

# Research progress on the etiology and pathogenesis of adolescent idiopathic scoliosis

Yue Peng, Sheng-Ru Wang, Gui-Xing Qiu, Jian-Guo Zhang, Qian-Yu Zhuang

Department of Orthopedics, Peking Union Medical College Hospital, Beijing 100730, China.

## Abstract

Etiology of adolescent idiopathic scoliosis (AIS), a complicated three-dimensional spinal deformity with early-onset, receives continuous attention but remains unclear. To gain an insight into AIS pathogenesis, this review searched PubMed database up to June 2019, using key words or medical subject headings terms including “adolescent idiopathic scoliosis,” “scoliosis,” “pathogenesis,” “etiology,” “genetics,” “mesenchymal stem cells,” and their combinations, summarized existing literatures and categorized the theories or hypothesis into nine aspects. These aspects include bone marrow mesenchymal stem cell studies, genetic studies, tissue analysis, spine biomechanics measurements, neurologic analysis, hormone studies, biochemical analysis, environmental factor analysis, and lifestyle explorations. These categories could be a guidance for further etiology or treatment researches to gain inspiration.

**Keywords:** Scoliosis; Pathogenesis; Etiology; Mesenchymal stem cells

## Introduction

Adolescent idiopathic scoliosis (AIS) is a three-dimensional spine deformity that takes place at the early age around 11 to 18 years, which is the most common type of idiopathic scoliosis in children. The prevalence of AIS is 0.47% to 5.20% around the world,<sup>[1]</sup> A review by Qiu<sup>[2]</sup> showed the incidence of scoliosis in the Chinese population varied from 0.6% to 2.0%, while 90% of them were AIS. Zheng *et al*<sup>[3]</sup> from China showed the prevalence of AIS is 2.4%, which is higher in girls.<sup>[1]</sup>

Various theories are trying to explain the pathogenesis of AIS, which contains the initiation and the progression of AIS. The latest papers regarding AIS pathogenesis mostly focus on the genetic factors, while there are still numerous theories explaining the pathogenesis from other factors. We classified the theories into the following groups to make a better understanding of the multifactorial pathogenesis of AIS: genetics, mesenchymal stem cells, tissues, spine biomechanics, neurology, hormones, biochemistry, environment, and lifestyle. We also showed a previous theory which tried to integrate multiple former studies.

This review searched PubMed database up to June 2019, using keywords or medical subject headings terms including “adolescent idiopathic scoliosis,” “scoliosis,” “pathogenesis,” “etiology,” “genetics,” “mesenchymal stem cells,” and their combinations, summarized existing literatures and categorized the theories or hypothesis into nine aspects. Literatures relevant to AIS pathogenesis which mainly published in recent 10 years were included. Publications focusing on AIS diagnosis, bracing treatment or surgical techniques were excluded.

## Bone Marrow-Derived Mesenchymal Stem Cells (BM-MSCs)

BM-MSCs possess multipotency of differentiating into osteoblasts, chondrocytes, or adipocytes.<sup>[4]</sup> Decreased osteogenetic ability of MSCs and inclination of MSCs towards adipogenic differentiation have been revealed in AIS patients.<sup>[5,6]</sup> The resultant low bone mineral density status has also been reported in AIS patients,<sup>[7-9]</sup> implying that bone marrow-derived MSCs may regulate bone mass formation in AIS patients, thereby participating in AIS development.

At the expression level, in a proteomic analysis of MSCs from AIS patients, five bone growth-related proteins including pyruvate kinase M2 (PKM2), annexin A2, heat shock 27 k protein (HSP27),  $\gamma$ -actin, and  $\beta$ -actin were

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**Correspondence to:** Dr. Qian-Yu Zhuang, Peking Union Medical College Hospital, 1 Shuai Fu Yuan, Beijing 100730, China  
E-Mail: zhuangqianyu@126.com

