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Immune Dysfunction in Autism Spectrum Disorder

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1. Introduction

Autism was first described in 1943 (Kanner, 1943) after examining a group of children with abnormal social characteristics and obsessive behavior. Initially considered a rare disorder, it did not receive much attention in the media or research circles until the latter end of the 1900's when an increasing number of cases were being diagnosed. The term Autism Spectrum Disorder (ASD) combines a group of syndromes with fundamental deficits in reciprocal social communications and repetitive stereotyped verbal and non-verbal behaviors (Volkmar et al., 2009). The severity spectrum varies widely and more severe forms can be accompanied by language regression, seizures and lower IQ. The diversity of specific behavioral deficits in different individuals suggests that autism is not a single disorder, but rather a collection of variants each with its own characteristics and perhaps etiologies (Altevogt et al., 2008). Despite the recognition that there has been an increase in public awareness, an improvement in patient ascertainment and a broadening of diagnosis, it is generally accepted that the incidence of autism and related ASDs is increasing (CDC, 2009) with current estimates being 1 in 110 children in the United States have ASD. There is much debate around the world, both in the research and parent communities, on the etiology of autism. Everything from childhood vaccines, exposure to mercury, maternal viral infections and autoimmune disorders has been blamed. Unfortunately, despite extensive research over the last decade, there is very little that is universally accepted about the etiology of autism except, of course, that autism results from abnormal brain function arising in either the prenatal period or infancy stage of life.

2. Infection

In the 1960's and early 70's a number of case studies associating autism with congenital infection appeared in the literature. Many of these cases were reports of autism associated with congenital rubella infection. In fact, at least 43 cases associating autistic symptoms with congenital rubella have been described (Hwang & Chen, 2010; Rimland, 1964). Congenital rubella is caused by first trimester infection with German measles. Resultant symptoms in

the infant may include deafness, developmental delay, mental retardation and seizures. In 1964 a rubella epidemic swept through the United States leaving behind a large group of rubella children that also suffered a higher than expected incidence of autism (Chess, 1971). It is estimated that the incidence of autism in children with congenital rubella syndrome is between 4-7%. Although these were clearly cases of congenital rubella with resultant autistic symptoms that represented a unique subset of patients, the association of a congenital infection resulting in autistic behaviors sparked interest in the theory that the immune system may play a vital role in protecting against or perhaps contributing to the onset of some cases of autism. After decades of research, evidence of a broader infectious role in this disorder remains elusive, yet findings of altered immune system parameters continually appear in the literature.

3. Familial studies

Familial clustering and twin studies indicate a strong genetic component to autism predisposition. Twin studies show the concordance rates of monozygotic twins at 36-96%, whereas dizygotic twins are 0-24% concordant, resulting in an estimated heritability of autism at >90% (Bailey et al., 1995; Folstein & Rutter, 1977; Steffenburg et al., 1989). Additionally, family studies have shown autism to have familial aggregation with 3-8% of subsequently born siblings either being autistic or showing some form of pervasive developmental disorder (PDD) (Bolton et al., 1994; Ritvo et al., 1989). This is a 30-80% increase in risk for siblings over the general population. At that time it was thought the data from family genetics studies and the phenotypic variability indicated that the likely cause of autism was due to specific genes in certain combinations (Freitag, 2007; Rutter, 2000). It became apparent that genetics was another area to study along with the immune system.

4. Genetics

When the ability to genotype one or more alleles became routine in the 1990s, candidate gene association studies became common. Many of these candidate gene association studies were unreliable and often contradictory, casting doubt on this approach (State, 2010). It is now realized that the probability of any candidate gene or allele being associated with a particular phenotype, let alone a spectrum of phenotypes, is extremely low. Modern microarray based technology allows for the genotyping of thousands of genetic polymorphisms on a single chip, however, other issues such as case/control selection and statistical evaluation are especially important when examining large amounts of subjects and polymorphisms.

Several large studies examining hundreds of thousands of single nucleotide polymorphisms (SNPs) have been exhaustively tested in thousands of cases and thousands of controls in an effort to find disease associations (Szatmari et al., 2007; Veenstra-VanderWeele et al., 2004). Three genome-wide association studies (GWAS) each with over 1,000 subjects did not replicate each other's findings for candidate genes (Anney et al., 2010; Wang et al., 2009; Weiss et al., 2009). At this stage it appears that none of the studies had a sufficient number of subjects to replicate findings for alleles having a small to moderate effect. Weiss et al. (2009) examined over 500,000 SNPs in 1,553 autistic subjects using the Affymetrix 5.0 microarray platform. No genome-wide associations were identified until single SNP genotyping was done on the most suggestive regions. Even after genotyping, only one SNP on chromosome

5p15 had a strong autism association. Although a number of loci causative of early childhood psychiatric disorders have been identified using GWAS, few of them have been validated in additional studies. The lack of success with this approach may be due to the fact that while GWAS are well suited for the discovery of common, low impact alleles causing a clinically well-defined disease, it is less effective for gene discovery when diseases with clinical and biochemical heterogeneity are caused by rare high impact genetic changes in many different genes.

Another method for looking at genetic differences involves copy number variation (CNV) by comparative genomic hybridization (Sebat et al., 2007) or by microarray analysis of single samples using SNP/CN chips, with observed CNVs being compared to the CNVs found in genomic databases. Normal CNV includes deletion and amplification of segments of the genome that occur very frequently without apparent phenotypic effect other than producing normal phenotypic variation. Deletions and amplifications of normally diploid genes can cause higher or lower levels of gene expression, or truncated or abnormal fusion gene products, producing pathological phenotypes. CNV is an area of considerable interest in autism as the effects of gene dosage may be important in conferring outcome (Toro et al., 2010). Difficulties with detection of abnormal CNVs by array methodology (Craddock et al., 2010; Sebat et al., 2007) include the confounding presence of extensive CNVs in all genomes, limitations in the size of genomic regions detected (typically 1 Mb or more) (Magi et al., 2011), and the variation in clinical phenotypes that can result from CNVs (Ching et al., 2010). Many copy number mutation differences have been reported in autism including genes involved in neuronal cell adhesion and ubiquitin degradation (Glessner et al., 2009). Mutations and CNVs in the neurexin-1 gene have been discovered that are associated with a variety of developmental disorders including autism, ASD and schizophrenia (Ching et al., 2010). Point mutations and deletions have been associated with ASD by several research groups (reviewed by Ching et al., 2010). Neurexin-1 (2p16.3) is one of the largest genes in the human genome with 24 exons in 1.1Mb. The neurexin-1 gene has two independent promoters that encode alpha and beta neurexin-1 proteins and alternate splicing of the 24 exons can result in over 1,000 possible neurexin isoforms with differential expression of isoforms in different cells or tissues. Similarly, CNVs and mutations have been identified in contactin associated protein-like 2 (CNTNAP2), first described as having a role in developmental delay in Old-Order Amish subjects with intractable epilepsy and autism (Strauss et al., 2006). Three other groups have now replicated the involvement of the CNTNAP2 gene in autism (Alarcón et al., 2008; Arking et al., 2008; Bakkaoglu et al., 2008). Both CNTNAP2 and neurexin-1 are illustrative of an additional hallmark of genes causing psychiatric illness; clinical phenotypes of identical rare variants suggest that ASD, intellectual disability, seizure disorder, schizophrenia, ADHD, Tourette syndrome, OCD, or a combination of these may result from functionally identical genetic changes (State, 2010).

