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'Hit and Run' Teratogenesis, with Specific Regards to Autism

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Abstract

In recent decades a process known as 'hit and run' oncogenesis has emerged. The principle is that a virus infects a person and is able to cause genetic mutations leading in a step-wise fashion towards cancer production, but by the time the cancer is detectable, the viral infection is gone. This paper proposes a similar process as an explanation for a certain teratogenic process, linking cellular changes instigated by various viruses to those of autism.

Keywords: Hit and run; Teratogen edits; Autism; Rubella; Influenza; Zika; Cytomegalovirus; CMV

Introduction

In recent decades a process known as 'hit and run' oncogenesis has emerged. The principle is that a virus infects a person and is able to cause genetic mutations leading in a step-wise fashion towards cancer production, but by the time the cancer is detectable, the viral infection is gone, as described in a paper documenting Epstein-Barr virus and cytomegalovirus (CMV) in breast cancers [1]. This intriguing process might also be a possible explanation for the teratogenic process of autism. Like the oncogenesis theory, a virus might infect a mother while pregnant causing teratogenic changes in the fetus, but only for a limited time. By the time the baby is delivered, the viral infection has passed, but the residual changes to the fetus are permanent, though possibly subtle and varied.

The cause of autism has been puzzling for decades. Genetics has long been at the forefront of the basis of autism. But with autism, genetics seems to be defied: First, possible genes underlying autism have been identified on every nuclear chromosome and also mitochondrial DNA. Mitochondrial DNA cannot be the full explanation as only the maternal lineage would be affected which is not the case in autism. Second, though autism has been linked to certain genetic disorders like tuberous sclerosis and fragile X syndrome, only a small percentage of children with genetic disorders show signs of autism [2]. Third, a large proportion of people with autism do not procreate meaning a genetic cause should die out as generations pass, [2] unless there is a proclivity towards new mutations of a similar mechanism across many ethnicities. Fourth, firstborn children are more often affected with autism which does not follow any genetic prospect. Fifth, boys are affected more than girls, but autism is not an X-linked disorder as male-to-male inheritance does occur. The common answer to this genetic defiance is that autism is a spectral disorder with many causes, and sometimes multiple causes within a single individual. Certain researchers have proposed that autism is a combination of various genetic mutations [3] much like oncogenesis. How might this relate to a 'hit and run' viral mechanism? During embryogenesis, a virus infects certain cells. As a virus can affect a vast variety of genes and at various stages of embryogenesis, then a range of genetic changes with differing severity may be realized, but because viruses utilize similar genes, especially those involved in the cell cycle of the nucleus and the energy production of the mitochondria, similar findings emerge.

Viruses alter genes involved in cell growth, signaling and cytoskeletal changes, reordering the cell to become a viral factory. Rubella virus increases the oncogenic protein p53, slows mitosis and causes "genetic

alterations, such as chromosomal breaks" [4]. Rubella utilizes the antiapoptic protein B cell lymphoma-2(Bcl-2), [5] binds and inhibits the apoptic protein B cell lymphoma-2 associated X (BAX), [6,7] and slows the cell cycle utilizing the phosphatidyl inositol 3 kinase (PI3K) – AKT, and Ras-Raf-MEK-ERK (extracellular signal-related kinase) pathways [8]. Influenza infection causes activation of the Raf-MEK/ERK, [9] and CMV similarly activates the mitogen-activated protein kinase (MAPK)/ERK pathway [10]. With these changes, viruses alter a cell's response to many growth factors. Such signal interruption of growth factors in embryogenesis can lead to abnormal growth and placement of cells, yet if only a small percentage of cells are affected, then many individuals will reveal little genetic change when investigated.

Interestingly, genes implicated in autism also commonly affect genes with similar functions as those utilized by viruses--genes related to cell growth, signaling, and cytoskeletal changes with the inclusion of synaptic regulation. Altered levels of the oncogene P53 and antiapoptic Bcl-2 levels have been demonstrated in various regions of autistic brains as compared to controls, [11-13] echoing genes and proteins affected by viruses. Though hundreds of autism susceptibility genes exist, they often converge within pathways such as PI3K – AKT, and Ras-Raf-MEK-ERK [14,15]. Genetic disorders including fragile X syndrome and tuberous sclerosis also converge with these pathways [15] leading one to wonder if those individuals with these genetic disorders and autistic features had an additional viral teratogenic'hit' to another gene along these converging pathways. Some alteration must occur within these converging pathways; the same signaling pathways leading to clusters of misguided and unconnected cells as commonly seen in the brains of autistic individuals [16].