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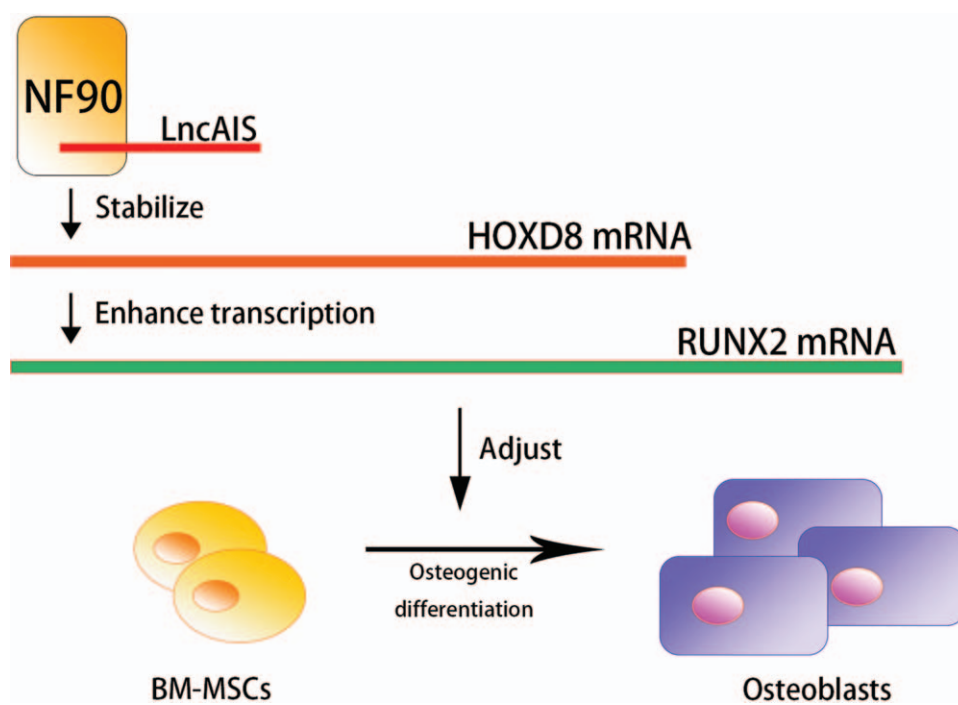
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identified to be altered.<sup>[10]</sup> In this study by Zhuang *et al*,<sup>[10]</sup> up-regulated PKM2 was speculated as associated with increased cell proliferation, while down-regulated annexin A2, HSP27,  $\gamma$ -actin, and  $\beta$ -actin were speculated as associated with the diminished ossification process and low bone mass status. In a further microarray and pathway analysis study of Zhuang *et al*,<sup>[11]</sup> several differentially expressed genes were discovered, down-regulated mitogen-activated protein kinase kinase 1, heat shock 70 kDa protein 6, and up-regulated SMAD family member 3 were speculated to inhibit the osteogenic differentiation, while up-regulated homeobox C6/9 affected the global patterning of vertebrate axial skeleton, other dysregulated genes including general transcription factor Iii, CREB binding protein, phosphoinositide-3-kinase, regulatory sub-unit 2, and dual-specificity phosphatase 2 may also play roles in osteogenesis and bone formation. Chen *et al*<sup>[12]</sup> discovered the expression of melatonin receptors in AIS MSCs were down-regulated, which may lead to the reduction of response to melatonin treatment, since melatonin increases alkaline phosphatase activity and glycosaminoglycan (GAG) synthesis and other differentiation-related genes expression, lack of response to melatonin might alter this process and then influence membranous and endochondral ossification. Leptin receptors in AIS MSCs were also found to be down-regulated in another study, which might result in hyposensitivity of MSCs to circulating leptin.<sup>[5]</sup> Thyroid hormone-inducible nuclear protein (Spot14) and its messenger RNA (mRNA) were found to be more expressed in adipogenic MSCs from AIS patients than controls, and the higher expression was also found in the AIS patients' adipose tissue, which also reflected the abnormal adipogenic differentiation.<sup>[13]</sup> Lower expression of mitogen-

activated protein kinase 7 (MAPK7) was also identified in AIS MSCs, which might result in disturbance of MSCs osteogenic differentiation.<sup>[14]</sup> G protein-coupled receptor 126 (*GPR126*) gene was showed to have higher expression in the vertebral bodies from the convex side of scoliosis, knocking down of *GPR126* would promote MSCs ossification.<sup>[15]</sup>