For many years, there was a consensus that the “common variant common disease” hypothesis would best explain the genetics behind autism. This model suggests that each common risk variant (greater than 5% in the population) only confers a small degree of risk and that disease is the result of the combination of many common variants (Risch & Merikangas, 1996). This genetic disease hypothesis has been entertained for over 100 years. After a decade of genetic research using modern microarray and sequencing technology it is now clear that “common risk variants” cannot explain the vast majority of genetic heritability for any human disease (Manolio et al., 2009). Both SNP and GWAS studies have found that rare alleles can be major contributors to complex diseases like ASD. However,

the “rare allele variant” can only explain a small proportion (about 10%) of the genetic risk for ASD (Goldstein, 2009; Manolio et al., 2009; State, 2010). It is now apparent that the rare allele is a major contributor not a minor contributor in diseases like breast and ovarian cancers (McClennen & King, 2010). The 90% “missing inheritance” may be explained, at least in part, by rare alleles that have not yet been detected (Goldstein, 2009). Current research suggests that rare mutations are important in neurodevelopmental disorders like autism and schizophrenia (Bucan et al., 2009; Guilmatre et al., 2009). It also appears that diseases with significant phenotype differences are characterized by marked genetic heterogeneity. Whole genome sequencing is becoming a viable experimental approach to attempt to clarify the issue of “missing inheritance” and determine whether it results from mutations in many different genes associated with CNS development and function, or whether it results from differences in the highly complex genes that regulate immune responses, linking genetics with inflammatory responses to infections or environmental insults.

Stubbs & Magenis (1980) first suggested over 30 years ago that the human leukocyte antigen (HLA) region might be involved in autism. Unraveling the relationship between the immune system and autism is difficult, not in the least because of the extraordinary complexity of the immune system. Analysis of the HLA class I and II genomic regions is challenging due to the abundance of genetic polymorphisms, which often occur within a few base pairs of each other. Genetic HLA allelic typing by standard polymerase chain reaction methods followed by DNA sequencing for questionable regions is very precise at a reasonable cost for classical HLA alleles. However, there may be genes that are being missed, as there are close to 100 genes in this region. Research in our laboratory has noted differences in certain HLA class I and class II alleles as well as C4 complement genes in the class III region (Torres et al., 2002; Torres et al., 2006; Warren et al., 1991; Warren et al., 1996).

5. Immune system

The word immune comes from the Latin “*immunis*” meaning free or exempt. It was noticed in about 1500 that survivors of a certain disease did not get sick after a second exposure. They were considered “exempt from” or “immune” from that disease. The field of immunology was solidified in 1796 with the observations of an English physician, Edward Jenner, when he noted that dairymaids and farmers lacked the characteristic pock-marked complexion of those who had been infected with smallpox. It was determined that individuals who acquired cowpox from cattle were immune from smallpox. In the late 1800s Louis Pasteur coined the term vaccination which means “derived from cows” in honor of Edward Jenner.

Modern immunology is the study of a system of cells, tissue and molecules that recognize and attack pathogens and tumor cells that endanger the individual. Physical barriers prevent most bacteria and viruses from entering the body. Once foreign organisms are inside the body the immune system has two arms of antigen response: innate and adaptive immunity. The innate immune system provides a non-specific response that is built into the organism and therefore always available, but does not elicit an immunological memory. The adaptive immune response is a slower system that is tailored for the individual to fight a specific pathogen (Figure 1). Both systems depend on the organism’s ability to recognize self from non-self molecules. Self molecules are components of the individual organism and non-self molecules are defined as substances that are recognized by the organism’s immune

receptors and elicit an immune response. There is an ever changing immunological memory in the adaptive immune response. For example, when Edward Jenner vaccinated individuals with cowpox an immunological memory was developed that protected them from infection with smallpox at a later date.

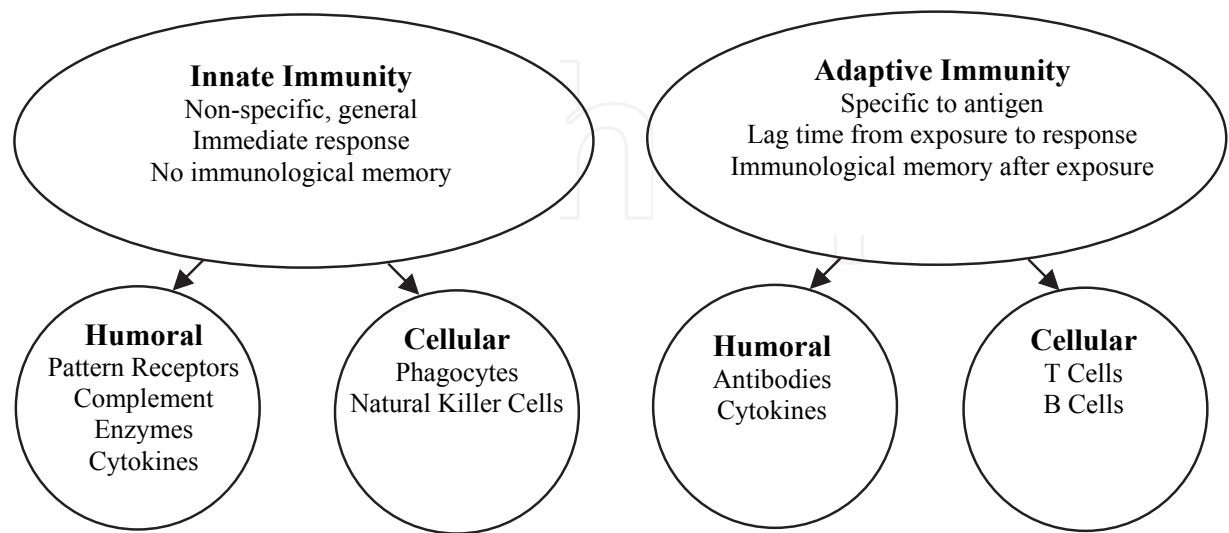


Fig. 1. Innate and Adaptive Immune Systems. The human immune system is divided into two main branches: innate and adaptive. These two branches are further divided into humoral and cellular immunity. Innate immunity provides a non-specific response that is built into the organism and therefore always available, but does not elicit an immunological memory. The adaptive immune response is a slower system that is designed to protect against foreign antigens and develops memory.

