

MicroRNA cross-involvement in Autism Spectrum Disorders and Atopic Dermatitis: a literature review

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Abstract

Autism Spectrum Disorders (ASD) are neurodevelopmental disturbances affecting social skills, whose incidence worldwide is dramatically increasing. Together with the rise of ASD prevalence, several immune conditions are following the same trend, including Atopic Dermatitis (AD), with a possible clinical relationship with ASD. To date, their pathogenesis is still unknown, but several studies highlighted the relevance of gene-environment interactions to the onset of both disorders. Among potential contributing factors, microRNAs (miRNAs), small molecules capable of controlling gene expression and targeting mRNA transcripts, might represent one of the major circulating link, unraveling the connections between neurodevelopmental and immune conditions.

We conducted a systematic literature review, under the PRISMA guidelines, trying to define the panel of common miRNAs involved in both ASD and AD. The review retrieved articles published until December 13, 2018, in PubMed, ScienceDirect, PsycARTICLES and Google Scholar.

We found a handful works dealing with miRNAs in ASD and AD, with the most overlapping dysregulated miRNAs being miR-146 and miR-155.

Two possible compounds are abnormally regulated in both ASD and AD subjects, possibly cross-contributing to the interactions between the two disorders, setting the basis to investigate more precisely the possible link between ASD and AD from another, not just clinical, perspective.

Keywords: Allergy; Autistic Disorder; Dermatitis; Genetics; Immunity; MicroRNAs

1. Introduction

Autism spectrum disorders (ASD) are a heterogeneous group of neurodevelopmental disorders characterized by impairments in social interaction and communication and restricted or stereotyped interests and behaviors [1], typically occurring before the fourth year of life [2]. Their prevalence has dramatically increased in last decades, from 4/10,000 in 2008 [3] to 1/68 cases in children living in the United States nowadays [4], with a gender (males vs. females) ratio of 4:1. It still remains unsolved whether this exponential increment may be due to a better knowledge on this topic and to an improved awareness along with broadening of the diagnostic criteria or, rather, may reflect a true increase in the incidence of ASD.

Nonetheless, ASD are the most heritable neuropsychiatric disorders, with genetic contributions accounting for more than 50% of ASD risk [5-7], and higher risk seen in siblings of autistic children [8]. Although epidemiological studies provide information on the genetic contribution to ASD, less is known about the putative genes involved and/or the frequency of specific polymorphisms and variants (single-nucleotide or copy number variants).

Whole-genome and candidate-gene analyses have shown a complex genetic background of ASD, characterized by high individual differences and variability, with many ASD-risk genes involved in synaptic plasticity and gene products modifying synaptic number and strength. In addition to inherited variants, individuals with ASD often carry de novo genetic variants, defined as variants not present in the parental genome and found for the first time in the proband [9]. Such mutated variants affect biological pathways involved in synaptic plasticity and connectivity at different levels. It has been proposed that both individual's genetic background and de novo and rare mutations converge in disrupting synaptic homeostasis [10].

The multigenic condition of ASD seems also be dependent on gene-environment interactions; epigenetic mechanisms involving DNA methylation, transcriptional regulations, and post-translational changes in histone proteins, are all relevant to neurodevelopmental processes that can be affected in-utero by maternal lifestyle factors [11]. Furthermore, chemicals and/or heavy metals exposure, appears to strongly contribute to ASD development [12-14].

Consistently, recent studies report the clinical association between ASD and atopic disorders, such as asthma or atopic dermatitis (AD) [15-18], strengthening the link between neurodevelopmental disorders and immune diseases.

In fact, in recent times, a clinical association between the two conditions was hypothesized [16,17], and the investigation of possible common genetic basis is critical for the current scientific knowledge.

As evidenced by Billeci and colleagues, AD, defined as a chronic inflammatory disease, puts at higher risk of developing one of more of the other atopic conditions, therefore it is considered as the beginning of the so-called "atopic march" [16].

This condition, also determined by a close gene-environment interaction [19], appears to be correlated with a number of mental health conditions including, according to recent literature, ASD [16].

Among the compounds which could possibly explain this link, up to now hypothesized from a clinical point of view, microRNAs (miRNAs) were recently seen to play a role in several molecular and cellular mechanisms, including neurodevelopment, brain plasticity and immunity [20,21].

miRNAs might participate in pathological process both in neurological conditions, including autism, and in atopic disorders, including AD [22]. The overlapping microRNAs in ASD and AD could therefore allow to explore the role of genetics in the hypothetical common pathophysiological pathways of these two conditions.

1.1 General insight into microRNAs

miRNAs are very short (18-25 nucleotides), single-stranded non-coding RNAs, able to control gene expression and to target mRNA transcripts, possibly bringing on their translational degradation or their repression, with particular degrees of complementarity [23]. The targeting of mRNA transcripts by miRNA occurs as one miRNA is able to target a number of mRNA transcripts, conversely a single mRNA transcript can be targeted by many miRNAs.

Actually, miRNAs have rapidly induced a great interest in humans, being potential biomarkers for diagnostic and prognostic aims [24,25], and being the number of classified miRNA increasing, till over 2,500 potential molecules in the *Homo Sapiens* genetic makeup [23]. Despite being small molecules, not capable of encoding proteins, miRNAs hold important structural, regulatory and catalytic functions.

miRNA genes are located in the introns of protein-coding genes or in independent non-coding DNA loci [26], whereas nearly half of the total miRNAs are pooled on chromosomes with a common promoter [27].

The biogenesis of miRNA is extremely complex, consisting of several phases, including: i) in the nucleus, the transcription of miRNA genes into primary miRNA transcripts by RNA polymerase II; ii) the freeing of pre-miRNA hairpin, through the trim of the primary miRNA transcripts by the RNase III Drosha endonuclease; iii) the active exportation of the pre-miRNA hairpin out of the nucleus in a process involving the nucleocytoplasmic shuttler Exportin-5; iv) the final maturation, in the cytoplasm, processed by Dicer RNase III endonuclease, splitting the pre-miRNA into a single-stranded mature miRNA [28]; v) the binding of the mature miRNA to proteins of the Ago family, and vi) the assembly of the RISC complexes together in order to employ its physiological functions.

The mature miRNA, once incorporated into the RISC, induces posttranscriptional gene silencing by binding RISC to be partially complementary to the target mRNA found mainly within the 3'-untranslated region (UTR) [29,30].

Flaws in miRNA expression deeply affect several pathways related to cell regulation, including apoptosis, stress responses, or cell proliferation throughout the human body [31-33]. Indeed, a single miRNA could repress around 100

mRNAs, while around 60% of human protein coding-genes are represented by conserved targets of miRNAs, thus a number of mRNA targets are regulated by miRNAs [34].

1.2 miRNAs linked to brain function

MiRNAs approximately regulate two-thirds of human mRNAs [34] and are, as much as for the 70%, expressed in the central nervous system (CNS), including the brain and spinal cord [35,36]. Their changes during childhood are different depending on the affected brain region [37].

In particular, miRNAs are abundant in neurons and glia, often placed at the synaptic level, able to regulate the structure of the dendritic spine, as happens with miR-134, that reduces, by targeting spine growth-promoting kinase Limk1, spine growth [38].

Indeed, dendritic spines are bulges on a dendritic tree of a neuron, composing the post-synaptic termination of a synapse, reflecting – through their structure – the degree of brain maturation and, somehow, brain plasticity.

Their density is abnormal in several conditions, including schizophrenia (dendritic spines loss) and ASD, the latter featuring an increase in the quantity of spines in specific brain areas [39-42].

Several other miRNAs are associated with dendritic spine structure, including miR-125b [43], miR-132 [44], miR-137 [45] and miR-138 [46].

