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Review

Ankylosing Spondylitis Associated Gene Polymorphism

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Abstract

Ankylosing Spondylitis (AS) is an autoimmune arthritis disease, mostly found in 20-30 years old adolescents. Genetic factors play an important role in the pathogenesis of AS. It is generally believed that the disease is a polygenic hereditary disease and has strong correlation with human leukocyte antigen B27 (HLA-B27). But the mechanism is still unclear. In recent years, it has been found that endoplasmic reticulum aminopeptidase1 (ERAP-1) gene, tumor necrosis factor-α (TNF-α) gene, interleukin gene, and cytotoxic T lymphocyte associated antigen 4 (CTLA-4) gene are also correlated with the pathogenesis of AS. The research on these related genes can provide a basis for the diagnosis of AS. This article reviews the mechanism and polymorphism of these genes in AS.

Key words: Ankylosing spondylitis (AS); Human leukocyte antigen B27 gene (HLA-B27); Endoplasmic reticulum aminopeptidase1 gene (ERAP-1); Interleukin 23 receptor gene (IL-23R); Cytotoxic T lymphocyte associated antigen-4 gene (CTLA-4).

Introduction

AS is an autoimmune disease and chronic inflammatory disease with an estimated incidence of 0.2-0.54% in Chinese Han population (1). It belongs to the category of rheumatoid diseases and is a kind of seronegative spondyloarthropathy. AS usually starts secretly and is easily neglected in the

early stage of the disease. Some AS patient's main features are the involvement of the spine and sacroiliac joints, who may have peripheral arthritis or peripheral joint adhesion (2). The typical manifestation of AS is inflammatory backache with varying degrees of vascular lesions. It has inflammation of tendons, ligaments and articular capsule fibers attached to bones, as well as extra articular manifestations such as colitis and psoriasis (3). The etiology of AS is unclear, but it may be caused by environmental factors based on genetic factors. It is generally believed that it is closely related to the expression of *HLA-B27*, but not all *HLA-B27* positive individuals develop into AS (4). In recent years, many other susceptibility genes have been found related to AS.

1. Human leukocyte antigen B27 gene (*HLA-B27*)

Human leukocyte antigen B27 (*HLA-B27*), encoded by the B gene, is located on chromosome 6 and belongs to I type MHC gene. Although HLA-B27 plays an important role in the pathogenesis of AS, recently research have shown that HLA-B27 accounts for only 20.1% of the total genetic susceptibility, and generally only 5% of HLA-B27 positive individuals develop into AS in the Chinese Han population in Beijing(5). The pathogenesis of HLA-B27 is still unclear, but there are mainly three hypotheses: the first theory is articular peptide: HLA-B27 on APC binds to self-peptide or environmental polypeptide and then activates CD8+T cells; the second unconfirmed theory is the HLA-B27 misfolding theory: the misfolding of HLA-B27 in the endoplasmic reticulum results in endoplasmic reticulum stress and activates unfolded protein response, leading to the up-regulate of IL-23 in dendritic cells, which leads to inflammation; the third one is the cell surface homodimer hypothesis: HLA-B27 folds abnormally on the surface of APC to form homodimer, which can bind to killer immunoglobulin-like receptor 3DL2 (KIR3DL2)(6, 7). The mechanism is shown in step 1 and 2 of Figure 1. *HLA-B27* has many subtypes, some of which play an important role in AS. *HLA-B27:09* is not correlated with the incidence of AS (8). *HLA-B27:04*, *HLA-B27:05* and *HLA-B27:02* have the strongest correlation with AS and *HLA-B27:04* is the main subtype of AS in Chinese Han population in Beijing (5). Through genotyping of AS patients in Xinjiang, it is found that *HLA-B27:05* is the main subtype of Xinjiang Uygur, while *HLA-B27:04* is the main subtype of Xinjiang Han population (9). Different living habits, geographical environments and ethnic groups may produce different dominant subtypes of gene that affect the disease. By studying the subtypes of *HLA-B27* gene, we can diagnose the disease as soon as possible.