5.1 Innate immune system

Microorganisms that get past surface barriers such as skin, tears and mucus will encounter the cells and mechanisms of the innate immune system. Microorganisms are targeted by pattern recognition receptors (PRR) on the surface of innate immune cells such as granulocytes, macrophages and dendritic cells which recognize and bind to pathogen-associated molecular patterns (PAMPs). These PAMPs include common molecules of bacterial carbohydrates and peptides, lipopolysaccharide, bacterial and viral RNA and DNA, and other microbial molecules that are non-self molecules.

Certain PRRs are secreted and these proteins bind to a variety of bacteria, fungi, viruses and protozoa. The complement system contains over 25 proteins and protein fragments that are mainly synthesized in the liver, but also exist in the brain. These proteins in a complicated manner help or “complement” antibodies and phagocyte cells to clear pathogens from the organism. The C4 complement proteins (C4A and C4B) are encoded by two separate genes in the class III HLA region. Although similar, C4A and C4B proteins have different binding characteristics and each have distinct associations with autoimmune diseases.

There are several classes of PRRs according to their ligand binding specificity. Signaling PRRs include the membrane bound Toll-like receptor (TLR) family. There are 11 TLRs with different binding characteristics and, like many molecules, were discovered in *Drosophila*. A series of events including the production of cytokines as well as the activation of cellular pathways occurs upon the engagement of PAMPs by membrane bound TLRs. After binding to a PAMP,

cytokine molecules are released to signal other innate and adaptive cells. After binding, endocytosis and phagocytosis of the infectious agent is triggered by the complement system.

The second arm of the innate immune system involves phagocytes (macrophages, dendritic cells, neutrophils, eosinophils and basophils), mast cells and natural killer (NK) cells. These cells recognize and kill pathogens by engulfing them or by rupturing the invader's cell membrane and have the ability to send signals to the adaptive immune system. NK cells are a subset of lymphocytes with the ability to produce cytokines and kill target cells without prior sensitization and are essential for self-tolerance. NK cells thus participate in early responses against virally infected and transformed cells by recognizing the lack of HLA class I proteins on cell surfaces, a phenomenon called "missing self".

5.2 Adaptive immune system

A slower immune reaction is elicited by the adaptive than the innate immune system, but more importantly, immunological memory is invoked. Memory involves the recognition of the signature invading organism for extended periods of time, often decades. This is done by the generation of memory cells that are tailor-made to each antigen.

The first arm of the adaptive immune system involves soluble antibodies and cytokines. Antibodies are glycoproteins from the immunoglobulin superfamily produced by memory B cells called plasma cells. Memory cells survive in the body for years and become activated to produce the respective antibody upon exposure to the particular antigen. There are an unlimited number of antibodies that can be produced in response to antigens. This is accomplished by recombination of genes in B cells followed by a complicated cellular selection process to create antibodies to particular antigens.

The second arm of the adaptive immune system involves T cells and B cells. T cells are important in cell-mediated immunity and are distinguished by the T cell receptors which recognize short peptides bound to HLA class I and class II proteins. Several subsets of T cells with distinct functions exist. Helper T cells assist B cells to mature into antibody producing memory B cells. Cytotoxic T cells seek and destroy virally infected cells and tumor cells. Memory T cells exist long term after an infection is resolved. Upon exposure to their particular antigen they quickly expand into effector T cells. Suppressor or regulatory T cells suppress auto-reactive T cells to limit tissue damage. In addition to all this complexity, while attacking pathogens, the immune system must maintain a balance and not attack self molecules.

Helper T cells have an important role in activating and directing other immune cells by the release of cytokines. These cytokines include interleukins, interferons, tumor necrosis factors, chemokines and growth factors. Helper T cells fall into two different subsets (Th1 and Th2) based on the cytokines they release and how they regulate the immune system. There is signaling or significant cross-talk that occurs between the innate and adaptive immune system which is accomplished through cytokines, chemokines and other small molecules. For example, IL-10 will act to inhibit macrophage activation and TNF- β can kill activated B cells. Also, HLA class I proteins bind to receptors on various adaptive immune T cells as well as innate immune NK cells.

6. Immunogenetics

The immune system must distinguish a wide variety of microorganisms including viruses, bacteria and parasitic worms from the organism's own cells and tissues and, therefore, has a complex genetic basis. The HLA region on chromosome 6 (Figure 1) is the most complex

region in the human genome and central to many immunological reactions, both innate and adaptive. There are over 100 genes and pseudogenes in this region. The HLA genes are grouped into three classes based on their function: class I, class II, and class III. Class I molecules are expressed on all nucleated cells and are responsible for presenting viral antigens to cytotoxic T cells which are specially designed to kill targeted cells. Class II molecules are typically expressed on B lymphocytes where they present antigens to helper T cells to stimulate the B cells to produce antibodies and they are also expressed on macrophages which are then activated to destroy the pathogen they have engulfed. Class III genes encode for numerous proteins, including C4 complement, involved in immune interactions. Complement C4 proteins are involved in numerous immune functions, including lysing pathogens and marking pathogens for clearance by immune cells. There are over 3,000 genetic alleles contained in the class I and class II HLA regions that encode proteins important in cellular discrimination of ‘self’ and ‘non-self’. The class I region is important in cellular immunology and the class II region is important in antibody production. For example, there are about 30 common HLA-B alleles and several hundred uncommon ones. This diversity endows the immune system with great plasticity in adaptive immune responses and allows researchers to precisely follow the inheritance of specific alleles. Haplotype from the Greek means one-fold, single, or simple. In genetics a haplotype refers to a set of closely linked DNA markers present on one chromosome. The HLA region was recognized in 1983 as consisting of several distinct linkage disequilibrium blocks (Dawkins et al., 1983). This information was helpful for the construction of large haplotypes of over 4 million base pairs containing over 150 protein-coding genes. Smaller ancestral haplotypes (AHs) that encode about 100 proteins and the classic HLA alleles (1.2 million base pairs) fit within these blocks. Haplotypes in the HLA region are probably the best characterized in the human genome due to the fact that there are so many alleles. By typing one or both parents as well as the subject of interest one can assign the inheritance as it is not common for both parents to have the same HLA class I and II alleles. Complete DNA sequences have been published for 8 of the most common AHs in an effort to expedite disease association research (Horton et al., 2008). It is difficult by current diploid genotyping methods to determine haplotypes.