Overall, several miRNAs affect brain functions and development, neuronal plasticity, maturation and differentiation [20,47]. Dysregulation of miRNA expression is particularly frequent within several neurological disorders, including ASD, therefore the association between some common miRNA families and ASD, despite still largely unknown, is nowadays less unclear than in the past.

1.3 miRNAs and skin disorders

Recently, many evidences were published about the role of miRNAs in several cellular processes, including immune response, DNA repair, apoptosis, proliferation and differentiation [48], but also in morphogenesis, differentiation, wound healing, psoriasis, and AD [49-51]. Specifically, also AD pathogenesis is associated with a complex gene-environment interaction, as well as with an alteration of the skin barrier function, and a deregulation of the immune system [52]. Several miRNAs, including miR-146a, miR-155, miR-203 and miR-483–5p, are also differentially expressed in AD and in other immunologic and inflammatory disorders.

2. Materials and Methods

A literature review of the articles published between January 1, 2005 and December 13, 2018, was conducted in PubMed, ScienceDirect, PsycARTICLES and Google Scholar following the PRISMA guidelines.

Studies about ASD

The search strategy for this part was as follows: (("micrornas"[MeSH Terms] OR "micrornas"[All Fields] OR "microrna"[All Fields]) AND (("autistic disorder"[MeSH Terms] OR ("autistic"[All Fields] AND "disorder"[All Fields]) OR "autistic disorder"[All Fields] OR "autism"[All Fields]) OR ("autism spectrum disorder"[MeSH Terms] OR ("autism"[All Fields] AND "spectrum"[All Fields] AND "disorder"[All Fields]) OR "autism spectrum disorder"[All Fields])))).

Studies about AD

In this part, the search strategy was as follows: (("microRNAs" [MeSH Terms]) AND ("skin" [MeSH Terms] OR "dermatitis" [MeSH Terms] OR "urticaria" [MeSH Terms] OR "eczema" [MeSH Terms] OR "hypersensitivity" [MeSH Terms])).

Overall, the search was limited to articles describing studies conducted on humans published in peer-reviewed journals. After having discarded duplicates, the obtained results were sorted by relevance and the most significant works related to ASD and miRNAs and to AD and miRNAs were selected. We will first present the results from the literature review and then discuss the possible associations between miRNAs in ASD and AD according to such findings.

3. Results

The literature search displayed 23 articles directly related to the relevant topic (Figure 1).

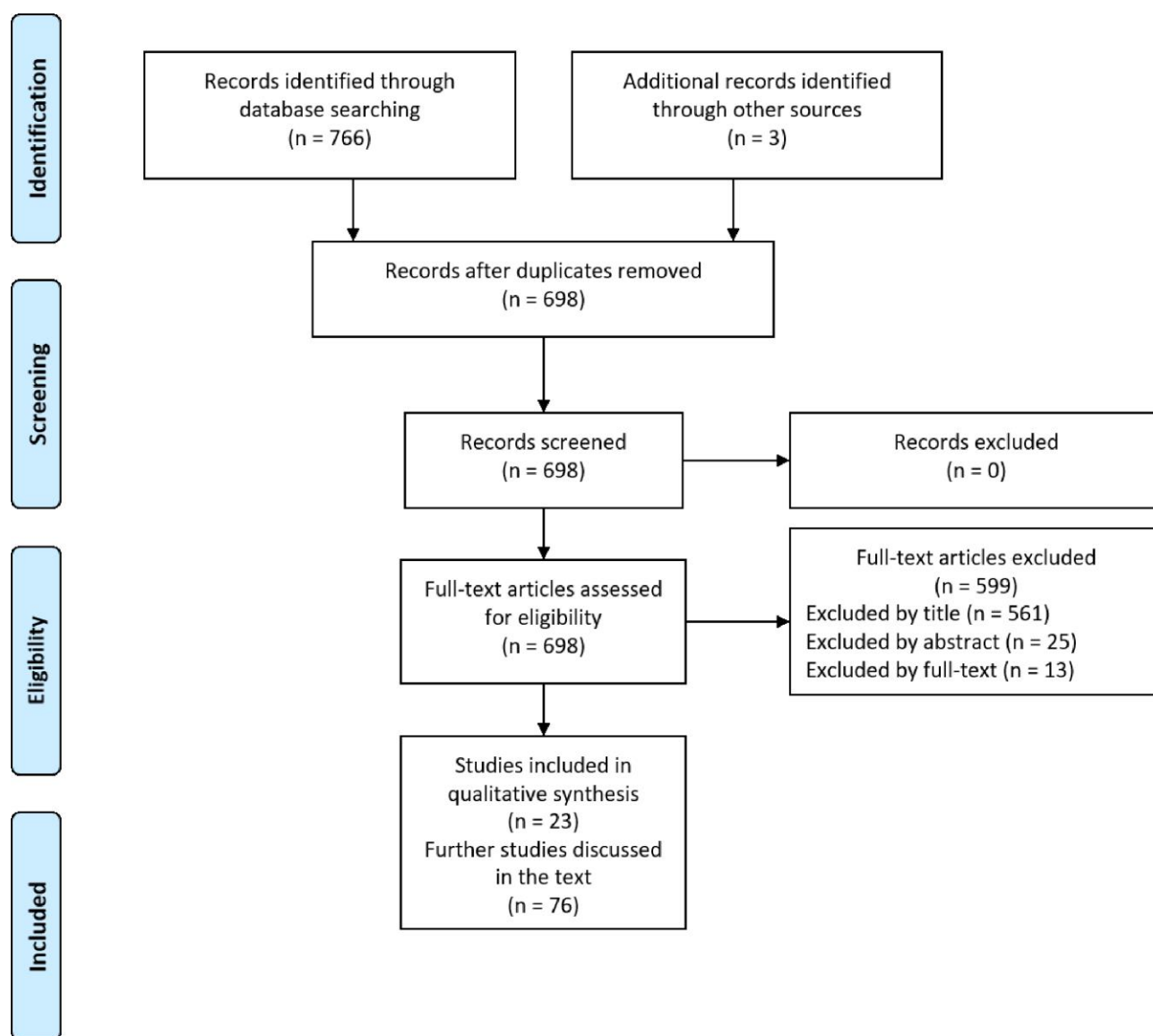


Figure 1. Study selection

3.1 Studies about ASD

According to the literature review, a number of miRNAs were found to be associated to ASD (Table 1). Specifically, the most overlapping dysregulated miRNAs appeared to be let-7, miR-23, miR-106 and miR-146.

Study	N (case/control)	Design	Findings	
			Up-regulated miRNA	Down-regulated miRNA
Abu-Elneel et al. (2008) [53]	26 (13/13)	Measure of the expression level of 466 human miRNAs from postmortem cerebellar	miR-106a, miR-106b, miR-140, miR-146b, miR-181d, miR-193b,	miR-7, miR-15a, miR-15b, miR-21, miR-23a, miR-27a, miR-93, miR-

