autistic individuals and in cancer to earn the term "super pathways" [2]. Mutations within PTEN alone are found in approximately 20% of persons with autism [2]. These "super pathways" also encompass mutations of genetic disorders with high autism prevalence such as tuberous sclerosis, neurofibromatosis type 1 (NF1), Noonan's syndrome, and fragile X syndrome (FXS) [5]. The genes affected in these disorders show that these two pathways not only control cell growth but help direct neuron development and synaptic plasticity [5,6]. As these pathways serve vital cell functions, they are apt to be vulnerable to other insults, such as those by viruses. Like cancer, viruses often alter genes in host cells to prolong their lifespans, sometimes even leading to cancerous changes [6], and certain viruses have been implicated as potential causes of autism [6-9]. Some viruses with associations to autism include rubella [7,9] CMV, EBV, HSV1, HSV2, HHV6, and polyomaviruses [8]. This article reviews how these viruses associated with autism might also target these two genetic pathways with mutations frequently observed in both autism and cancer.

Viruses with associations to autism, including rubella, CMV, EBV, HSV1, HSV2, HHV6, and polyomaviruses, target genes and proteins along the Ras-MAPK and the PI3K-AKT-mTOR/PTEN pathways, as shown in Table 1 [10-33]. This compilation of studies summarizes some of the viral effects on these two pathways with mutational overlaps in autism and cancer. Certain viruses have more robust data, specifically CMV, EBV, HSV1, and HSV2, due to prolonged interest in these viruses. Rubella research somewhat wanes after the 1980s [9], whereas polyomavirus and HHV6 data are all quite recent [28-31]. Viral effects on the Ras-MAPK and PI3K-AKT-mTOR/PTEN pathways are rather complex with multiple control mechanisms within both the nucleus and the cytoplasm [11,16,24,31]. Within the studies of Table 1, up or down regulation of genes within these pathways was demonstrated by comparing levels of mRNA before and after infection [12,16,22-23,26,28-31]. Similarly, increased or decreased expression, and activation or inhibition of the pathways was proven by respectively measuring levels of proteins, and phosphorylated proteins as a reflection of kinase activity, both before and after infection [10,14,18,20,22-23,29-31]. Most studies show up regulation and activity of these pathways; however, some studies show the opposite. This reflects the fact that typically viruses, especially herpes viruses, have both lytic and latent phases. The lytic phase promotes cell proliferation and or apoptosis with increased viral production, while the latent phase prolongs the host cell life with little viral replication. Studies showing upregulation and activation of these pathways typically infect cells in vitro and monitor their outcomes within 24 hours [10,14,20,27]. This timeline favors a lytic process. Those demonstrating down regulation or inhibition either follow infected in vitro cell over 48 hours [10,15,25] or use chronically infected cell lines such as comparing lymphomas, cancerous cell lines, or brain tissue tested to be EBV, HSV1, or HHS6 positive versus those tested to be EBV, HSV1, or HHV6 negative [18,21-23,26-28]. These longer, chronic timelines represent more latent mechanisms. Viruses appear to start cellular infection in a lytic phase, and then settle into a latent phase by signaling through these pathways at various steps. For example, with HSV1, PI3K and AKT appear to be "critical parameters regulating latency in neurons," [25] and EBV can induce "cell cycle arrest at G0/G1 phase through downregulation of the PI3K/Akt pathway" [21]. Switching to replication, viruses must not only be able "to activate the PI3K–Akt–mTOR pathway but also to counteract the inhibition of this pathway" [32]. While in the lytic phase, many studies demonstrate the addition of molecular inhibitors at various steps within these pathways results in decreased viral replication [14-15,27,29,31]. Likewise in the latent phase, when the virus resides within the cell host without replication, a disruption of inhibition of the pathways leads to viral replication [25]. Viruses must then "selectively activate and/or repress specific components of these host-cell pathways in a temporally coordinated manner, in order to promote virus replication" [33]. During this tumultuous orchestration over these two pathways, viruses also directly damage DNA and inhibit "a range of DNA-repair genes" which is "controlled principally by the PI3K-related protein kinases" [33]. "Two JCV proteins have been shown to have an effect on DNA repair resulting in the accumulation of mutations and restricted cell growth after DNA damage" [33]. Some viruses, such as HHV6, not only set up latency, but have "the ability to integrate into human chromosomes" [29]. Viruses up regulate and down regulate, activate and inhibit these pathways, with certain genetic changes becoming permanent as cellular repair of DNA is then also damaged. Cellular growth and proliferation may ensue, with many genes becoming upregulated with overexpression and activation as cancer cells [19,22,26]. PTEN is a tumor suppressor gene inactivated in many cancers, and by certain viruses [22]. The gene pathways highlighted here are involved in cellular proliferation, differentiation, migration, and DNA repair [19,29]. How viruses might utilize these pathways for their survival, and eventually contribute to cancer is logical. Other viruses, including coxsackievirus, influenza virus A, respiratory syncytial virus, adenovirus, human papillomavirus, human herpesvirus 8 (Kaposi's sarcoma herpesvirus), and adeno-associated virus, also utilize these pathways, [10,11,33] and it is estimated that "viral infections contribute to 15-20% of all human cancers." [22] The virus to cancer association is recognized, and certain viruses as discussed here have been implicated in autism with clear genetic targeting of pathways linked to both autism and cancer.