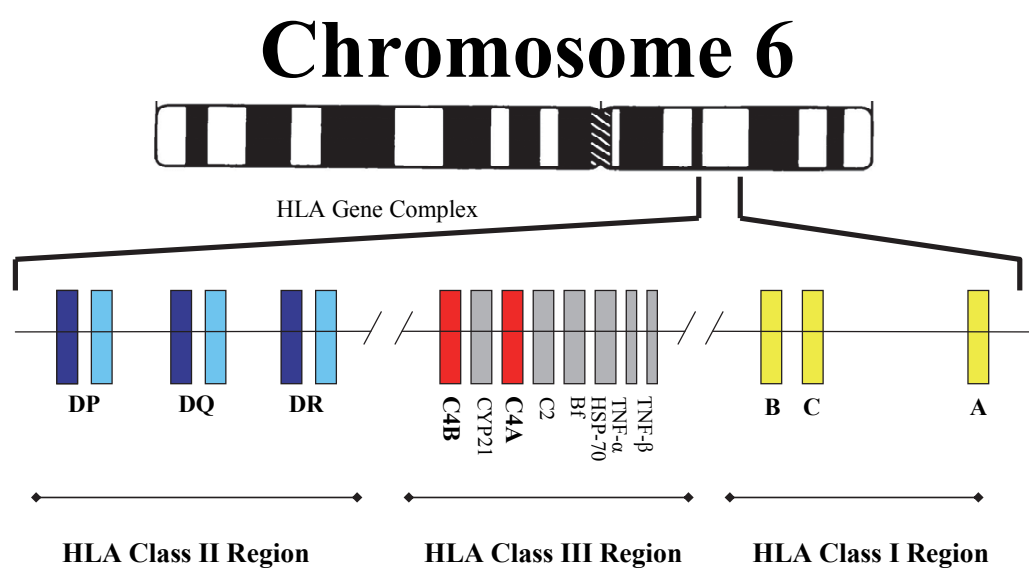


Fig. 2. A simplified map of the HLA region on human chromosome 6.

Some of the genes in these AHs encode for HLA class I and class II proteins which are important in antigen presentation to cytotoxic T cell (CD8⁺) and helper T cell (CD4⁺) lymphocytes, respectively. The HLA region of the human genome also encodes for important innate immune proteins, such as the complement C4A and C4B proteins, as well as many proteins vital in immune regulation like HSP-70 and TNF- α . Complement C4 proteins are involved in numerous immune functions, including lysing pathogens and marking pathogens for clearance by immune cells.

7. Cytokines

In Greek the term cytokine means cell movement. All cytokines are peptides/proteins/glycoproteins that serve as immune signals from one cell to regulate other cells. They are very potent molecules with systemic concentrations in the picomolar (10^{12}) range. Virtually all nucleated cells produce cytokines and the target cells have highly specific receptors to the respective cytokine. Cytokines have pronounced effects on many cellular functions in all branches of the immune system, most importantly inflammation and brain chemistry. Since cytokines bind to specific receptors on the membrane of target cells, triggering signal transduction pathways that ultimately alter gene expression in the target cells, they can significantly alter neural development and maintenance, especially in the developing fetus.

Th1 cytokines such as interferon- γ , TNF- α , TNF- β , IL-3 and GM-CSF are considered to be pro-inflammatory. They are involved in the cellular immune system and act to maximize the killing efficacy of macrophages and the proliferation of cytotoxic T cells. Th2 cytokines are non-inflammatory and promote the humoral immune system with cytokines IL-4, IL-5, IL-6, IL-10, IL-13 and TGF- β . IL-6 for example, can determine B cell antibody class switching by driving the proliferation and differentiation of B cells into antibody-secreting plasma cells and is also an endogenous pyrogen so it can cause a fever to help eliminate infections by acting in the hypothalamus. The adverse effects of unusually high levels of certain cytokines have been documented in several disease states like cancer, depression and Alzheimer's disease. The therapeutic application of cytokines such as IL-2 and interferon- γ can result in severe systemic reactions referred to as "cytokine storm".

8. Immune system abnormalities in autism

8.1 Humoral innate system

The complement C4A and C4B genes exist in a region of the genome that demonstrates a particularly complex morphology including CNV. Previous research in our laboratory utilizing a protein immunoelectrophoresis assay demonstrated a significant link to a deficiency of C4B protein and autism (Warren et al., 1991). It was reported that a C4B null allele (C4B gene deletion) was significantly more common in subjects with autism than in subjects without autism. This initial finding was supported by additional research in our laboratory that showed a relative risk of 4 for subjects with autism who have a C4B null allele (Odell et al., 2005). Interestingly, Mostafa & Shehab (2010) supported this observation with an odds ratio of 6 for autism subjects with a C4B null allele and an odds ratio 6.26 for children with autism and a family history of autoimmune diseases in an Egyptian population. Relative risk and odds ratio are different mathematical models for describing the chances of developing a certain disease.

Other humoral innate system genes/proteins have not been investigated as closely as C4 CNV. However, Torres et al. (2001) examined the neighboring TNF- α gene and found that TNF- α microsatellite markers in autistics favored a microsatellite known for lower TNF- α production. Accordingly, plasma TNF- α levels were lower in the subjects with autism compared to controls.