At the epigenetic level, long non-coding RNA (lncRNAs) and microRNAs (miRNAs) were analyzed in previous studies. lncRNAs are the transcripts that have the length longer than 200 nucleotides, which do not contain any functional open reading frame, lncRNAs can regulate gene expression by interfering the chromatin modification, transcriptional/post-transcriptional regulation. lncRNAs are expressed differently in different types of tissues and cells, a review has discussed the existence of relationships between lncRNAs of MSCs and various bone-related diseases such as osteoporosis, osteosarcoma and ankylosing spondylitis, it was speculated that lncRNAs participates in osteogenic differentiation of MSCs.<sup>[16]</sup> By applying microarray analysis of BM-MSCs in AIS patients and the control groups, Zhuang *et al*<sup>[17]</sup> have identified a novel lncRNA (ENST00000453347) that was prominently down-regulated, which was later named as *lncAIS*, in normal conditions, *lncAIS* was reported to maintain the stability of Homeobox D8 mRNA by interacting with nuclear factor 90 protein and further enhance Runt-related transcription factor 2 (RUNX2) transcription [Figure 1], and the down-regulation of *lncAIS* would inhibit RUNX2 expression, thus alter the osteogenic differentiation of MSCs, and finally result in osteopenia in AIS patients. RUNX2 as a transcription factor was also previously



**Figure 1:** *lncAIS* interacts with NF90, stabilizing the HOXD8 mRNA and further enhances the transcription of RUNX2, which alters the osteogenic differentiation process of BM-MSCs. BM-MSCs: Bone marrow-derived mesenchymal stem cells; HOXD8: Homeobox D8; *lncAIS*: Long non-coding AIS (gene symbol: ENST00000453347); NF90: Nuclear factor 90; RUNX2: Runt-Related transcription factor 2.

reported to participate in reduced bone mineral density (BMD) in AIS patients.<sup>[18]</sup> miRNAs are also non-coding RNA which are shorter than 20 nucleotides, miRNAs target specific mRNA and resulted in changes in gene expression. Through analysis of miRNA expression profile, gene ontology terms and Kyoto encyclopedia of genes and genomes, a novel study of Hui *et al*<sup>[19]</sup> has identified seven most significantly central up-regulated miRNA in AIS BM-SCs including miR-17-5p, miR-106a-5p, miR-106b-5p, miR-16-5p, miR-93-5p, and miR-181b-5p, which could suppress osteogenic differentiation and bone formation, while miR-15a-5p could regulate cell apoptosis.

## Genetics

Previous twin study of Simony *et al*,<sup>[20]</sup> aiming to found out the heritability of AIS, showed a higher concordance rate in monozygotic pairs (0.13) than dizygotic pairs (0.00). The higher prevalence in female inspired studies investigating the possibility of X-linked inheritance, a study by Justice *et al*<sup>[21]</sup> gave evidence of a region on the X chromosome that might be linked to AIS, another study by Ward *et al*<sup>[22]</sup> indicated the polygenic inheritance of AIS, the study also showed male to male transmission examples that negated the former X-linked inheritance hypothesis. Despite the controversies of inheritance pattern, current researches showed that chromosome abnormality, variations of gene loci caused primary expressional alterations, and the epigenetic changes resulted from environmental factors further regulated the gene expression; these elements worked together inducing a dysfunction of cell activities, which further led to AIS development.

## Chromosome abnormality and gene variations

Linkage and association studies are primary techniques to analyze the genotype-phenotype relationship.<sup>[23]</sup> linkage analysis identified mutants in gene loci such as MAPK7<sup>[24]</sup> and allele marker DS1034 on chromosome 19p13.3,<sup>[25]</sup> both of which were relevant to AIS etiology.

Genome-wide association study (GWAS) is another powerful tool to analyze the relationship between single nucleotide polymorphism (SNPs) in gene loci and phenotypes, it was widely used in genetic studies of polygenic diseases, a study by Ogura *et al*<sup>[26]</sup> showed ladybird homeobox 1 (*LBX1*), were related to AIS pathogenesis. GWAS was also used to analyze the copy number variants (CNV) associated with AIS, it has been revealed that CNV in chromosome 1q21.1, 2q13, 15q11.2, 16p11.2 harbor in AIS.<sup>[27]</sup> It is worth mentioning that Liu *et al*<sup>[28]</sup> found SNPs and CNV (such as deletion in *TBX6*) could also locate at one locus thus distort the calculations of the significance in associating SNPs to AIS.

Asides from the above gene loci where SNPs harbor, other gene loci including cell adhesion molecule L1 like, fibrillin (*FBN*), *GPR126*, insulin-like growth factor 1, *LBX1*, matrilin-1, matrix metalloproteinases-3, and interleukin-6 (*IL-6*), paired box 1, proteome of centrioles 5, transforming growth factor beta 1 (*TGFB1*), *VANGL* planar cell polarity protein 1 were shown to be possibly related with the pathogenesis of AIS.<sup>[29-38]</sup> Recently, Zhang

*et al*<sup>[39]</sup> found a mutation of *uts2ra* could cause spinal curvature in zebrafish, the mutation could down-regulate the urotensin neuropeptides receptors of slow-twitch muscle fibers of the somite and; therefore, change the straightening of vertebrae axis process. Further researches can investigate the expressional alterations and regulation of these genes in AIS patients.