		tissue by multiplex real-time PCR. 377 miRNAs detected and used for further analysis	miR-320a, miR-381, miR-432, miR-539, miR-550, miR-652	95, miR-128, miR-129, miR-132, miR-148b, miR-212, miR-431, miR-484, miR-598
Sarachana et al. (2010) [54]	14 (5/9)	Lymphoblasts derived from peripheral lymphocytes were obtained. miRNA expression profiling performed by high-throughput miRNA microarray analysis. Differentially expressed miRNAs confirmed by qRT-PCR analysis, putative target genes of two of the confirmed miRNA validated by knockdown and overexpression of the respective miRNAs	miR-16-2, miR-106b, miR-132, miR-133b, miR-136, miR-139, miR-148b, miR-153, miR-182, miR-189, miR-190, miR-199b, miR-211, miR-219, miR-326, miR-367, miR-455, miR-495, miR-518a, miR-520b	miR-23a, miR-23b, miR-25, miR-29b, miR-30e, miR-93, miR-103, miR-107, miR-185, miR-186, miR-191, miR-194, miR-195, miR-205, miR-342, miR-346, miR-376a-AS, miR-451, miR-519c, miR-524
Talebizadeh et al. (2008) [55]	12 (6/6)	6 ASD (3 males, aged 5, 12 and 14 years, and 3 females, aged 6, 11 and 13 years), 6 age- and gender-matched TD controls. Lymphoblastoid cell lines, quantitative PCR	miR-23a, miR-23b, miR-132, miR-146a, miR-146b, miR-663	miR-92, miR-320, miR-363
Mundalil Vasu et al. (2014) [56]	110 (55/55)	55 ASD (48 males, 6 females, aged 11.29 ± 5.45 years), 55 TD controls (41 males, 14 females, aged 11.3 ± 2.37 years). RNA extracted from serum, mature miRNAs selectively converted into	miR-19b-3p, miR-27a-3p, miR-101-3p, miR-106-5p, miR-130a-3p, miR-195b-5p	miR-151a-3p, miR-181b-5p, miR-320a, miR-328, miR-433, miR-489, miR-572, miR-663a

		<p>cDNA. The expression of 125 mature miRNAs was compared between pooled control and ASD samples. The differential expression of 14 miRNAs further validated by SYBR Green quantitative PCR of individual samples. Target genes and pathways of miRNAs predicted by DIANA mirPath software</p>		
<p>Popov et al. (2012) [57]</p>	<p>55 (30/25)</p>	<p>30 ASD (24 males, 6 females, aged 3-20), 25 TD controls (20 males, 5 females, aged 3-20 years). Whole blood collection, analysis of gene expression changes applying LC expression profiling service, using pooled whole blood-derived total RNA samples</p>		<p>miR-486-3p</p>
<p>Seno et al. (2011) [58]</p>	<p>42 (20/22)</p>	<p>20 severe ASD (13 males and 7 females), 22 unaffected siblings (19 males and 3 females). Lymphoblastoid cell lines, RNA was extracted and assayed using Illumina gene and miRNA expression arrays. Control quality in BeadStudio (Illumina)</p>	<p>miR-10a, miR-30a, miR-181a, miR-181b, miR-181c, miR-199b-5p, miR-338-3p, miR-486-3p, miR-486-5p, miR-500, miR-502-3p, miR-548</p>	<p>miR-199a-5p, miR-455-3p, miR-577, miR-656</p>

Mor et al. (2015) [59]	24 (12/12)	Brain tissue samples taken from postmortem Brodmann's area 10	miR-7-5p, miR-19a-3p, miR-19b-3p, miR-21-3p, miR-21-5p, miR-142-3p, miR-142-5p, miR-144-3p, miR-146a-5p, miR-155-5p, miR-219-5p, miR-338-5p, miR-379-5p, miR-451a, miR-494, miR-3168	miR-34a-5p, miR-92b-3p, miR-211-5p, miR-3960
Ander et al. (2015) [60]	18 (10/8)	Brain tissue samples taken from postmortem Brodmann's areas 22, 41, 42	miR-664-3p, miR-4709-3p, miR-4753-5p	miR-1, miR-297, miR-4742-3p
Wu et al. (2016) [61]	56 (28/28)	Tissue samples taken from postmortem cerebellar cortex, Brodmann area 9	miR-10a-5p, miR-18b-5p, miR-20b-5p, miR-21-3p, miR-23a-3p, miR-107, miR-129-2-3p, miR-130b-5p, miR-148a-3p, miR-155-5p, miR-218-2-3p, miR-221-3p, miR-223-3p, miR-335-3p, miR-363-3p, miR-424-3p, miR-424-5p, miR-425-3p, miR-449b-5p, miR-450b-5p, miR-484, miR-629-5p, miR-651-5p, miR-708-5p, miR-766-3p, miR-874-3p, miR-887-3p, miR-940, miR-1277-3p, miR-	miR-204-3p, miR-491-5p, miR-619-5p, miR-3687, miR-5096

			3938, miR-2277-5p, let-7g-3p	
Huang et al. (2015) [62]	40 (20/20)	Peripheral blood sample taken, microarray (5 ASD/5 controls) and quantitative Real-Time PCR (15 ASD/15 controls)	miR-34b-3p, miR-34c-3p, miR-483-5p, miR-494, miR-564, miR-642a-3p, miR-574-5p, miR-575, miR-921, miR-1246, miR-1249, miR-1273c, miR-4270, miR-4299, miR-4436a, miR-4443, miR-4516, miR-4669, miR-4721, miR-4728-5p, miR-4788, miR-5739, miR-6086, miR-6125	miR-15a-5p, miR-15b-5p, miR-16-5p, miR-19b-3p, miR-20a-5p, miR-92a-3p, miR-103a-3p, miR-195-5p, miR-451a, miR-574-3p, miR-940, miR-1228-3p, miR-3613-3p, miR-3935, miR-4436b-5p, miR-4665-5p, miR-4700-3p, let-7a-5p, let-7d-5p, let-7f-5p
Hicks et al. (2016) [63]	45 (24/21)	Salivary samples	miR-7-5p, miR-28-5p, miR-127-3p, miR-140-3p, miR-191-5p, miR-218-5p, miR-335-3p, miR-628-5p, miR-2467-5p, miR-3529-3p	miR-23a-3p, miR-27a-3p, miR-30e-5p, miR-32-5p
Nguyen et al. (2016) [64]	14 (8/6)	Samples taken from olfactory mucosal stem cells and skin fibroblasts or Peripheral Blood Mononuclear Cells. Measured through microarray and quantitative Real-Time PCR validation	miR-146a	miR-221, miR-654-5p, miR-656

Kichukova et al. (2017) [65]	60 (30/30)	Blood samples. Quantitative Real-Time PCR validation	miR-18b-3p, miR-106b-5p, miR-142-3p, miR-210-5p, miR-365a-3p, miR-374b-5p, miR-619-5p, miR-664a-3p, miR-3620-3p, miR-4489, miR-8052	hsa-let-7i-3p, miR -15a-5p, miR -20b-3p, miR -29c-5p, miR -96-5p, miR -145-5p, miR -183-5p, miR -193b-3p, miR -197-5p, miR-199a-5p, miR -301a-3p, miR -328-3p, miR -424-5p, miR -486-3p, miR -487b-3p, miR -500a-5p, miR -504-5p, miR -576-5p, miR -587-3p, miR-589-3p, miR -664b-3p, miR -671-3p, miR -3064-5p, miR -3135a, miR -3674, miR -3687, miR-3909, miR -6799-3p, miR -6849-3p
Jyonouchi et al. (2017) [66]	96 (69/27)	Peripheral blood monocytes samples. miRNA expression determined by high-throughput sequencing	hsa-let-7a-1, hsa-let-7a-2, hsa-let-7a-3, hsa-let-7f-1, hsa-let-7f-2, hsa-let-7g, hsa-let-7i, miR-17, miR-26a-2, miR-30b, miR-30c-1, miR-30c-2, miR-98, miR-106b, miR-130a, miR-148a, miR-148b, miR-150, miR-186, miR-301a, miR-374b, miR-	hsa-let-7b, miR-15a, miR-15b, miR-16-1, miR-16-2, miR-18a, miR-19a, miR-19b-1, miR-19b-2, miR-20a, miR-21, miR-27a, miR-27b, miR-29a, miR-29b-1, miR-29b-2, miR-29c, miR-30e, miR-93, miR-101-1, miR-101-2, miR-103a-

			494, miR-1248, miR-3607, miR-3609	1, miR-103a-2, miR-107, miR-126, miR-142, miR-145, miR-146a, miR-151a, miR-181a-1, miR-181a-2, miR-199b, miR-221, miR-222, miR-320a, miR-376c, miR-409, miR-423, miR-484, miR-625, miR-4433b, miR-5701-1, miR-5701-2
Nguyen et al. (2018) [67]	11 (5/6)	Post-mortem analysis of temporal lobe in ASD children and controls. miRNA expression performed using Taqman assay	miR-146a	N/A
Yu et al. (2018) [68]	43 (20/23)	Serum samples. quantitative reverse transcription-PCR to examine miRNAs	miR-486-3p, miR-557	N/A

Table 1. MicroRNAs directly involved in autism

3.2 Studies about AD

A few works studied microRNAs involved in AD (Table 2). Here, the main dysregulated miRNAs are miR-146, miR-155, and miR-203.