8.2 Cellular innate system

8.2.1 Natural killer cells

Warren et al. (1987) noted reduced NK cell killing (or cytotoxicity) in subjects with autism when using a standard K562 target cell assay. The K562 tumor cell line is used to stimulate NK cells because it lacks HLA class I surface proteins (missing-self) and is targeted by NK cells for destruction. This deficiency in NK cell killing in subjects with autism has been observed by at least two more research groups (Enstrom et al., 2009; Vojdani et al., 2008). Enstrom et al. (2009) also noted decreased NK cell killing upon stimulation with K562 cells in ASD subjects. They examined resting NK cell killing and RNA expression and observed an increase in killing in resting NK cells from ASD subjects as determined by higher levels of interferon- γ and the enzymes perforin and granzyme B. The microarray experiment demonstrated the increased expression of inhibitory killer-cell immunoglobulin-like (KIR) receptors in ASD subjects, which is in agreement with the decreased killing of K562-stimulated NK cells. In the resting state this increased expression of interferon- γ in ASD subjects could have profound long term effects, especially in the brain.

8.2.2 Monocytes

Progenitor cells called monocytes circulate in the blood and differentiate into macrophages upon leaving the blood and entering other body tissues. Macrophages are a type of phagocyte that engulf and digest microorganisms then present the antigens to lymphocytes. Some macrophages are resident cells within specific organs taking on different names depending on the organ they inhabit, for example, in the liver they are referred to as Kupffer cells and in the brain microglial cells. When stimulated by interferon- γ , monocytes and macrophages produce increased amounts of the molecule neopterin. High levels of neopterin serve as an indicator of monocyte/macrophage activation and are indicative of pro-inflammatory immune status. Increased monocyte counts and neopterin levels were observed in autistic children compared to gender and age-matched healthy controls (Sweeten et al., 2003a) suggesting that the immune system is over-activated in the ASD group. Enstrom et al. (2010) isolated monocytes from ASD and control subjects then stimulated the monocytes with several different TLR ligands. The researchers noted marked increases or decreases in pro-inflammatory cytokines following TLR stimulation depending on the particular ligand used.

Since interferon- γ normally activates monocytes/macrophages, an increase in the resting state production of interferon- γ by NK cells in autistic subjects could be over stimulating monocytes/macrophages and altering their function. If microglial cells in the brain are activated this way, it could have profound effects on neurochemistry, brain development and ultimately behavior. For instance, one mechanism whereby microglial cells could alter brain chemistry and development is by increased production of nitric oxide (NO). Interferon- γ activated immune cells such as microglia produce high levels of NO as a means to kill pathogens by oxidative stress. In the brain NO is typically produced by neurons where

it acts as an intercellular messenger modulating synaptogenesis, dendrite and axonal growth, and neuronal release of various neurotransmitters (Hess et al., 1993; Lizasoain et al., 1996; Lonart et al., 1992). Increased NO production by interferon- γ responsive immune cells in the brain would likely alter these processes.

NO production has been shown to be elevated in the blood of autistic subjects and was positively correlated with plasma interferon- γ concentration (Sweeten et al., 2004). Vargas et al. (2005) showed that microglia as well as monocyte and macrophages are activated and produce high levels of interferon- γ in the brain tissue of autistic patients. Interferon- γ levels in cerebrospinal fluid were increased over 200-fold in the autistic subjects versus controls.

8.3 Humoral adaptive system

Since autism is a neurodevelopmental disorder, one hypothesis proposes that autism could be caused by an antibody attack against one or more brain proteins. By examining total serum proteins and serum concentrations of antibodies, Croonenberghs et al. (2002) found that children with autism had significantly increased concentrations of albumin and gamma globulin as well as significantly increased levels of IgG subclasses IgG2 and IgG4. Autoantibodies have been detected against several brain proteins including myelin basic protein (Jyonouchi et al., 2001), neuron-axon filament protein and glial fibrillary acidic protein (Singh et al., 1997), nerve growth factor (Bashina et al., 1997), cell nuclei (Stubbs, 1988), brain endothelium (Connolly et al., 1999), Purkinje cells of the cerebellum (Zimmerman et al., 1993), cerebellar proteins (Goines et al., 2011), serotonin 5-HT receptors (Todd & Ciaranello, 1985), and most recently to tissue transglutaminase-2 which is present in the brain and involved in cell adhesion and synaptic stabilization (Rosenspire et al., 2011). Although autoantibodies have been detected against several proteins important in neuronal function, there is no evidence of pathological brain lesions in autism.

8.4 Cellular adaptive system

The cellular arm of the adaptive immune system involves T cells and B cells, both of which have been reported to be altered in subjects with autism. For example, decreased numbers of T lymphocytes and an altered ratio of helper T cells to suppressor T cells were observed as early as 1986 (Denney et al., 1996; Warren et al., 1986). More recently, alterations in lymphocyte subsets was observed when data showed a significant decrease in CD4⁺ naïve and an increase in CD4⁺ memory T cells in autistic subjects who also bore the HLA-A*02 and HLA-DR β 1*11 alleles (Ferrante et al., 2003). In addition, the production of numerous autoantibodies in autism that was discussed above provides evidence that indirectly points to B cells playing a role in autism.

Alterations in cytokine levels or production can indicate abnormal cellular immunity. A study that compared the production of several cytokines in peripheral blood mononuclear cells found that levels of both Th2 and Th1 cytokines were significantly higher in the autism group (Molloy et al., 2006). However, when 12 children with autism were compared to children with other neurological disorders, only TNF receptor II was elevated (Zimmerman et al., 2005). When children with ASD were examined for cytokine production, Ashwood et al. (2011) found an association between increased levels of some Th1 pro-inflammatory cytokines and severity of clinical behavioral outcomes, specifically, aberrant behaviors and impaired communication. As previously mentioned, Vargas et al., (2005) found elevated cerebrospinal fluid interferon- γ levels in autistic subjects. This finding was accompanied by

an elevated pro-inflammatory profile of cytokines in the brain tissue and cerebrospinal fluid, including macrophage chemoattractant protein-1 and TGF- β 1. A prominent theory for the pathophysiology of autism is that increased cytokines produced as a result of inflammation or other aberrant immune processes in the brain may alter neurochemistry and neurodevelopment resulting in the behavioral profile characteristic of autism.