2. Endoplasmic reticulum aminopeptidase1 gene (*ERAP-1*)

ERAP-1 is another gene found mostly associated with AS after the discovery of *HLA-B27*. ERAP-1 is an aminopeptidase located in the endoplasmic reticulum, and *ERAP-1* gene is located at chromosome 5q15 (5). ERAP-1 is involved in the presentation processing of antigenic peptides. After the antigen peptides are pruned to the appropriate length for antigen presentation, they are bound to MHC-I molecules and migrate the cell membrane to induce an immune response. ERAP-1 polymorphism changes the function of the enzyme and leads to the peptide expression and free heavy chain formation of HLA-B27 (10). Studies have shown that there is interaction between *HLA-B27* gene and *ERAP-1* gene mutation, and that *ERAP-1* gene mutation is only associated with *HLA-B27* (+). ERAP-1 abnormalities produce abnormal antigenic peptide spectrum, resulting in aberrant expression of HLA-B27. The mechanism is shown in step 3 of Figure 1. *rs27434* and *rs275825* polymorphisms of

ERAP-1 in *HLA-B27:02* and *HLA-B27:04* positive patients are associated with AS in Beijing area, but the *rs27434* is weakly associated with AS (5). According to Su's finding, *rs30183, rs27434, rs27044* have no correlation with AS in the Chinese Han population (11). However, *rs27044* polymorphism is associated with AS in a higher incidence of AS in CG genotype carriers by Tang's finding in Chinese Han population (12). This indicates that geographical factors may be an important reason for the difference. It is necessary to explore the correlation between *ERAP-1* gene polymorphism and the pathogenesis of AS through a lot of research and data analysis to provide more reasonable methods for the clinical diagnosis and treatment.

3. Interleukin 23 receptor gene (*IL-23R*)

Interleukin-23 receptor (*IL-23R*) is located on chromosome 1p31.3(13). Interleukin-23 receptor (IL-23R) encoded by *IL-23R* gene is a specific subunit of IL-23R/IL12Rβ1 complex, that mediates the signal transduction of IL-23(14). IL-23R/IL-17 axis plays an important role in the pathogenesis of AS. IL-23, produced by dendritic cells and monocytes, promotes the polarization of activated T cells to helper Th17 cells and induces the production of IL-17A. IL-17A is pro-inflammatory cytokine, leading to bone destruction in AS patients (15). The mechanism is shown in step 4 of Figure 1. Changes in *IL-23R* gene polymorphism may cause dysfunction of the IL-23R/IL-17 axis, leading to the pathogenesis of AS. Many *IL-23R* gene polymorphisms have been discovered through a lot of research. By analyzing the polymorphism of *IL-23R rs10889677*, it is found that A allele is significantly correlated with the incidence of AS in European (13). So, *IL-23R rs10889677* polymorphism in the Asian remains to be further researched. *rs1004819, rs1495965* and *rs2201841* are susceptible to AS. *rs10489629, rs1209026, rs11465804* and *rs1343151* have protective effects on AS, but *rs1209629* and *rs11465804* do not appear in Asian patients with AS (14). The different results may be due to the few numbers of cases and the small sample size, resulting in the limitation of experimental results. So, the undiscovered polymorphisms can be found through deeply research of *IL-23R* gene to provide a better method for the diagnosis of disease.

4. Cytotoxic T lymphocyte associated antigen-4 gene (*CTLA-4*)

CTLA-4 is also known as CD152. CTLA-4 is a transmembrane receptor on T cells and plays an important role in inhibiting the activation and tolerance of T cells. The *CTLA-4* gene is located in the 2q33 region of chromosome (16). T cells activation requires the co-stimulation of CD28 and CTLA-4. CD28 activates T cells, while CTLA-4 inhibits T cells activation by competing with CD28 for B7 in Algeria population (17). The mechanism is shown in step 5 of Figure 1. CTLA-4 regulates T cells activation through the balance of CD28 activation and CTLA-4 inhibition. After genotyping of *CTLA-4*, three high risk gene polymorphisms (*CTLA-4-318C/T, CTLA-4-CT60 and CTLA-4+49 A/G*) are found related to the pathogenesis of AS. The soluble CTLA-4 (sCTLA-4) in peripheral blood of patients with AS and normal subjects is detected. It is found that the sCTLA-4 in peripheral blood of AS patients is higher than normal controls, but the level of sCTLA-4 is not related to the severity of AS (18). *CTLA-4+49A/G* study shows that it has no significant correlation with the incidence of AS. It suggested that *CTLA-4+49A/G* might not be the main susceptibility gene in AS patients (19). Polymorphisms of *CTLA-4 +49A/G* and *CTLA-4-318T/C* are also not significantly correlated with the incidence of AS in Chen's finding(16). Genotyping of *CTLA-4/CT60* shows that the *CT60*G* allele is significantly correlated in women over 30

years old and the risk of AS is increased in HLA-B27 negative patients(17). In order to provide a new method for the diagnosis and treatment of AS in the future, the polymorphism of the *CTLA-4* gene needs further researches.