## Epigenetics

The definition of epigenetics is the change in DNA or the paired proteins, with DNA sequence variation excluded, epigenetics plays roles in gene expression and cell division.<sup>[40]</sup> A study by Fendri *et al*<sup>[41]</sup> using microarray analysis and quantitative Reverse-transcription PCR found 145 genes differently expressed in AIS osteoblasts, which might be related with epigenetic regulation.

At the DNA methylation level, in the study by Mao *et al*,<sup>[42]</sup> the positive methylation on the cartilage oligomeric matrix protein (*COMP*) promoter resulted in the low expression of the *COMP* gene, which influenced the bone formation, correlating with young chronological age and high Cobb angle of main curve. Meng *et al*<sup>[43]</sup> found the hypo-methylation of site cg01374129, which located near *HAS2* gene, was reported to have a negative correlation with AIS curve severity. The positive methylation in the promoter of pituitary homeobox 1 gene was also related to larger Cobb angles of main curve.

At the non-coding RNAs level, miRNAs and lncRNAs were also reported to be related with the pathogenesis,<sup>[17,19,44-46]</sup> the epigenetic alterations were located in both peripheral blood and MSCs.

## Tissues

### Bone

Histological methods, computed tomography scan with higher resolution<sup>[47]</sup> and reconstruction were used, identified the bone formation abnormalities at morphologic level which is in accordance with low BMD status. In the study of Tanabe *et al*,<sup>[48]</sup> from the histological sections of the spinous process taken from AIS patients, 67% showed sub-normal bone volume and 76% showed a high bone turnover rate. It has also been revealed from a study by Wang *et al*<sup>[49]</sup> that AIS patients with low or normal BMD both have abnormal bone quality and it might be resulting from altered endocortical apposition.

### Muscle

Studies of paravertebral muscles have implied the alteration and asymmetry of paravertebral muscles caused the inharmony of the posture and movement control of the spine, thus resulted in AIS progression. A study by Acaroglu *et al*<sup>[50]</sup> showed a higher concentration of calmodulin in muscle tissue of the convex side, which might affect the contractility of muscles. In the study by Wang and Pessin,<sup>[51]</sup> through the biopsy from AIS patients, muscles of convex side have an increased portion of type I fibers than type II while a decreased portion was found in

the concave side, Type I fiber has higher fatigue resistant but slower contractile speed, and may occur under long duration,<sup>[52]</sup> Stetkarova *et al*<sup>[53]</sup> considered that this change might be a secondary adaption to the higher load demand on the convex side, and are related with curve progression. Moreover, the alterations of paravertebral muscle have been verified at the genetic level, Buchan *et al*<sup>[38]</sup> identified rare variants in *FBN1* and *FBN2*, which were correlated with curve progression, *FBN* genes were observed to up-regulate the TGF- $\beta$  signaling pathway in paravertebral muscles. In the study of Nowak *et al*,<sup>[54]</sup> muscles of the concave side showed a higher transcript abundance of *TGF- $\beta$ 2*, *TGF-3*, and transforming growth factor beta receptor 2 (*TGFBR2*), these genetic expressions mostly affect the extracellular region of the paravertebral muscles.

### Spine Biomechanics

Relative anterior spinal overgrowth (RASO) and the contraction from the anterior part of the torso led to asymmetry of the spinal growth. Back to 1996, Murray *et al*<sup>[55]</sup> built a simple model of idiopathic scoliosis to analyze the possible biomechanics behind the deformity, it was shown that the overgrowth of the anterior column relative to the posterior one caused the model to form a shape of idiopathic scoliosis. In the study by Shi *et al*,<sup>[56]</sup> finite elements model has then been simulated, verified the accelerated growth pattern affecting scoliotic progression, while it has also been speculated that RASO was a secondary change in the development of AIS since the model with a pre-set small kyphosis in the study did not develop scoliosis. Nevertheless, Crijns *et al*<sup>[57]</sup> built a hypokyphosis model with an anterior band simulating the contraction from the anterior muscles and ligaments, demonstrating that even without a pre-set left-right asymmetry of the spine, the restraining force from the anterior of the body can cause a lateral curve, which indicated the unmatched growth speed of the spine with that of the anterior banding components might induce the scoliotic deformity after the decrease of kyphosis or increase of lordosis resulting from RASO. A study by Guo *et al*<sup>[58]</sup> has revealed that the main ossification type of vertebral bodies of AIS patients was endochondral ossification, which was also faster than the membranous ossification of pedicles as parts of the posterior structure, which explained the principle of RASO.