9. HLA associations in autism

There are numerous associations between autism and genes located in the HLA region (Table 1). Researchers in our laboratory demonstrated a significant association between autism and the allele HLA-A2 (Torres et al., 2006). This may be important as HLA class I molecules have been shown to be involved in brain development (Boulanger & Shatz, 2004). HLA class II molecules have been shown to be associated with numerous autoimmune disorders. In a very elegant paper Warren et al. (1996) reported that the third hypervariable region of DR β 1, which is part of the shared epitope binding pocket (DR β 1*0401, *0404, and *0101), has a strong association with autism. This is an interesting observation as the shared epitope has been associated with certain autoimmune diseases (De Alemeida et al., 2010). Torres et al. (2002) confirmed the association of the HLA-DR4 allele and also found that the DR13 and DR14 alleles occurred less often in subjects with autism, suggesting a possible protective mechanism. Interestingly, the DR13 allele was inherited less frequently than expected from the mothers. Associations with autism and the DR4 allele have since been confirmed in two additional laboratories. Lee et al. (2006) demonstrated that boys with autism and their mothers had a significantly higher frequency of DR4 than normal control subjects (odds ratios 4.20 and 5.54, respectively), suggesting that a maternal-fetal immune interaction could be involved in autism. Johnson et al. (2009) reported significant transmission disequilibrium for HLA-DR4 (odds ratio 4.67) from maternal grandparents to mothers of children with autism which also suggests a maternal-fetal interaction for HLA-DR4. The HLA class III region encodes for many components involved in the immune system such as the C4 complement proteins, cytokines (TNF- α), and heat shock proteins. Although C4A and C4B proteins are encoded in the HLA class III region, they are considered part of the humoral innate system as they are not classical HLA proteins.

In addition to single genes and alleles, several publications have shown haplotypes to be associated with autism (Table 1). Warren et al. (1991) first reported that the AH 44.1-SC30-DR4 was associated with autism with a relative risk of 7.9. That result was confirmed in a new case/control population (Daniels et al., 1995). Interestingly, the individual components of AH 44.1-SC30-DR4 include C4B null and HLA-DR4, both of which have been shown independently to be significantly associated with autism, although not in the population reported on by Daniels et al. (1995). In autistic children bearing both the HLA-A2 and DR11 alleles, Ferrante et al. (2003) observed a significant decrease in CD4⁺ naïve and an increase in CD4⁺ memory T cells compared to the HLA-A2, DR11 negative autistic children. Two HLA haplotypes, TNF-MIB-B*38-Cw12 and D6S265-A*38-MOG, were shown to be transmitted more often to subjects with ASD than their unaffected siblings after performing linkage analysis (Guerini et al., 2011). Guerini et al. (2011) also examined the individual components of these two haplotypes using a family based TDT analysis and showed that the D6S2239*105 allele and the MOGc*131 allele were more often transmitted to children with ASD from the fathers.

HLA Region	Gene/Allele	Reference
HLA Class I	A2	Ferrante et al., 2003 Torres et al., 2006
HLA Class II	Third hypervariable region of DRβ1	Warren et al., 1996
	DR4	Torres et al., 2002
	DR13,14	Torres et al., 2002
	DR4	Lee et al., 2006
	DR4	Johnson et al., 2009
HLA Class III	C4B null allele	Warren et al., 1991
	TNF-α microsatellites	Torres et al., 2001
	C4B null allele	Odell et al., 2005
	C4B null allele	Mostofa & Shehab, 2010
HLA Haplotypes	AH 44.1-SC30-DR4	Warren et al., 1992
	AH 44.1-SC30-DR4	Daniels et al., 1995
	TNF-238, TNF-308-MIB*332-HLA-B*38-HLA-Cw12	Guerini et al., 2011
	D6S265*218-HLA-A*23-MOGc*131-rs2857766	Guerini et al., 2011

Table 1. HLA alleles, genes and haplotypes associated with autism.

10. Autoimmunity

Autoimmunity occurs when a person’s immune system treats its own DNA, proteins, cells or tissues as non-self. About 5% of the population has an autoimmune disease such as celiac disease, type 1 diabetes, systemic lupus erythematosus (SLE), Graves' disease, multiple sclerosis (MS) and rheumatoid arthritis (RA). Autoimmune diseases involve both innate and adaptive systems and often cause severe tissue damage. For example, in celiac disease there is destruction of villi in the small intestines, psoriasis and SLE both have skin lesions, RA has joint destruction and diabetes has destruction of the beta cells of the pancreas. Human C4 complement genes have strong associations with several autoimmune diseases such as SLE and MS (Pickering & Walport, 2000; Tegla et al., 2009) as well as central nervous system disorders like Alzheimer’s (Kolev et al., 2009). HLA class I and class II alleles have been shown to be associated with various autoimmune diseases. For example, HLA-DR4 (DR4) has an association with RA with a relative risk of 4 and HLA-DR3 (DR3) is associated with diabetes with a relative risk of 5. If an individual has both DR3 and DR4 the relative risk for diabetes increases to 15. A large scale study found that the frequency of autoimmune disorders in the families with autistic children was found to be higher than in control subjects, especially mothers of autistic children (Comi et al., 1999). Another group showed that autoimmunity was increased significantly in families with ASD compared with those of healthy control subjects (Sweeten et al., 2003b), suggesting a link between the two disorders.

Some very interesting research has surfaced where physicians/ researchers treated Crohn’s disease and ulcerative colitis using nematode parasites. This is consistent with the increase

in the rate of autoimmune disease in more developed countries and in urban environments (Grant, 2011). Therefore, it has been hypothesized that the lack of parasite infection may lead to autoimmune diseases (Summers et al., 2003).

11. Childhood infections

A number of retrospective studies have investigated the histories of infections in autistic children. One study found a significant difference in rates of ear infections in children with autism compared to normal controls. No difference was found in the frequency of colds or fevers unrelated to ear infections in the two groups (Kostantareas & Homatidis, 1987). However, another survey did not find increased rates of ear infection, glue ear or hearing grommets in autistic children (Fombonne et al., 1997). Researchers in Japan compared the histories of 145 autistic children and 224 normal children for various diseases including pneumonia, seizures, high fever, measles, meningitis, significant diarrhea, hydrocephalus, rubella, varicella, mumps and otitis media in the first 18 months of life. No significant difference in rates of illness between groups was found (Tanoue et al., 1988). No difference was found for overall infections in the first 2 years of life when records of 403 children with autism and 2100 matched controls were analyzed in a California study (Rosen et al., 2007). A study of past illness utilizing a questionnaire found no significant difference between autistics and healthy controls in the occurrence of chickenpox, reactions to immunizations, meningitis, encephalitis, influenza or repeated infections (Comi et al., 1999).

The role of infection in the child as a possible autism trigger remains unclear. As stated earlier, the literature does support that congenital rubella and perhaps some herpes family viruses may contribute to the onset of autistic behavior in a small percentage of cases. Yet consistent evidence of a broader infectious role in this disorder remains elusive. It is yet to be seen if future research in this area will reveal a larger role for infection in autism and other neuropsychiatric disorders (Yolken & Torrey, 2008).