Summarizing, the association between ASD and AD revealed a common unbalance for miR-146 and miR-155.

Study	N (case/control)	Design	Findings	
			Up-regulated miRNA	Down-regulated miRNA

Sonkoly et al. (2010) [49]	47 (18/29)	Skin samples	miR-155	
Lv et al. (2014) [69]	58 (30/28)	Serum and urine samples	miR-203, miR-483-5p (serum)	miR-203 (urine)
Ralfkiaer et al. (2014) [70]	75 (20/55)*	Skin samples	miR-149, miR-Plus-C1070, miR-205, miR-141, miR-23b, miR-221, miR-27b, miR-203, miR-7b, miR-19b, miR-27a, miR-455-3p, miR-200a, miR-211, miR-23a, miR-214	miR-181a, miR-342-5p, miR-766, miR-7i, miR-186, miR-342-3p, miR-664, miR-425, miR-9, miR-331-3p, miR-146b-5p, miR-10a, miR-663, miR-937, miR-361-3p, miR-605, miR-146a, miR-940, miR-150, miR-1913, miR-155, miR-302c
Rebane et al. (2014) [71]	18 (9/9)	Skin samples	miR-146a	
Ma et al. (2015) [72]	64 (33/31)	Skin samples	miR-155	
Ding et al. (2016) [73]	22 (14/8)	Skin samples	miR-148b, miR-152, miR-324	
Yang et al. (2017) [74]	37 (37/0)	Skin samples		miR-124

Table 2. MicroRNAs in atopic dermatitis (*control cohort represented by patients with early-stage mycosis fungoides (MF1))

4. Discussion

4.1 The overlap between atopy and autism

Recent data strongly support the clinical association between atopy and ASD [15,16]. It has been widely demonstrated that allergic diseases, especially food allergies, are more frequent among ASD children [75,76].

Notably, a large observational study, comparing 14,812 atopic subjects with 6,944 non-atopic subjects, with no lifetime atopic disease, highlighted a strong association between atopy and the risk of developing ASD [77]. Furthermore, also autoimmune disorders, including psoriasis (2-fold risk) are frequently identified in ASD [78].

Beside the robust clinical evidence for the association between atopy and ASD, an intriguing neuroinflammatory hypothesis has been advanced for ASD, involving the disruption of the brain blood barrier induced by inflammatory molecules, brain mast cells activation and mast cells-microglia interactions [79].

In addition, specific environmental factors, including infectious pathogens, food allergens, toxins, toxic metals (e.g., aluminum, lead, mercury) may negatively act on neurodevelopment through the alteration of the immune response [80-82].

However, the hypothesis that the pro-inflammatory cascade induced by AD could lead, in the presence of genetic susceptibility, to ASD is supported by the clinical association and by a shared pattern of cellular damage, with epigenetic changes as a common pathogenic mechanism.

4.2 Role for overlapping miRNAs in ASD and AD

The main literature finding concerning miRNAs in AD and ASD is represented by miR-146a. miR-146a, upregulated in various neurodevelopmental disorders [64], was reported to be highly expressed throughout the cortex, hippocampus, and amygdala, key structures for higher cognitive functioning [83]. Furthermore, it was demonstrated that reproducing abnormal miR-146a expression in mouse primary cell cultures leads to impaired neuronal dendritic arborization - producing shriveled dendritic trees with branching points at more proximal levels compared to controls, proving the defective neural connectivity typical of ASD - and to increased astrocyte glutamate uptake capacities [64], in turn modifying fast synaptic transmission at the CNS level. miR-146a, expressed in the developing brain, is enclosed within neurons, with poor expression in the glial lineage in adult mice. However, it generally inhibits the expression of neuron-specific targets, including Nlgn1 and Syt1, preventing glial cells from mistakenly adopting neuron-specific phenotypes.

In addition, the neuron excitation at cortex is probably affected by miR-146a deregulation through the involvement of potassium two pore domain channel subfamily K member 2 (KCNK2), having a key role in neural excitability and migration at the cortex level of the developing mice, a critical issue in ASD.

Furthermore, miR-146a expression contributes to neuroinflammation in the brain of ASD subjects, having a role in immune system regulation.

Its function in the regulation of inflammatory processes could partially fill the gap between ASD (and neurodevelopmental disorders in general) and AD (and atopic conditions in extenso).

It is evident indeed that an increased miR-146a expression is present in the lesional skin of AD patients [84], as it inhibits nuclear factor κ B (NF- κ B)-mediated proinflammatory cytokines and chemokines, bringing to alleviation of the inflammation directly linked to AD and similar conditions [71].

In AD, during skin inflammation, miR-146a is increased in keratinocytes, controlling chronic inflammatory processes triggered by IFN- γ and the activation of NF- κ B. Indeed, the relevance of miR-146a in inflammatory skin disorders is confirmed by evidence from psoriasis research [85]. Furthermore, the expression of miR-146a is strongly dependent on NF- κ B, and the miRNA has been shown to suppress the NF- κ B signaling pathway through a direct targeting of a number of compounds, including IL-1 receptor-associated kinase 1 (IRAK1), TNF receptor-associated factor 6 [86], v-rel avian reticuloendotheliosis viral oncogene homolog B (RELB) [87], and CARD10 [88].

Moreover, it was discovered that mice with a deficiency of miR-146a develop a late autoimmunity caused by an impaired activation of NF- κ B in T cells and signal transducer and STAT1 activator in regulatory T cells [89].

Of note, previous work demonstrated that both an enhanced opioidergic activity and reduced vitamin D levels could represent shared features of AD [90] and ASD [91], and possibly miR-146a and miR-155 could interact with the genetic milieu in subjects with these disorders. Indeed, both miR-146a and miR-155 have been tested in models of LPS tolerance and miR-146 was able to amplify the severity of morphine-mediated hyper-inflammation [92].

Finally, the regulatory role of miR-146a also occurs at lung alveolar epithelial cells, where the release of IL-8 and CCL5 occurs independently from IL-1 β signaling.

Concerning miR-155, its role in ASD is not yet known, whereas in AD it appears to modulate T helper type 17 (Th17) cells differentiation and function [72] and to directly target the suppressor of cytokine signalling-1 (SOCS1) gene, taking part in a negative feedback loop to attenuate cytokine signaling [93]. Interestingly, miR-155 is also linked to inflammation and immunity, thanks to its potent upregulation in immune cell lineages, including lymphocytes, fibroblasts, macrophages, mast cells, and dendritic cells, in turn implicated in the pathogenesis of chronic skin inflammation [94-99]. Briefly, miR-155 seems to be also involved in the regulation of T-cell responses through a suppression of cytotoxic T-lymphocyte antigen 4 and by enhancing T-cell proliferation [49]. Its deregulation, seen as

increased expression, in peripheral CD4 T cells of AD patients, was correlated to disease severity, supporting its role in AD pathogenesis [72].