5. Tumor necrosis factor-α gene (*TNF-α*)

Tumor necrosis factor-α (TNF-α) belongs to the TNF family, which is encoded by the *TNF-α* gene located on the chromosome 6p21.3 (20). TNF is secreted by macrophages and regulated by two distinct receptors, TNFR1 and TNFR2. TNFR1 promotes inflammation, while TNFR2 promotes neuroprotection in Russian Caucasian population (21). The mechanism is shown in step 6 of Figure 1. TNF is a key pro-inflammatory cytokine in chronic inflammation and highly expressed in sacroiliac joint cells of AS patients in Chinese Han population (22). *TNF-α-238 GA/AA* and *TNF-α-308 GA/AA* genotype are found to be associated with improved spinal cord function (23). *TNF-α-1211c* (*rs1799964*) and *TNF-α-308* (*rs1800629*) reduce the risk of AS in Chinese Han population, but *TNF-α-238* (*rs361525*) is not associated with AS (22). The study of *TNF-α-308* (*rs1800629*) gene in Norwegian population shows that it is also not associated with AS, but a new AS risk site is found in *TNF-α-238* (*rs361525*) (24). The difference may be due to geographical factors, ethnic factors or too few samples. With further study of TNF-α, TNF-α inhibitor is a good drug for the treatment of AS in recent years.

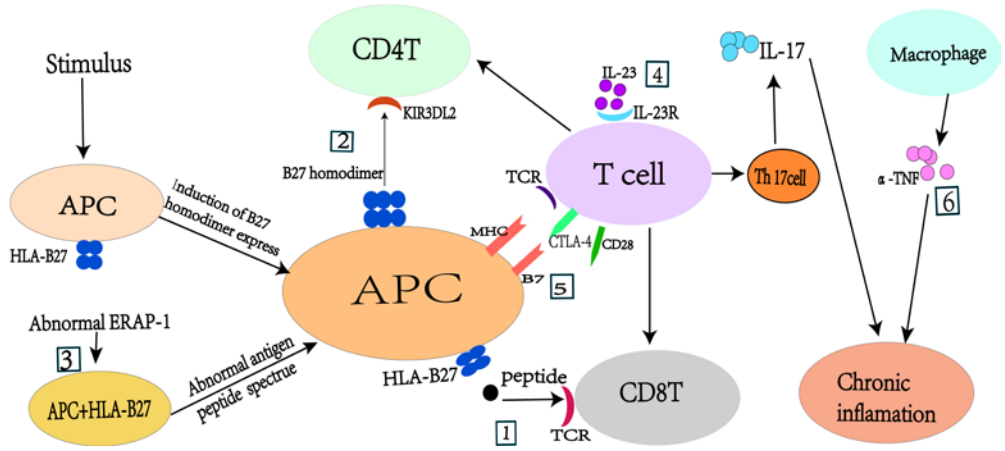

Figure 1. Molecular Mechanism of Ankylosing Spondylitis

1. HLA-B27 on APC binds to peptide and activates CD8+T cells.
2. HLA-B27 folds abnormally on the surface of APC to form homologous dimer and binds to the killer immunoglobulin-like receptor 3DL2 (KIR3DL2).
3. ERAP-1 is involved in the processing of antigen peptide presentation. Abnormal ERAP-1 produces abnormal antigen peptide spectrum, resulting in abnormal expression of HLA-B27.
4. IL-23 promotes the polarization of activated T cells to the helper Th17 cells and induces the production of IL-17A by T helper 17 cells.
5. T cell activation requires the co-stimulation of CD28 and CTLA-4. CD28 activates T cells, while CTLA-4 inhibits T cell activation by competing with CD28 for B7.
6. TNF-α is secreted by macrophages and has pro-inflammatory effects.