12. Maternal immune factors

Since there are many children who show signs of autistic behavior at a very early age and are thus thought to be born with autism, it is reasonable to assume that something acting on the developing fetus contributes to the disorder in these children. While a mother and fetus do not normally share or even mix blood during pregnancy, hormones, cytokines and antibodies do cross the placenta. An atypical maternal immune response during pregnancy could have a profound impact on the developing fetal brain, thus, contributing to autism. Maternal infection during pregnancy has been shown to increase the risk of several neurodevelopmental disorders in the fetus. Since associations with numerous infectious agents have been observed, it has been proposed that the maternal induction of pro-inflammatory cytokines may be the link between maternal infection and adverse effects on the fetal brain (Meyer et al., 2009).

In rats, maternal exposure to bacterial infection led to altered cytokine levels in the fetal environment by significantly increasing placental IL-1 β , IL-6 and TNF- α which may have profound effects on the developing fetal brain (Urakubo et al., 2001). Patterson (2002) suggested that maternal immune response to human influenza virus respiratory infections during pregnancy can have both short-term and long-lasting deleterious effects on developing brain structure in the progeny through increased levels of circulating cytokines. Hsiao & Patterson (2011) used a mouse model to investigate how the maternal immune

system plays a role in the development of autism by mimicking a virus infection and activating the maternal immune response. They observed increases in IL-6 mRNA (pro-inflammatory cytokine) as well as maternally-derived IL-6 protein in the placenta.

To test the hypothesis that ASD is caused by exposure of the fetal brain to maternal autoantibodies during pregnancy, Martin et al. (2008) studied rhesus monkeys gestationally exposed to IgG class antibodies from mothers of children with ASD. These exposed monkeys consistently demonstrated increased whole-body stereotypies across multiple testing paradigms and were also hyperactive compared to controls. Monkeys exposed to IgG antibodies purified from mothers of typically developing children did not display stereotypical or hyperactive behaviors. These findings support the potential for a maternal immune system etiology in patients with autism.

Another theory is that antibodies present in the mother's sera react directly against fetal proteins. Warren et al. (1990) found that mothers with an autistic child are more likely to have plasma antibodies that react against their child's lymphocytes. Zimmerman et al. (2007) tested the serum reactivity of mothers and their autistic children as well as control mothers and unaffected children to adult rat brain proteins. They found antibody reactivity against myelin basic protein and glial fibrillary acidic protein in the sera from mothers with autistic children. Both of these proteins are expressed in the brain of fetuses suggesting a mechanism by which antibodies that cross the placenta could affect fetal brain development. Maternal autoimmune disease, immune dysfunction and other immune-related disorders have been reported to be associated with autism. Croen et al. (2005) showed that maternal psoriasis diagnosed around the time of pregnancy is significantly associated with a subsequent diagnosis of autism in the child. Additionally, they showed a 2-fold increase in risk for a child having ASD if the mother was diagnosed with asthma or allergies during pregnancy. An association between a family history of type 1 diabetes and infantile autism as well as a significant association between maternal histories of either RA or celiac disease and ASDs was observed by Atladóttir et al. (2009) who stated that these associations between familial autoimmunity and ASDs/infantile autism are probably attributable to a combination of a common genetic background and a possible prenatal antibody exposure or alteration in fetal environment during pregnancy.

Comi et al. (1999) also found that during pregnancy 43% of the mothers of autistic children, compared to 26% of the control mothers had an influenza-like illness, upper respiratory tract infection, urinary tract infection or vaginal infection. An investigation of children born in Denmark from 1980 through 2005 revealed no association between maternal infection over the entire pregnancy and autism in the child; however, admission into the hospital due to maternal viral infection in the first trimester and maternal bacterial infection in the second trimester were found to be associated with diagnosis of ASD in the offspring (Atladóttir et al., 2010). Another study found a trend toward increased infections during pregnancy in mothers bearing autistic children (Gillberg & Gillberg, 1983), and two studies found a significant increase in viral infections including rubella (Harper & Williams, 1974; Wilkerson et al., 2002), yet at least seven other studies have found no such correlations (Juul-Dam et al., 2001; Lobascher et al., 1970).

13. Vaccines

Over the past decade an energetic debate has brood around the possible role of the measles-mumps-rubella (MMR) vaccine in the development of autism. Although this debate has surfaced in headlines and news reports, the body of scientific data overwhelmingly fails to

show any association between autism and the MMR vaccine. However, many parents of children with autism report that their child was normal until receiving vaccinations and they therefore felt there was something to this story: Is there a government or vaccine company cover-up? The initial paper proposing a correlation between the MMR vaccine and autism onset (Wakefield et al., 1998) has been retracted amid reports of unethical research (Full retraction 2010). At least 15 epidemiological studies from around the world have found no connection between autism and vaccines (Honda et al., 2005; Madsen et al., 2002; Mäkelä et al., 2002). These epidemiological findings have been substantiated by biological studies finding no evidence of persistent measles virus infection in autistic individuals (Afzal et al., 2006; Hornig et al., 2008). Interestingly, Pangborn (2002) reported that autism onset-at-18 months of age has increased more than 10 times the 1980 levels while the onset-at-birth cases has increased 3-4 times.

One common response to infection in the animal kingdom is the induction of fever. A vaccination is basically an artificial infection and it is common to give fever suppressors such as acetaminophen after a vaccination to suppress the fever and discomfort. Torres (2003) proposed that perhaps the acetaminophen given to suppress fever was disrupting a normal immune mechanism that in certain subjects could lead to autism. It is known that acetaminophen usage has increased greatly in the last three decades. In 1980 the CDC reported that aspirin was associated with Reye's syndrome, a rare but often fatal disease in children. This resulted in a sharp decrease in the purchase of aspirin between 1980 and 1985 and a reciprocal increase in the purchase of acetaminophen-containing drugs (Arrowsmith et al., 1987). Schultz et al. (2008) found that children given acetaminophen for reactions to the MMR vaccines were more likely to become autistic than children given ibuprofen. The use of acetaminophen by pregnant mothers has also increased over the last few decades.