The intervertebral discs might be another source of spinal asymmetry. In the study of Will *et al*,<sup>[59]</sup> it was shown that rather than vertebrae body, the discs wedging was found to contributed the most to scoliosis progression at the beginning of the growth spurt of AIS patients but gradually reversed along with the spurt. Another study by Brink *et al*<sup>[60]</sup> revealed the increase of the height of discs also accounted for the development of RASO, but the study considered RASO as the secondary phenomenon since RASO was also observed in other types of scoliosis as well.

The biomechanics between spine and other parts of the torso might also contribute to AIS. Zhu *et al*<sup>[61]</sup> found out the rib length asymmetry was most likely a secondary change to the scoliosis deformity. Another hypothesis

proposed by Yang *et al*<sup>[62]</sup> was that the left-right handedness and the location and gravity of heart and aorta might play roles in the curve patterns of AIS, it was hypothesized that right handedness induced a stronger right extrinsic back muscles which cannot be counteracted by the intrinsic muscle, which caused the convexity of the right side. While comments have also been made to question the handedness part.<sup>[63]</sup> Another study of Chen *et al*<sup>[64]</sup> found that imbalance of growth between sternum and thoracic vertebrae might lead to scoliosis.

### Neurology

#### Brain

The research of association between brain abnormalities and spinal deformity focused mainly on the neuroanatomical and neurofunctional alterations which were observed in the cerebrum, brain stem, and cerebellum.

Of the studies regarding cerebrum and brain stem, magnetic resonance imaging (MRI) images with a morphometric study by Shi *et al*<sup>[65]</sup> showed white matter attenuation in the corpus callosum and left internal capsule of the AIS patients with left thoracic curves. In another study by Wang *et al*<sup>[66]</sup> also found cerebrum abnormality that the cortical thickness of AIS patients was different from the normal control group, the differences were mostly observed in the region involving in motor and vestibular function. Opposite opinion was also given, a study by Lee *et al*<sup>[67]</sup> showed no significant glucose metabolic difference was found between AIS groups and normal groups, giving the contrary evidence of cerebrum abnormalities taking part in the pathogenesis of AIS. Another study by Geissele *et al*<sup>[68]</sup> regarding the brain stem discovered the ventral pons or medulla asymmetry in the area of the corticospinal tracts from 7 AIS patients. To sum up, despite abnormalities were observed in AIS patients, there is currently no solid evidence proves the alterations in the cerebrum and brain stem are primary changes in AIS development, nor it has been proved that the alterations in the cerebrum found in AIS patients affect neurological function yet.

Of the studies regarding cerebellum, it is known that cerebellum has crucial functions to adjust or coordinate the muscle movements and posture. In the study of Cheng *et al*,<sup>[69]</sup> tonsillar ectopia was found in a small part (7.3%) of AIS patients, this part of patients in the study had a higher prevalence of severe curve. Another study by Lee *et al*<sup>[70]</sup> showed a higher prevalence of 48% AIS patients, whose MRI images were taken under an upright rather than a supine position, had cerebellar tonsillar descent. The first study analyzing the regional cerebellum volume characteristics quantitatively revealed the enlargement of several cerebellar regions.<sup>[71]</sup> Another study by Chau *et al*<sup>[72]</sup> observed the prolonged latency of somatosensory-evoked potential (SEP) in AIS girls, among AIS patients with abnormal SEP, 58% were found to have cerebellar tonsillar ectopia. This study might show the functional impairments of morphological changes in the cerebellum of AIS patients. With these studies, we can speculate the possibility of cerebellum growth and functional changes having a relationship with AIS development.