5. Conclusions

Beyond the clinical evidence [16,17], a possible, yet speculative, role for genetics (miRNAs in particular) can be hypothesized to justify the clinical association between AD and ASD.

Yet, both miR-146a and 155 appear to be involved in this common pathogenetic pathway, despite being the role of the latter still poorly known. However, several other aspects differentiating these diseases remain elusive, including the identification of putative environmental injuries and the complex role of vitamin D in immune and neurologic disorders. Therefore, further studies focusing on the association between vitamin D and opioid receptors in skin and neurologic disorders should investigate the role of target genes for common dysregulated miRNAs, in order to discover specific overlapping features of these conditions.

It remains evident that an inflammatory component is active in both diseases and the actual data support future applications for miR-146a both as a biomarker and as a target for therapy.

Interestingly, it can be speculated that a deregulation of miR-146a occurs earlier, during embryonic development, thus participating in the development of ASD. Apart from the well-described effect on NF- κ B activity and the associated inflammatory pathways strictly linking miR-146a with AD, the deregulation of miR-146a and miR-155 could influence a wide range of their validated targets (Figure 2), essential for brain development and function. However, it remains complex to determine the major source (skin vs brain) of miR-146a and/or miR-155 and whether they are potentiating each other or having more organ- or disease-specific effects. These aspects warrant future larger longitudinal studies. Finally, a better understanding of the link ASD/AD might be useful to investigate whether a specific miRNA could act as a biomarker for the risk of developing ASD for patients with AD and potentially represent a target for ASD prevention.

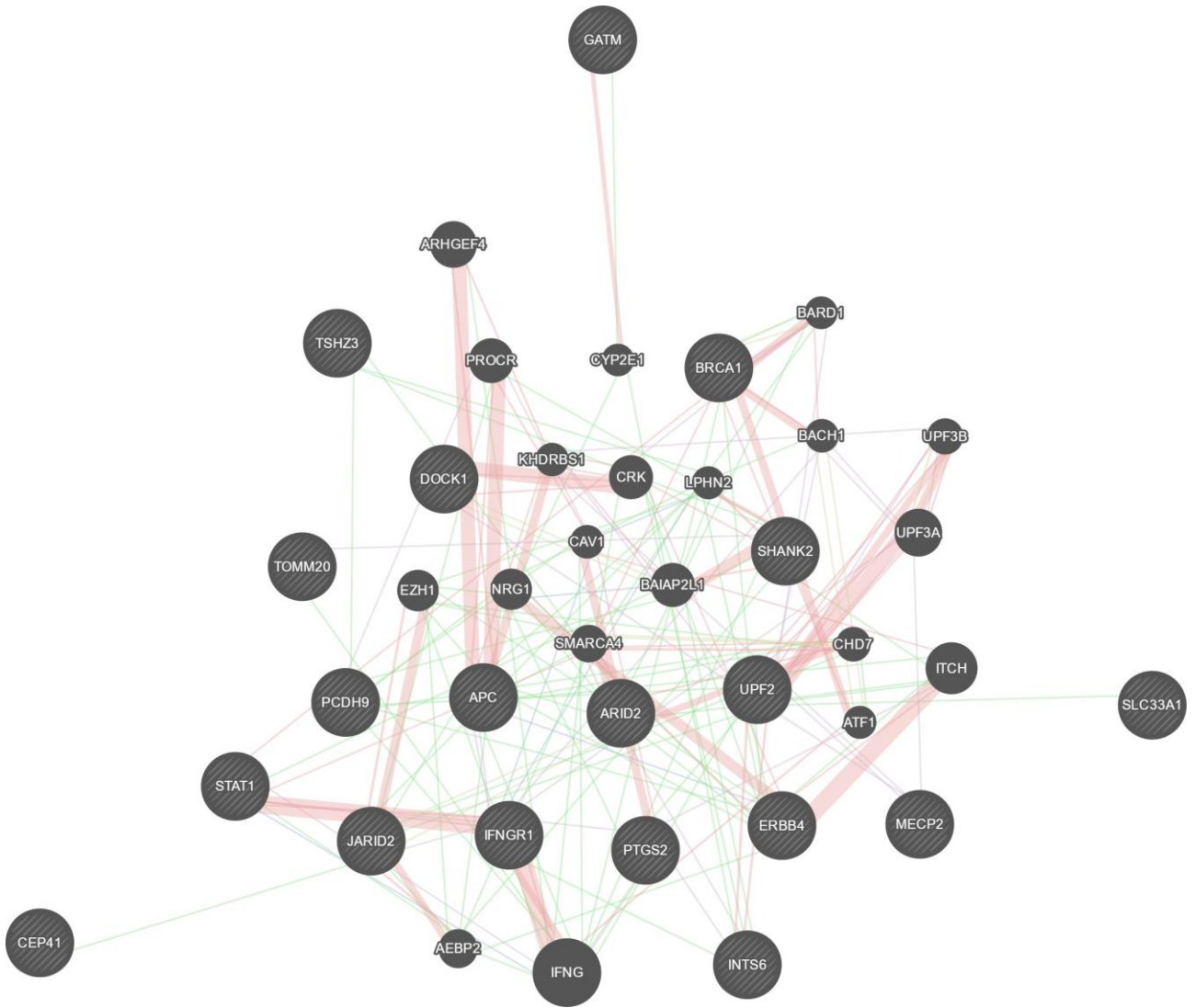


Figure 2. Validated targets for miR-146a and miR-155.

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References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed. Washington, DC, American Psychiatric Association, **2013**.
2. Barger, B.D.; Campbell, J.M.; McDonough, J.D. Prevalence and onset of regression within autism spectrum disorders: a meta-analytic review. *J Autism Dev Disord.* **2015**, *43*(4), 817-828.
3. CDC. Prevalence of autism spectrum disorders—autism and developmental disabilities monitoring network, 14 sites, United States, 2008. *MMWR Surveillance Summaries* **2012**, *61*, 1–19.
4. Centers for Disease Control and Prevention (CDC), United States Department of Health and Human Services, 2014. http://www.cdc.gov/ncbddd/autism/states/comm_report_autism_2014.pdf. Accessed December 10, 2018.
5. Gaugler, T.; Klei, L.; Sanders, S.J.; Bodea, C.A.; Goldberg, A.P.; Lee, A.B., et al. Most genetic risk for autism resides with common variation. *Nat Genet.* **2014**, *46*(8), 881–885.
6. Gupta, A.R.; State, M.W. Recent advances in the genetics of autism. *Biol Psychiatry.* **2007**, *61*, 429–437.
7. Beaudet, A.L. Autism: highly heritable but not inherited. *Nat Med.* **2007**, *13*, 534–536.
8. Ozonoff, S.; Young, G.S.; Carter, A.; Messinger, D.; Yirmiya, N.; Zwaigenbaum, L., et al. Recurrence risk for autism spectrum disorders: a Baby Siblings Research Consortium study. *Pediatrics.* **2011**, *128*(3), e488-495.
9. Vorstman, J.A.S.; Parr, J.R.; Moreno-De-Luca, D.; Anney, R.J.L.; Nurnberger, J.I. Jr.; Hallmayer, J.F. Autism genetics: opportunities and challenges for clinical translation. *Nat Rev Genet.* **2017**, *18*, 362-376.
10. Bourgeron, T. From the genetic architecture to synaptic plasticity in autism spectrum disorder. *Nat Rev Neurosci.* **2015**, *16*, 551-563.
11. Hertz-Picciotto, I.; Schmidt, R.J.; Krakowiak, P. Understanding environmental contributions to autism: Causal concepts and the state of science. *Autism Res.* **2018**, *11*(4), 554-586.
12. Meek, S.E.; Lemery-Chalfant, K.; Jahromi, L.B., Valiente, C. A review of gene-environment correlations and their implications for autism: a conceptual model. *Psychol Rev.* **2013**, *120*(3), 497-521.
13. Gorini, F.; Muratori, F.; Morales, M.A. The Role of Heavy Metal Pollution in Neurobehavioral Disorders: a Focus on Autism. *Review J Autism Dev Disord.* **2014**, *1*(4), 354-372.
14. Kalkbrenner, A.E.; Schmidt, R.J.; Penlesky, A.C. Environmental chemical exposures and autism spectrum disorders: a review of the epidemiological evidence. *Curr Probl Pediatr Adolesc Health Care.* **2014**, *44*(10), 277-318.
15. Tonacci, A.; Billeci, L.; Ruta, L.; Tartarisco, G.; Pioggia, G.; Gangemi, S. A systematic review of the association between allergic asthma and autism. *Minerva Pediatr.* **2017**, *69*(6), 538-550.
16. Billeci, L.; Tonacci, A.; Tartarisco, G.; Ruta, L.; Pioggia, G.; Gangemi, S. Association Between Atopic Dermatitis and Autism Spectrum Disorders: A Systematic Review. *Am J Clin Dermatol.* **2015**, *16*(5), 371-388.