14. Future directions

Despite several decades of research using cutting-edge technologies, the etiology of autism is unknown. This is not to say that progress has not been made. However, we will use the term used by most researchers that "more research is needed". We anticipate additional advances in autism genetics and perhaps more importantly research that ties together genetics and immune dysfunction in autism. The phenotypic heterogeneity among children with autism who participate as subjects in research studies has added to the inconsistent results. There is increasing interest in using phenotypic subgroups of psychiatric disorders in the detection of susceptibility genes (Tsuang, 2001). Szatmari et al. (2007) discusses ways to increase sample size and identify genetically informative phenotypes which will segregate with susceptibility loci and ultimately lead to a causative gene.

Recent advances in genetic analysis methods are positively impacting autism research. Researchers in the genetics field are very excited about the findings of "rare alleles" in the neurexin superfamily of genes so one can expect to see a great amount of research in this area. As stated above, the neurexin genes are incredibly complex and it will take years to understand how these genes are involved in the etiology of autism. However, one must remember that the "common variant common disease" model has not held up after 15 years of scrutiny leaving the genetic area ripe for discovery.

Whole genome sequencing will result in the identification of mutations or deletions/insertions in many additional genes involved in neurologic development and function as causes of autism. The impact of single DNA molecule sequencing by Third-Generation

instruments should have a significant impact in genetics as single molecule sequences result in haplotypes. Current methods cannot determine haplotypes with any certainty. This is reminiscent of gold companies extracting considerable amounts of gold from the tailing of old mining operations. Perhaps current genetic data that identifies regions of interest will prove golden for single molecule haplotype sequencing.

It is entirely possible that unknown genes in the HLA region that are in linkage disequilibrium with classical genes including C4 are involved in the etiology of autism. For example, there are several AHs that have been associated with autism by Warren et al. (1992). The AH 44.1 (B44, C4B null allele, DR4) has the strongest association. The AH 8.1 (A1, C7, B8, C4A null allele, DR3, DQ2) also referred to as COX has been entirely sequenced providing information on all of the genes in this haplotype. The AH 44.1 has the DR4 allele that has been associated with RA and the DR3 DQ2 portion of the AH 8.1 is associated with autoantibodies to tissue transglutaminase-2 as is seen in celiac disease (Rosenspire et al., 2011). The C4 null alleles in these two ancestral haplotypes associate with several autoimmune diseases like SLE. Although the current methods work very well for typing classical HLA alleles, newer microarray beads such those from Illumina will find autism associations when interrogating the 100 non-classical HLA genes.

Another area of developing interest in autism is epigenetics (reviewed by Grafodatskaya et al., 2010). Epigenetics is the field of research focused on the interaction between the environment and genetics. Epigenetic effects cause alterations in gene expression, resulting in phenotypic changes, without changes in the primary DNA sequence. Epigenetic mechanisms include DNA methylation, histone modifications, nucleosome repositioning, higher-order chromatin remodeling, non-coding RNAs, and RNA and DNA editing. One known example of an epigenetic cause of ASD is the alteration in DNA methylation caused by a mutation in the methyl CpG binding protein 2 (Rett syndrome). Most areas of epigenetic research in autism are largely unexplored. In addition, the expression of genes in the many cells in the brain is an incredibly complex process and it will take years to understand how these genes are involved in the etiology of autism.

Evidence continues to mount implicating an involvement of immune molecules in the etiology of autism. The evidence for pathogen involvement in autism does not appear to be strong as all children get infections and children with autism did not appear out of the norm. On the other hand, immune differences continue to mount and it is our belief that discoveries will be made that tie together seemingly unrelated immune findings. Autoimmune associations, differences in NK cells, cytokine levels and maternal influences appear to be the most fruitful areas for research. One legitimate question raised about autoimmunity in autism is, "Why is there no tissue damage as seen in typical autoimmune diseases?". Autism does not appear to be an autoimmune disease in a traditional sense, but it has similar immune associations. Some differences are that most autoimmune diseases appear late in life whereas autism appears very early and autoimmune diseases generally affect more females than males where autism disproportionately affects more males.

Another interesting research area involves NK cells in autism. It is fairly well established that NK cells from subjects with autism have decreased killing. Perhaps more importantly, resting NK cells from autistic subjects have higher cytolytic activity and produce higher levels of interferon- γ . Higher baseline levels of interferon- γ have been measured in CSF and the brain in subjects with autism. Vargas et al. (2005) noted an increase of over 200-fold in interferon- γ in CSF in subjects with autism. At this time, these levels have unknown consequences, however, cytokines have powerful effects on cells including those in the

brain. There are two major subsets of NK cells (CD56^{dim} and CD56^{bright}) as determined by flow cytometry and they have somewhat different functions. NK cells CD56^{dim} have more cytolytic activity but produce less interferon- γ than CD56^{bright}. How and which type of NK cell enters the brain could be significant. Also, since the NK cell is the major immune cell at maternal-fetal interfaces during pregnancy, the characterization of NK cells from mothers who have borne children with autism may be important. The NK cell is sentinel in pregnancy and environmental factors can change their phenotype by epigenetic pathways (Karimi & Arck, 2010). Therefore, the maternal/fetal NK cell population could be of major importance in autism.

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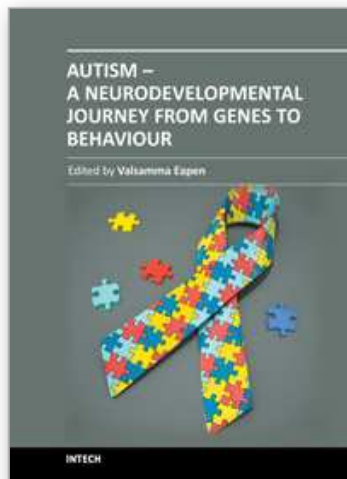
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The book covers some of the key research developments in autism and brings together the current state of evidence on the neurobiologic understanding of this intriguing disorder. The pathogenetic mechanisms are explored by contributors from diverse perspectives including genetics, neuroimaging, neuroanatomy, neurophysiology, neurochemistry, neuroimmunology, neuroendocrinology, functional organization of the brain and clinical applications from the role of diet to vaccines. It is hoped that understanding these interconnected neurobiological systems, the programming of which is genetically modulated during neurodevelopment and mediated through a range of neuropeptides and interacting neurotransmitter systems, would no doubt assist in developing interventions that accommodate the way the brains of individuals with autism function. In keeping with the multimodal and diverse origins of the disorder, a wide range of topics is covered and these include genetic underpinnings and environmental modulation leading to epigenetic changes in the aetiology; neural substrates, potential biomarkers and endophenotypes that underlie clinical characteristics; as well as neurochemical pathways and pathophysiological mechanisms that pave the way for therapeutic interventions.

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