## Vestibular system

Deficits of the vestibular system may lead to asymmetrical body activities and senses thus contributes to AIS development. The vestibular system collects the postural information which is further integrated with other sensory information to maintain body balance. Byl *et al*<sup>[73]</sup> reported a postural imbalance in AIS patients and it was hypothesized that an asymmetric vestibular system which causes a rise in the asymmetric paraspinal muscle tone might play a role in the genesis of AIS.<sup>[74]</sup> Another study by Zeng *et al*<sup>[75]</sup> also showed a difference in the morphology of the vestibular system in the AIS patients. However, a systematic review by Catanzariti *et al*<sup>[76]</sup> in 2014 concluded that there has not been adequate evidence showing the unilateral contribution of vestibular dysfunction to the AIS pathogenesis. In the following study by Hitier *et al*,<sup>[77]</sup> lateral semicircular canal asymmetry was found in AIS patients, which was also associated with functional anomalies such as lower excitability and higher canal paresis, this asymmetry might even have developed before birth. Novel research by Antoniadou *et al*<sup>[78]</sup> also found vestibular deficits might cause verticality perception disorder, thus described the sensorimotor integration impairment in AIS.

## Hormones

### Melatonin and calmodulin

Whether the deficiency of melatonin accounts for the development of AIS remains controversial since studies have shown inter-opposite results of evaluating the serum melatonin level.<sup>[79,80]</sup> Experiments of pinealectomy in animals have shown a tendency to induce scoliosis, but Man *et al*<sup>[81]</sup> concerned that the surgery itself accounted for scoliosis and the differences existed between humans and chickens which were used in the experiments. Pinchuk *et al*<sup>[82]</sup> proposed that the disturbed biorhythm of secretion, rather than the deficiency of melatonin, might be the cause of scoliosis, which resulted from the imbalance of the suprachiasmatic nucleus/pineal gland activities. However, alterations in melatonin functioning may result in imbalance of cell proliferation and differentiation in different types of cells, thus disturb the regular bone mass formation and might lead to AIS development. Melatonin improves osteoblast cells proliferation and their secretion of osteoprotegerin (OPG), OPG further inhibits the binding of osteoclast differentiation factors to RANK, thus reduces the differentiation of osteoclast cells.<sup>[83]</sup> Melatonin receptor 1B (MT2) was expressed in osteoblasts cells, a study of Yim *et al*<sup>[84]</sup> discovered a quantitatively lower expression of MT2 in AIS osteoblast cells than the normal group, which was statistically related to a longer arm span of AIS patients. Man *et al*<sup>[85]</sup> found AIS osteoblasts without MT2 expression showed a weakened proliferative ability, and gene polymorphisms of the MT2 gene such as rs4753426 were considered to be related with the risk of AIS.<sup>[86]</sup> In addition to the osteoblasts, growth plate chondrocytes (GPCs) were also found to had a decreased MT2 expression, melatonin was found to reduce GPCs proliferation and differentiation, lack of response to melatonin in AIS GPCs might result in an altered

endochondral ossification.<sup>[87]</sup> As mentioned above, AIS MSCs had a lower MT2 expression which might be related to membranous and endochondral ossification as well.<sup>[12]</sup>

Calmodulin may be related to the muscle function and bone formation, which leads to AIS development. Calmodulin participates in different metabolism systems as a secondary messenger, it is widely expressed in different varieties of cells and takes part in the contractile system of cells and is also an inhibitor of melatonin.<sup>[83]</sup> According to the study of Lowe *et al*,<sup>[88]</sup> early studies showed an increased concentration of calmodulin in platelets of AIS patients, but whether it reflected the muscular changes or spine deformity remained controversial. Imbalance of the concentrations in the paraspinal muscles of AIS patients was discovered, but studies showed different results of which side has a higher concentration.<sup>[50,89]</sup> In the articular process of AIS patients, the expression of calmodulin was also found to be lower.<sup>[90]</sup>

### Leptin

Leptin has central and peripheral functions to bone formation, the leptin-neurology functions are central functions, its direct interactions with bone-related tissues are peripheral functions, alterations in these functions can cause AIS development. Leptin is the hormone that takes part in the regulation of bone formation, and is regulated by hypothalamic nuclei and the sympathetic nerve system.<sup>[91]</sup> In the study of Qiu *et al*,<sup>[92]</sup> decreased circulating leptin level was found in AIS patients, and was believed to be related with lower body mass index (BMI) and BMD. Another study by Liang *et al*<sup>[5]</sup> proposed that the circulating leptin might be a secondary alteration caused by the low adipogenesis ability of AIS patients which resulted from their lower fat accumulation, the study also regarded the peripheral functions, leptin receptors were found to be down-regulated in induced AIS MSCs which explained their hyposensitivity to leptin and their weakened adipogenesis ability, the study also considered Janus tyrosine kinase 2/signal transducers and activators of transcription defects might exist in AIS patients. In the study of Wang *et al*,<sup>[93]</sup> the lower expression of membrane leptin receptors was found in the chondrocyte cells of AIS patients' facet joints, it might be resulted from an imbalance between endocytosis and insertion of new receptors to the membrane, this alteration may cause decreased leptin sensitivity.