17. Billeci, L.; Tonacci, A.; Tartarisco, G.; Ruta, L.; Pioggia, G.; Gangemi, S. Reply to Fluegge: Association Between Atopic Dermatitis and Autism Spectrum Disorders: A Systematic Review. *Am J Clin Dermatol.* **2016**, *17(2)*, 189-190.
18. Heffler, E.; Allegra, A.; Pioggia, G.; Picardi, G.; Musolino, C.; Gangemi, S. MicroRNAs Profiling in Asthma: Potential Biomarkers and Therapeutic Targets. *Am J Respir Cell Mol Biol.* **2017**, *57(6)*, 642-650.
19. Simpson, E.L. Atopic dermatitis: a review of topical treatment options. *Curr Med Res Opin.* **2010**, *26(3)*, 633–640.
20. Tonelli, D.D.P.; Pulvers, J.N.; Haffner, C.; Murchison, E.P.; Hannon, G.J.; Huttner, W.B. miRNAs are essential for survival and differentiation of newborn neurons but not for expansion of neural progenitors during early neurogenesis in the mouse embryonic neocortex. *Development.* **2008**, *135(23)*, 3911–3921.
21. Dai, R.; Ahmed, S.A. MicroRNA, a new paradigm for understanding immunoregulation, inflammation, and autoimmune diseases. *Transl Res.* **2011**, *157(4)*, 163-179.
22. Mannucci, C.; Casciaro, M.; Minciullo, P.L.; Calapai, G.; Navarra, M.; Gangemi, S. Involvement of microRNAs in skin disorders: A literature review. *Allergy Asthma Proc.* **2017**, *38(1)*, 9-15.
23. Kozomara, A.; Griffiths-Jones, S. MiRBase: integrating microRNA annotation and deep-sequencing data. *Nucleic Acids Res.* **2011**, *39(1)*, D152–157.
24. Radojicic, J.; Zaravinos, A.; Vrekoussis, T.; Kafousi, M.; Spandidos, D.A.; Stathopoulos, E.N. MicroRNA expression analysis in triple-negative (ER, PR and Her2/neu) breast cancer. *Cell Cycle.* **2011**, *10(3)*, 507–517.
25. Zaravinos, A.; Radojicic, J.; Lambrou, G.I.; Volanis, D.; Delakas, D.; Stathopoulos, E.N., et al. Expression of miRNAs involved in angiogenesis, tumor cell proliferation, tumor suppressor inhibition, epithelial-mesenchymal transition and activation of metastasis in bladder cancer. *J Urol.* **2012**, *188(2)*, 615–623.
26. Krol, J.; Loedige, I.; Filipowicz, W. The widespread regulation of microRNA biogenesis, function and decay. *Nat Rev Genet.* **2010**, *11(9)*, 597–610.
27. Kim, V.N.; Han, J.; Siomi, M.C. Biogenesis of small RNAs in animals. *Nat Rev Mol Cell Biol.* **2009**, *10(2)*, 126–139.
28. Bartel, D.P. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell.* **2004**, *116(2)*, 281–297.
29. Jansson, M.D.; Lund, A.H. MicroRNA and cancer. *Mol Oncol.* **2012**, *6(6)*, 590–610.
30. Sabina, S.; Vecoli, C.; Borghini, A.; Guarino, R.; Andreassi, M.G. Analysis of miRNAs Targeting 3'UTR of H2AFX Gene: a General in Silico Approach. *Microna.* **2015**, *4(1)*, 41-49.
31. Furdulj, C. Ionizing radiation: mechanisms and therapeutics. *Antioxid Redox Signal.* **2014**, *21(2)*, 218–220.
32. Li, X.Y.; Luo, Q.F.; Wei, C.K.; Li, D.F.; Li, J.; Fang, L. MiRNA-107 inhibits proliferation and migration by targeting CDK8 in breast cancer. *Int J Clin Exp Med.* **2014**, *7(1)*, 32–40.

33. Wojtas, B.; Ferraz, C.; Stokowy, T.; Hauptmann, S.; Lange, D.; Dralle, H., et al. Differential miRNA expression defines migration and reduced apoptosis in follicular thyroid carcinomas. *Mol Cell Endocrinol.* **2014**, *388(1-2)*, 1–9.
34. Friedman, R.C.; Farh, K.K.H.; Burge, C.B.; Bartel, D.P. Most mammalian mRNAs are conserved targets of microRNAs. *Genome Res.* **2009**, *19(1)*, 92–105.
35. Adlakha, Y.K.; Saini, N. Brain miRNAs and insights into biological functions and therapeutic potential of brain enriched miRNA-128. *Mol Cancer.* **2014**, *13*, 33.
36. Liu, N.K.; Xu, X.M. MicroRNA in central nervous system trauma and degenerative disorders. *Physiol Genomics.* **2011**, *43(10)*, 571–580.
37. Ziats, M.N.; Rennert, O.M. Identification of differentially expressed microRNAs across the developing human brain. *Mol Psychiatry.* **2014**, *19(7)*, 848–852.
38. Schrott, G.M.; Tuebing, F.; Nigh, E.A.; Kane, C.G.; Sabatini, M.E.; Kiebler, M., et al. A brain-specific microRNA regulates dendritic spine development. *Nature.* **2006**, *439*, 283–289.
39. Hutsler, J.J.; Zhang, H. Increased dendritic spine densities on cortical projection neurons in autism spectrum disorders. *Brain Res.* **2000**, *1309*, 83–94.
40. Glantz, L.A.; Lewis, D.A. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. *Arch Gen Psychiatry.* **2000**, *57*, 65–73.
41. Kolomeets, N.S.; Orlovskaya, D.D.; Rachmanova, V.I.; Uranova, N.A. Ultrastructural alterations in hippocampal mossy fiber synapses in Schizophrenia: a postmortem morphometric study. *Synapse.* **2005**, *57*, 47–55.
42. Sweet, R.A.; Henteleff, R.A.; Zhang, W.; Sampson, A.R.; Lewis, D.A. Reduced dendritic spine density in auditory cortex of subjects with schizophrenia. *Neuropsychopharmacology.* **2009**, *34*, 374–389.
43. Edbauer, D.; Neilson, J.R.; Foster, K.A.; Wang, C.F.; Seeburg, D.P.; Batterton, M.N., et al. Regulation of synaptic structure and function by FMRP-associated microRNAs miR-125b and miR-132. *Neuron.* **2010**, *65*, 373–384.
44. Impey, S.; Davare, M.; Lasiek, A.; Fortin, D.; Ando, H.; Varlamova, O., et al. An activity-induced microRNA controls dendritic spine formation by regulating Rac1-PAK signaling. *Mol Cell Neurosci.* **2010**, *43*, 146–156.
45. Smrt, R.D.; Szulwach, K.E.; Pfeiffer, R.L.; Li, X.; Guo, W.; Pathania, M., et al. MicroRNA miR-137 regulates neuronal maturation by targeting ubiquitin ligase mind bomb-1. *Stem Cells.* **2010**, *28*, 1060–1070.
46. Siegel, G.; Obernosterer, G.; Fiore, R.; Oehmen, M.; Bicker, S.; Christensen, M., et al. A functional screen implicates microRNA-138-dependent regulation of the depalmitoylation enzyme APT1 in dendritic spine morphogenesis. *Nat Cell Biol.* **2009**, *11*, 705–716.
47. Davis, T.H.; Cuellar, T.L.; Koch, S.M.; Barker, A.J.; Harfe, B.D.; McManus, M.T., et al. Conditional loss of Dicer disrupts cellular and tissue morphogenesis in the cortex and hippocampus. *J Neurosci.* **2008**, *28(17)*, 4322–4330.