The Ras-MAPK and the PI3K-AKT-mTOR/PTEN pathways function developmentally to regulate cellular division, migration, and differentiation. Viral interference could disrupt neurodevelopment, but evidence is limited. Viral infections associated with autism are not commonly diagnosed in real-time, but rather thought of as possible past intrauterine or early-life events; and therefore, attributing genetic changes with largely undiagnosed past viral infections is extremely challenging. For example, some 85-95% of infants infected with CMV at birth are asymptomatic [34], and congenital polyomavirus infections are barely on the clinical radar [35]. Pinpointing when and how these viruses might infect individuals and whether any resulting changes could lead to autism, then, becomes mostly hypothetical. Viruses have been implicated in the cause of autism, but no one virus seemingly appears to cause autism. And although viral causes of autism are seemingly rare, viral infections in humans are not rare events, even the more recently recognized polyomaviruses are estimated to infect some 50-90% of the human population [30-31]. A study by Lintas looked for viral evidence of CMV, EBV, HSV1, HSV2, and polyomaviruses in postmortem brains of persons with and without autism isolating viral genomes in postmortem

brains of both autistics and non-autistics, more specifically in 12 of 15 (80%) autistic and 8 of 13 (62%) control specimens [8]. Astoundingly, viruses found within postmortem human brain specimens appear rather ubiquitous in this small, but compelling study. If viruses infect most humans' brains and affect highly conserved oncogenes, then perhaps nearly all humans have some probability of a resulting neurological outcome. Viruses may quietly persist in a dormant state as found in postmortem brains or live only briefly. In the case of varicella virus (VZV), the dormant virus can emerge from its dormant state to produce a shingles outbreak but may also have a finite lifespan.

"VZV studies are potentially important because they demonstrate that a virus can invade the brain, selectively destroy specific groups of cells depending on the stage of brain development, and then disappear from the brain after only a few days, leaving no genomic trace but causing a permanent attenuation of transmitter levels and alteration in behavior. These VZV studies might reflect parallel events in the human brain, in which a virus can infect a subset of neurons or glia, and then be eliminated, leaving a neurological or psychiatric disease with no detectable cause [36]".

Viruses might clear in this sort of "hit and run teratogenesis" [6] or the virus may persist indefinitely in a dormant state with little to no change noted after its initial insult [8]. Either way, viral exposures are a somewhat unavoidable part of life. Intrauterine or early-life exposure to viral insults within the Ras-MAPK and the PI3K-AKT-mTOR/PTEN pathways could potentially impair neurological development resulting in varied phenotypic developments, of which autism is one.

Virus	Ras-MAPK (up/down regulation)	Ras-MAPK (increase/ decrease expression of proteins)	Ras-MAPK (activate/ inhibit pathway)	PI3K-AKT-mTOR/PTEN (up/down regulation	PI3K-AKT-mTOR/ PTEN (increase/ decrease expression of proteins)	PI3K-AKT-mTOR/ PTEN (activate/ inhibit pathway)
Rubella		Increase [10]	Activate [10,11]		Increase [10]	Activate [10,11]
CMV		Increase [12,13]	Activate [14,15]	Up [16]	Increase [16]	Activate [15-17] Inhibit [16,17]
EBV	Up [18]	Increase [18]	Activate [18-20]	Up [18] Down [21-23]	Increase [18] Decrease [23]	Activate [18-20] Inhibit [19,21]
HSV1, HSV2	Up [24]	Increase [19]	Activate [24-27]	Down [26]	Decrease [26]	Activate [24,25,27] Inhibit [26]
HHV6	Up [28] Down [19]			Up [29]	Increase [29]	Activate [29]
Polyoma-viruses	Up [30,31]	Increase [30,31]	Activate [30-32]	Down [30]	Increase [30]	Activate [30,32,33]

Table 1: How Viruses with Associations to Autism Target Genes and Proteins along the Ras-MAPK and the PI3K-AKT-Mtor/ PTEN Pathways.

Conclusion

Viruses with associations to autism, including rubella, CMV, EBV, HSV1, HSV1, HHV6, and polyomaviruses, alter genes along the Ras-MAPK and the PI3K-AKT-mTOR/PTEN pathways—two pathways with many mutational overlaps in autism and cancer. These pathways are highly conserved to regulate cellular proliferation and differentiation. In early development, these pathways play a role in neural migration and synaptic formations, and the addition of viral insults could alter neurodevelopment. Viruses with associations to autism regulate these genetic pathways in multiple ways. Viruses upregulate and activate the pathways through their lytic phase, and then downregulate and inhibit the pathways to affect their latent phase. Viruses even manipulate the modulators of these pathways and impede the repair of any resulting DNA damage. Viruses implicated in autism affect these pathways and have been found in human brain tissue from persons with and without autism [8]. As viral exposure throughout life is not rare, more research regarding viral targeting of genes with frequent mutations seen in whole exome testing of autistics is warranted.

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