### Estrogen

As one of the sex hormones resides in human body, estrogen has numerous functions, lack of estrogen leads to deficits of bone maturation which can further participate in AIS development. Reviews by Zhou *et al* and Leboeuf *et al*<sup>[94,95]</sup> have discussed that the response of cells to estrogen of AIS patients was altered and thus might result in the delay of menarche and osteopenia, which disturbed the maturation of bone. It was also speculated that estrogen receptors might influence the response of growth plates to strain which affected bone formation. The interactions between estrogen and other hormones were also discussed, melatonin and estrogen had opposite

influences in the regulation of cAMP level in cells, calmodulin might also influence the estrogen functioning in signal pathways. It is clear that estrogen influences the growth pattern of spine, further research may reveal the specific mechanism and whether other environmental factors have effects on estrogen secretion or functions that can induce the development of AIS.

### Growth hormone

The growth hormone (GH) has been considered to regulate the overall growth of the body, alterations in GH secretion and functions may affect the growth of the skeleton, which is related to AIS etiology. Studies have shown AIS patients were relatively taller than the normal groups,<sup>[96,97]</sup> In the study of Willner *et al*,<sup>[98]</sup> the basal hormone level was also found to be higher in AIS patients. Yang *et al* and Zhuang *et al*<sup>[99,100]</sup> identified gene polymorphisms of GH receptors in AIS patients, which were associated with the higher GH concentration in the blood and the low BMD condition. However, the GH gene promoter was considered not related to AIS etiology.<sup>[101]</sup> Through these studies we can conclude that GHR alterations may play as a more primary role than GH itself, despite GH still may participate in the etiology of AIS, further studies are needed to reveal the specific role of GH and the interactions between GH and other hormones.

### Biochemistry

#### Bone mineral metabolism

Various mechanisms were considered to account for the low BMD status in AIS, low BMD might also result in stress increase and curve progression. In the study of Suh *et al*,<sup>[102]</sup> imbalance of the disturbed interaction between receptor activator of nuclear factor- $\kappa$ B ligand (RANKL) and OPG has been found to be related with low spinal BMD (LSBMD) and femoral neck BMD (FNBMD), the serum RANKL to OPG ratio was increased. Not only in the serum, but the increased RANKL expression was also found in osteoblasts by Zhou *et al*.<sup>[103]</sup> The RANK system plays an important role in bone metabolism, which induces the osteoclastic cells to generate bone resorption. In the study of Eun *et al*,<sup>[104]</sup> OPG gene and *IL-6* gene, which was a candidate gene of osteopenia, were both confirmed to have polymorphisms in AIS patients and were considered to be associated with AIS pathogenesis. RUNX2 as an important transcription factor regulating osteoblast differentiation and skeletal formation, Wang *et al*<sup>[118]</sup> discovered that the expression of Runx2 decreased in osteoblasts cells of AIS patients and might be related to the LSBMD and FNBMD. Using the finite element model, Song *et al*<sup>[105]</sup> confirmed that low BMD in the concave side of thoracic scoliosis could enlarge the stress to the cortical bone, discs, and facets, altered their regular growth, thus caused curve progression.

#### Vitamin D

Vitamin D is correlated with calcium metabolism, besides, Ng *et al*<sup>[106]</sup> considered that it might also have influences on fibrosis regulation, postural control, which might result

in AIS development. Vitamin D receptor (VDR) is another research point of vitamin D metabolism. It is still controversial whether the gene polymorphism of VDR Bsm1 contributes to the development of AIS.<sup>[107-109]</sup> Further researches should be taken to define which signaling pathway Vitamin D takes part in and whether it acts as a causal factor of AIS.

#### Lipid metabolism

Disrupted lipid metabolism has been found in a serum metabolic analysis study by Sun *et al*,<sup>[110]</sup> the categories of lipids altered in the AIS patients were glycerophospholipids, glycerolipids, and fatty acid esters. Since the lipid metabolism are related with various kinds of hormones and regulative systems, it is necessary to find out the roles altered lipid metabolism played in the pathogenesis of AIS and to integrate the findings to other theories.