48. Fiorucci, G.; Chiantore, M.V.; Mangino, G.; Percario, Z.A.; Affabris, E.; Romeo, G. Cancer regulator microRNA: Potential relevance in diagnosis, prognosis and treatment of cancer. *Curr Med Chem.* **2012**, *19*, 461–474.
49. Sonkoly, E.; Janson, P.; Majuri, M.L.; Savinko, T.; Fyhrquist, N.; Eidsmo, L., et al. MiR-155 is overexpressed in patients with atopic dermatitis and modulates T-cell proliferative responses by targeting cytotoxic T lymphocyte-associated antigen 4. *J Allergy Clin Immunol.* **2010**, *126*, 581–589.
50. Wei, T.; Orfanidis, K.; Xu, N.; Janson, P.; Ståhle, M.; Pivarcsi, A., et al. The expression of microRNA-203 during human skin morphogenesis. *Exp Dermatol.* **2010**, *19*, 854–856.
51. Hawkes, J.E.; Nguyen, G.H.; Fujita, M.; Florell, S.R.; Callis Duffin, K.; Krueger, G.G., et al. microRNAs in psoriasis. *J Invest Dermatol.* **2016**, *136*, 365–371.
52. Nutten, S. Atopic dermatitis: Global epidemiology and risk factors. *Ann Nutr Metab.* **2015**, *66(1)*, 8–16.
53. Abu-Elneel, K.; Liu, T.; Gazzaniga, F.S.; Nishimura, Y.; Wall, D.P.; Geschwind, D.H., et al. Heterogeneous dysregulation of microRNAs across the autism spectrum. *Neurogenetics.* **2008**, *9*, 153–161.
54. Sarachana, T.; Zhou, R.; Chen, G.; Manji, H.K.; Hu, V.W. Investigation of post-transcriptional gene regulatory networks associated with autism spectrum disorders by microRNA expression profiling of lymphoblastoid cell lines. *Genome Med.* **2010**, *2*, 23.
55. Talebizadeh, Z.; Butler, M.G.; Theodoro, M.F. Feasibility and relevance of examining lymphoblastoid cell lines to study role of microRNAs in autism. *Autism Res.* **2008**, *1*, 240–250.
56. Mundalil Vasu, M.; Anitha, A.; Thanseem, I.; Suzuki, K.; Yamada, K.; Takahashi, T., et al. Serum microRNA profiles in children with autism. *Mol Autism.* **2014**, *5*, 40.
57. Popov, N.T.; Madjirova, N.P.; Minkov, I.N.; Vachev, T.I. Micro RNA HSA-486-3P Gene Expression Profiling in the Whole Blood of Patients with Autism. *Biotechnol Biotechnol Equip.* **2012**, *26(6)*, 3385-3388.
58. Weber, F.; Teresi, R.E.; Broelsch, C.E.; Frilling, A.; Eng, C. A limited set of human microRNA is deregulated in follicular thyroid carcinoma. *J Clin Endocrinol Metab.* **2006**, *91*, 3584-3591.
59. Mor, M.; Nardone, S.; Sams, D.S.; Elliott, E. Hypomethylation of miR-142 promoter and upregulation of microRNAs that target the oxytocin receptor gene in the autism prefrontal cortex. *Mol Autism.* **2015**, *6*, 46.
60. Ander, B.P.; Barger, N.; Stamova, B.; Sharp, F.R.; Schumann, C.M. Atypical miRNA expression in temporal cortex associated with dysregulation of immune, cell cycle, and other pathways in autism spectrum disorders. *Mol Autism.* **2015**, *6*, 37.
61. Wu, Y.E.; Parikshak, N.N.; Belgard, T.G.; Geschwind, D.H. Genome-wide, integrative analysis implicates microRNA dysregulation in autism spectrum disorder. *Nat Neurosci.* **2016**, *19(11)*, 1463-1476.

62. Huang, F.; Long, Z.; Chen, Z.; Li, J.; Hu, Z.; Qiu, R., et al. Investigation of gene regulatory networks associated with autism spectrum disorder based on MiRNA expression in China. *PLoS One*. **2015**, *10*(6), e0129052.
63. Hicks, S.D.; Ignacio, C.; Gentile, K.; Middleton, F.A. Salivary miRNA profiles identify children with autism spectrum disorder, correlate with adaptive behavior, and implicate ASD candidate genes involved in neurodevelopment. *BMC Pediatr*. **2016**, *16*, 52.
64. Nguyen, L.S.; Lepleux, M.; Makhlof, M.; Martin, C.; Fregeac, J.; Siquier-Pernet, K., et al. Profiling olfactory stem cells from living patients identifies miRNAs relevant for autism pathophysiology. *Mol Autism*. **2016**, *7*(1), 1.
65. Kichukova, T.M.; Popov, N.T.; Ivanov, I.S.; Vachev, T.I. Profiling of Circulating Serum MicroRNAs in Children with Autism Spectrum Disorder using Stem-loop qRT-PCR Assay. *Folia Med (Plovdiv)*. **2017**, *59*(1), 43-52.
66. Jyonouchi, H.; Geng, L.; Streck, D.L.; Dermody, J.J.; Toruner, G.A. MicroRNA expression changes in association with changes in interleukin-1 β /interleukin10 ratios produced by monocytes in autism spectrum disorders: their association with neuropsychiatric symptoms and comorbid conditions (observational study). *J Neuroinflammation*. **2017**, *14*(1), 229.
67. Nguyen, L.S.; Fregeac, J.; Bole-Feysot, C.; Cagnard, N.; Iyer, A.; Anink, J., et al. Role of miR-146a in neural stem cell differentiation and neural lineage determination: relevance for neurodevelopmental disorders. *Mol Autism*. **2018**, *9*, 38.
68. Yu, D.; Jiao, X.; Cao, T.; Huang, F. Serum miRNA expression profiling reveals miR-486-3p may play a significant role in the development of autism by targeting ARID1B. *Neuroreport*. **2018**, *29*(17), 1431-1436.
69. Lv, Y.; Qi, R.; Xu, J.; Di, Z.; Zheng, H.; Huo, W., et al. Profiling of serum and urinary microRNAs in children with atopic dermatitis. *PLoS One*. **2014**, *9*(12), e115448.
70. Ralfkiaer, U.; Lindahl, L.M.; Litman, T.; Gjerdrum, L.M.; Ahler, C.B.; Gniadecki, R., et al. MicroRNA expression in early mycosis fungoides is distinctly different from atopic dermatitis and advanced cutaneous T-cell lymphoma. *Anticancer Res*. **2014**, *34*, 7207–7217.
71. Rebane, A.; Runnel, T.; Aab, A.; Maslovskaja, J.; Rückert, B.; Zimmermann, M., et al. MicroRNA-146a alleviates chronic skin inflammation in atopic dermatitis through suppression of innate immune responses in keratinocytes. *J Allergy Clin Immunol*. **2014**, *134*, 836–847.
72. Ma, L.; Xue, H.B.; Wang, F.; Shu, C.M.; Zhang, J.H. MicroRNA-155 may be involved in the pathogenesis of atopic dermatitis by modulating the differentiation and function of T helper type 17 (Th17) cells. *Clin Exp Immunol*. **2015**, *181*(1), 142-149.
73. Ding, Y.; Shao, X.; Li, X.; Zhai, Y.; Zhang, Y.; Wang, S., et al. Identification of candidate genes in atopic dermatitis based on bioinformatic methods. *Int J Dermatol*. **2016**, *55*(7), 791-800.