Another area with overlap between cellular changes seen by both viral infections and in autism involve mitochondrial function. Many known teratogenic viruses utilize and alter mitochondria. An older study (1971) injected Zika virus intracerebrally into newborn mice. Some nerve cells lacked nuclei, and mitochondria clustered in the cytoplasm around viral factories. These pathological changes were proposed to lead to disorganization of the pyriform layer [17]. Both rubella and CMV employ mitochondria for energy needed in their replication. Rubella alters microtubules and the mitochondrial associated protein p32 to cluster mitochondria nearer for viral replication, [18] and then incorporates cardiolipin from the mitochondrial membrane into its own envelope [7]. Rubella upregulates genes to increase mitochondrial respiratory chain complexes from both nuclear and mitochondrial origin. This study compared rubella to measles, not a teratogenic virus, which did not alter mitochondrial function [19]. The mitochondrial dependence of viruses like Zika, CMV, and rubella likely adds to their teratogenicity.

In autism, mitochondrial dysfunction is thought to play a role in the changes seen within these individuals. Within autistic persons, children with true mitochondrial respiratory chain disorders, including genetic alterations such as deletions, make up a small, but notable percentage,0-10%, with 39% girls and 61% boys [3,20]. Most mitochondrial dysfunction (>79%) seen in autism is not due to a genetic alteration, but some other secondary mechanism, such as toxic or infectious, and may represent "tissue heteroplasmy" [3]. Many children with autism show mitochondrial dysfunction in certain regions of the brain [2,21]. These changes could represent a viral 'hit' to infrequent clusters of cells during embryogenesis. A few cells with such mitochondrial changes might not make a difference everywhere in the body, but would in the brain with its high energy demands.

Most believe the cause of autism is genetic, but more recently data is emerging that the cause is infectious or inflammatory. Finding a viral culprit has not been proven except with the case of rubella In the 1970s [22]. Studies of rubella have shown that the immature immune system of a fetus often does not recognize the virus as foreign and therefore, does not make antibodies [16]. Mothers vaccinated to rubella have asymptomatic infections that are still capable of causing congenital rubella syndrome in offspring [23]. More mothers likely exist with limited infections. If the infection is self-limited, like influenza, the virus would doubtfully be found in umbilical blood at birth. Evidence of a congenital infection may not be easily identified in the case of a 'hit and run' effect.

Though a viral 'hit and run' scenario offers a plausible way to merge the infectious and genetic causes of autism, the theory has limitations. First, both viral infections and autism affect hundreds of genes, and the fact that there is overlap of affected genes in cell division, cell signaling and energy production may be coincidental. Second, in mice certain studies show that nonspecific maternal inflammation may be enough to induce changes in the fetal brain regardless of any infection [24]. Lastly, much of the genetic changes were studied in *in vitro* cell lines, and sometimes the outcome varied with the cell line studied. Apoptosis is a host response to limit viral spread. Rubella, in certain cell lines, seems to prolong its survival by inhibiting apoptosis, while in other cell lines rubella

survives regardless of apoptosis [25]. Further, rubella can quickly evolve to shelter itself within cells, even through cell division in serum with rubella antibodies setting up a persistent infection [26]. This persistent infection sheltering without apoptosis appears to be favored both *in vitro* and *in vivo*, as postmortem studies of congenitally infected fetuses note little cytolysis [5]. As the rubella virus is the greatest viral link to autism, increasing autistic rates 200 fold in the 1970s in those affected with congenital rubella, [22] its mechanisms are most cited.

Thinking of the ways autism defies genetics, a viral 'hit and run' scenario offers an explanation of how genes on all chromosomes and the mitochondria might be affected as viruses utilize genes common to cell life and energy; how individuals with genetic mutations already involved in certain pathways, such as fragile X syndrome and tuberous sclerosis, then also affected by viruses could be more susceptible to the viral changes associated with autism; how even though individuals with autism tend not to procreate, similar genetic mutations emerge in persons with autism of many ethnicities; and how firstborn children may be more affected as a mother's immune system might protect subsequent pregnancies. But as to why males are more affected than females, a viral mechanism offers little clue, but may have to do with innate differences in their respective immune functions [27].

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