#### Biochemical characteristics in scoliotic disc

The biochemical alterations may also cause histological changes of discs, which may be accordance with some biomechanical effects, thus result in AIS curve progression. In the study of Ghosh *et al*,<sup>[111]</sup> the distribution of GAGs was reported to shift away from its original location in scoliotic vertebral discs, originally, the concentration should be highest in the nucleus pulposus. Another study by He *et al*<sup>[112]</sup> showed an increase of type I and type II collagen at the convex side of the discs relative to the concave side, which might result from the degeneration of the discs.

### Environment and Lifestyle

#### High environmental selenium

After gathering the information of guppy fish developed an "S" curve deformity in the high-selenium environment, Yang *et al*<sup>[113]</sup> gave the hypothesis that high-selenium environment-induced uncoupled spinal neuro-osseous growth, and the overgrowth of the spine relative to the spinal cord resulted in the tethering of the spine, which might thus cause the curvature. Another cohort study by Ji *et al*<sup>[114]</sup> proved the hypothesis by giving evidence that the relative risk was 2.88.

#### Chlorine and the neurotoxic influences

A hypothesis by McMaster *et al*<sup>[115]</sup> postulated that the chloroform generated from heat swimming pools has a neurotoxic effect thus induces AIS development. It has been observed that the normal teenagers introduced to indoor heated swimming pools had a high prevalence (83%) of developing vertical spinous process asymmetry, this phenomenon was also observed in infants.<sup>[116]</sup>

#### Gut microbiome induced plasma proteome alterations in AIS patients

A novel hypothesis has been built on the findings of different structures of gut microbiome between AIS patients and healthy control groups.<sup>[117]</sup> It was found

that the differences may result in alterations of the plasma proteins, and the abundance of fecal prevotella positively correlated with Cobb angles of the AIS patients. Although there is not sufficient evidence of direct participation of microbiome in the initiation or progression of the AIS.

### Physical activities as controversial risk factors

Different physical activities with different training strategies may induce different outcomes, which may be associated with AIS etiology. Besides from the previously described indoor swimming pool exposure, several other physical activities have been evaluated. The better ability of toe touching was found to have a positive correlation with AIS occurrence, which might be resulted from connective tissues deficits.<sup>[118]</sup> In the same study, AIS children were shown to participated less frequently in dance, skating, gymnastics or karate, and football or hockey classes. Another study<sup>[119]</sup> discovered that different physical activities had different associations with AIS, the odds ratio of ballet training with AIS was reported to be 1.38.

### Integrated theory

The double neuro-osseous theory, proposed by Burwell *et al* concluded the pathogenesis theories of AIS into a developmental disharmony between autonomic and somatic nervous systems of the spine and trunk, which was further exaggerated by hormones and thus induced a systemic skeletal overgrowth.<sup>[91]</sup> This theory postulated a leptin-hypothalamic-sympathetic nervous system involved in the pathogenesis of AIS, which showed the central functions of leptin, the genetic mutations of AIS patients induced an increased sensitivity of hypothalamus to leptin, exaggerated by somatotrophic axis, then affected the skeletal growth. The somatic nervous system of AIS was described as a failure to control and compensate for the spinal deformity. As relatively low BMI was found in AIS patients in several studies,<sup>[96,120,121]</sup> it was also integrated into the double neuro-osseous theory, and were considered as a substitutional measure for body fat and circulating leptin levels.<sup>[122]</sup> The integrated theory was based on the former studies and required later confirmation.

### Conclusions

The management of scoliosis includes surgery and conservative treatment<sup>[123-126]</sup>; however, the prevention of AIS are still under research, which partly because the etiology and pathogenesis of AIS is currently indefinite. Despite there have already been numerous theories or hypotheses investigating the pathogenesis of AIS, novel findings are still emerging constantly. In this review, we classified the known mechanisms of AIS pathogenesis and confirmed AIS as a multifactorial disease with intrinsic and extrinsic alterations. Limitations of our review exist because of the relatively simple inclusion and exclusion criteria, which may cause selective bias. According to the review, bone formation seems to be one of the key points of the etiology and pathogenesis of AIS, and was found to be related with changes in almost every field we classified from genetic to environmental factors. If further studies

focus more on the bone formation differences of AIS patients, the connections between different fields may be well established. Moreover, the treatment of AIS may also find inspiration from the alteration in BM-MSCs and hormones. However, further studies are also expected to clarify the controversial parts and integrate the existing theories and findings.

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### Conflicts of interest

None.

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