74. Yang, Z.; Zeng, B.; Wang, C.; Wang, H.; Huang, P.; Pan, Y. MicroRNA-124 alleviates chronic skin inflammation in atopic eczema via suppressing innate immune responses in keratinocytes. *Cell Immunol.* **2017**, *319*, 53-60.
75. Jyonouchi H. Autism spectrum disorders and allergy: observation from a pediatric allergy/immunology clinic. *Exp Rev Clin Immunol.* **2010**, *6(3)*, 397-411.
76. Bakkaloglu, B.; Anlar, B.; Anlar, F.Y.; Oktem, F.; Pehlivanürk, B.; Unal, F., et al. Atopic features in early childhood autism. *Eur J Paediatr Neurol.* **2008**, *12*, 476-479.
77. Chen, M.H.; Su, T.P.; Chen, Y.S.; Hsu, J.W.; Huang, K.L.; Chang, W.H., et al. Is atopy in early childhood a risk factor for ADHD and ASD? a longitudinal study. *J Psychosom Res.* **2014**, *77(4)*, 316-321.
78. Zerbo, O.; Leong, A.; Barcellos, L.; Bernal, P.; Fireman, B.; Croen, L.A. Immune mediated conditions in autism spectrum disorders. *Brain Behav Immun.* **2015**, *46*, 232-236.
79. Theoharides, T.C. Is a subtype of autism an allergy of the brain? *Clin Ther.* **2013**, *35(5)*, 584-591.
80. Shaw, C.A.; Seneff, S.; Kette, S.D.; Tomljenovic, L.; Oller, J.W. Jr.; Davidson, R.M. Aluminum-induced entropy in biological systems: implications for neurological disease. *J Toxicol.* **2014**, *2014*, 491316.
81. Verlaet, A.A.; Noriega, D.B.; Hermans, N.; Savelkoul, H.F. Nutrition, immunological mechanisms and dietary immunomodulation in ADHD. *Eur Child Adolesc Psychiatry.* **2014**, *23*, 519-529.
82. Adams, J.B.; Baral, M.; Geis, E.; Mitchell, J.; Ingram, J.; Hensley, A., et al. The severity of autism is associated with toxic metal body burden and red blood cell glutathione levels. *J Toxicol.* **2009**, *2009*, 532640.
83. Lukiw, W.J.; Zhao, Y.; Cui, J.G. An NF-kappaB-sensitive micro RNA-146a-mediated inflammatory circuit in Alzheimer disease and in stressed human brain cells. *J Biol Chem.* **2008**, *283(46)*, 31315-31322.
84. Kim, J.E.; Kim, J.S.; Cho, D.H.; Park, H.J. Molecular Mechanisms of Cutaneous Inflammatory Disorder: Atopic Dermatitis. *Int J Mol Sci.* **2016**, *17(8)*.
85. Srivastava, A.; Nikamo, P.; Lohcharoenkal, W.; Li, D.; Meisgen, F.; Xu Landén, N., et al. MicroRNA-146a suppresses IL-17-mediated skin inflammation and is genetically associated with psoriasis. *J Allergy Clin Immunol.* **2017**, *139(2)*, 550-561.
86. Taganov, K.D.; Boldin, M.P.; Chang, K.J.; Baltimore, D. NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. *Proc Natl Acad Sci U S A.* **2006**, *103*, 12481-12486.
87. Etzrodt, M.; Cortez-Retamozo, V.; Newton, A.; Zhao, J.; Ng, A.; Wildgruber, M., et al. Regulation of monocyte functional heterogeneity by miR-146a and Relb. *Cell Rep.* **2012**, *1*, 317-324.

88. Crone, S.G.; Jacobsen, A.; Federspiel, B.; Bardram, L.; Krogh, A.; Lund, A.H., et al. microRNA-146a inhibits G protein-coupled receptor-mediated activation of NF-kappaB by targeting CARD10 and COPS8 in gastric cancer. *Mol Cancer*. **2012**, *11*, 71.
89. Zhao, J.L.; Rao, D.S.; O'Connell, R.M.; Garcia-Flores, Y.; Baltimore, D. MicroRNA-146a acts as a guardian of the quality and longevity of hematopoietic stem cells in mice. *Elife*. **2013**, *2*, e00537.
90. Kanda, N.; Hau, C.S.; Tada, Y.; Sato, S.; Watanabe, S. Decreased serum LL-37 and vitamin D3 levels in atopic dermatitis: relationship between IL-31 and oncostatin M. *Allergy*. **2012**, *67*(6), 804-812.
91. Pioggia, G.; Tonacci, A.; Tartarisco, G.; Billeci, L.; Muratori, F.; Ruta, L., et al. Autism and lack of D3 vitamin: a systematic review. *Res Autism Spectr Disord*. **2014**, *8*, 1685-1698.
92. Banerjee, S.; Meng, J.; Das, S.; Krishnan, A.; Haworth, J.; Charboneau, R., et al. Morphine induced exacerbation of sepsis is mediated by tempering endotoxin tolerance through modulation of miR-146a. *Sci Rep*. **2013**, *3*, 1977.
93. Lu, L.F.; Thai, T.H.; Calado, D.P.; Chaudhry, A.; Kubo, M.; Tanaka, K., et al. Foxp3-dependent microRNA155 confers competitive fitness to regulatory T cells by targeting SOCS1 protein. *Immunity*. **2009**, *30*, 80–91.
94. Song, L.; Lin, C.; Wu, Z.; Gong, H.; Zeng, Y.; Wu, J., et al. miR-18a impairs DNA damage response through downregulation of ataxia telangiectasia mutated (ATM) kinase. *PLoS One*. **2011**, *6*, e25454.
95. Sand, M.; Skrygan, M.; Georgas, D.; Sand, D.; Gambichler, T.; Altmeyer, P., et al. The miRNA machinery in primary cutaneous malignant melanoma, cutaneous malignant melanoma metastases and benign melanocytic nevi. *Cell Tissue Res*. **2012**, *350*, 119-126.
96. Sonkoly, E.; Ståhle, M.; Pivarcsi, A. MicroRNAs: Novel regulators in skin inflammation. *Clin Exp Dermatol*. **2008**, *33*, 312–315.
97. Xiao, C.; Rajewsky, K. MicroRNA control in the immune system: Basic principles. *Cell*. **2009**, *136*, 26-36.
98. Lu, T.X.; Rothenberg, M.E. Diagnostic, functional, and therapeutic roles of microRNA in allergic diseases. *J Allergy Clin Immunol*. **2013**, *132*, 3–13.
99. Rebane, A.; Akdis, C.A. MicroRNAs: Essential players in the regulation of inflammation. *J Allergy Clin Immunol*. **2013**, *132*, 15-26.