Table1: **Ankylosing spondylitis associated gene polymorphism**

Gene	Polymorphism	Mechanism	Result	References
HLA-B27	HLA-B27:05 B27:09 B27:04 B27:02	HLA-B27 on APC binds to peptide and activates CD8+T cells. HLA-B27 folds abnormally on the surface of APC to form homologous dimer that binds to KIR3DL2.	HLA-B27:09 is not correlation with the incidence of AS. HLA-B27:04, HLA-B27:05 and HLA-B27:02 has the strongest correlation with AS in Beijing population.	5-9
ERAP-1	rs27434 rs275825 rs30183 rs27044	ERAP-1 takes part in the presentation of antigen peptide, pruning the peptide to the appropriate length of antigen presentation and then transferring to the cell membrane to activate the immune response.	rs27434 and rs275825 polymorphisms of ERAP-1 are associated with AS. rs30183 and rs27044 have no correlation with AS in Chinese Han population.	5, 10-12
IL-23R	rs1004819 rs1495965 rs2201841 rs10489629	IL-23 produced by monocytes and dendritic cells, promotes the polarization of activates T cells to helper Th17 cells and induces IL-17A.	rs1004819, rs1495965 and rs2201841 are susceptible to AS. rs10489629 gene is decreased in AS.	13-15
CTLA-4	-318*C/T +49*A/G CT60	T cell activation requires the co-stimulation of CD28 and CTLA-4. CD28 activates T cells, while CTLA-4 inhibits T cell activation.	There is no correlation between CTLA-4+49A/G, CTLA-4-318T/C polymorphisms and the AS. The CT60*G allele increases the risk of AS in HLA-B27 negative group.	16-19
TNF-α	TNF-α-308 TNF-α-238 TNF-a-1211c	TNF is secreted by macrophages and regulated by TNFR1 and TNFR2.	TNF-a-1211c and TNF-α-308 reduce the risk of AS, but TNF-α-238 is not associated with AS.	20-24

6. Other genes

In addition to the above genes, there are many other susceptible genes associated with the development of AS. *IL-10* gene is located in 1q31, and its *819C/T* polymorphism is significantly correlated with AS, *but 592 C/A* polymorphism is not correlated with AS (25). By analyzing the polymorphism of *PON 1* gene *rs662* and *rs854560*, it is found that the GG genotype and G allele of *rs662* polymorphism are closely related to the increased risk of AS, but the *rs854560* polymorphism is not associated with the onset of AS in Chinese Han population (26). The polymorphism of *PON1 rs662* gene can inhibit the activity of *PON1* and lead to the pathogenesis of AS. AS is also associated with Toll like receptor 4 (*TLR-4*) gene, transforming growth factor β1 (*TGF-β1*) and cytochrome P450 2D6 *(CYP2D6*). However, at present, the number of gene studies is small, and needs to do a lot of researches to verify it.

Conclusion

As a genetic associated disease, AS is closely related to many genes, such as *HLA-B27*, *ERAP-1*, *TNF-α*, *IL-23R* and *CTLA-4*. This review summarizes the mechanisms of these genes and draws the pictures above. In addition to genetic factors, AS may also be related to immunity, environment, drugs and infection and so on. We also need more and further studies of the polymorphism of AS susceptibility gene to understand the pathogenesis of AS, which can provide many new ways for the diagnosis and treatment of AS. It can also be used in accordance with the characteristics of gene polymorphism to make the clinical treatment individualized. It is also expected to find new susceptibility genes through many researches to provide more beneficial methods for clinical

diagnosis and treatment of AS.

Declarations

1) ***Consent to publication***
We declare that all authors agreed to publish the manuscript at this journal

based on the signed Copyright Transfer Agreement and followed publication ethics.

2) ***Ethical approval and consent to participants***
Not applicable.

3) ***Disclosure of conflict of interests***
We declare that no conflict of interest exists.

4) ***Funding***
None

5) ***Availability of data and material***
We declare that the data supporting the results reported in the article are available in the published article.

6) ***Authors' Contributions***
Authors contributed to this paper with the design (SL), literature search (SL), drafting (SL), revision (SL and YMW), editing (SL and YMW) and final approval (SL).

7) ***Acknowledgement***
None

8) ***Authors' biography***
None

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