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The Association Between MODY and the Immune System

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Abstract:

This article explores the relationship between maturity-onset diabetes of the young (MODY) and the immune system. MODY is a monogenic form of diabetes characterized by autosomal dominant inheritance. To date, 11 causative genes have been identified, and mutations in each gene lead to different MODY subtypes with distinct clinical manifestations. Studies have shown that some patients with MODY may present with positive autoimmune markers; however, the presence of these markers is more often related to environmental influences or coincidental factors rather than being directly caused by specific genetic mutations. Certain MODY patients may also exhibit immune dysfunction. For example, patients with DNAJC3 mutations may present with diabetes, neurodegenerative changes, hearing loss, and hypothyroidism. Genetic testing is the key tool for diagnosing MODY and is essential for achieving early diagnosis and precision treatment. Future studies will further investigate the molecular mechanisms of MODY and the associated immune abnormalities, thereby providing a basis for personalized therapy.

Keywords: maturity-onset diabetes of the young (MODY) ; Auto-immune; Diabetes; Molecular mechanism.

1. Genetics and Clinical Characteristics of MODY

1.1 Genetic Background

MODY is a monogenic form of diabetes inherited in an autosomal dominant pattern. At present, 11 genes associated with MODY have been identified, including HNF4A, GCK, HNF1A, IPF1, and HNF1B [1]. Mutations in these genes give rise to different MODY subtypes, each with its own characteristic clinical manifestations and treatment responses [2,3]. For example, mutations in the GCK gene cause MODY2, which typically presents with mild hyperglycemia. Patients with this subtype usually do not require insulin therapy and instead manage blood glucose through lifestyle modification [5]. By contrast, mutations in HNF1A cause MODY3, which is characterized by severe impairment of insulin secretion and early-onset diabetes. Patients with this subtype may require insulin therapy because pancreatic β-cell function is substantially compromised [6].

1.2 Clinical Features

The clinical manifestations of MODY are heterogeneous and may include early-onset diabetes, pancreatic exocrine insufficiency, kidney disease, reproductive abnormalities, and intellectual disability. The occurrence of these manifestations is not only related to the underlying genetic mutations but may also be influenced by environmental factors. Some MODY patients may also present with other systemic disorders, such as immune deficiency or hearing loss.

One case reported in the literature described a 7-year-old girl diagnosed with both MODY2 and type 1 diabetes. Genetic testing confirmed an L134P mutation in GCK, and she also had a high-risk HLA background. During follow-up, she not only developed type 1 diabetes but also manifested obesity-related metabolic syndrome. This case suggests that MODY patients may simultaneously display multiple

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metabolic and immune-related features [7,8].

2. The Association Between MODY and the Immune System

2.1 Autoimmune Markers

Some patients with MODY may test positive for islet-cell autoantibodies, which are traditionally regarded as a hallmark of type 1 diabetes mellitus (T1DM). For example, the literature describes a 7-year-old girl diagnosed with both MODY2 and T1DM [9,10]. Genetic testing confirmed an L134P mutation in GCK, and she carried a high-risk HLA profile. However, the occurrence of autoantibodies in MODY patients is generally considered coincidental rather than the result of a distinct genetic cause. Studies cited in the literature have shown that the frequency of autoimmune-associated genes is not increased in MODY patients, suggesting that the presence of autoimmune markers in MODY is more likely related to environmental influences or chance rather than being directly caused by specific pathogenic mutations.

2.2 Immune Dysfunction

Certain MODY patients may also present with severe immune dysfunction. For example, patients carrying DNAJC3 mutations may exhibit not only diabetes but also neurodegenerative abnormalities, hearing loss, and hypothyroidism [9,11]. These immune abnormalities may be linked to the pathogenesis of MODY, although the precise mechanisms remain unclear. The literature suggests that DNAJC3 mutations may induce endoplasmic reticulum stress, thereby impairing pancreatic β-cell function. This stress response may further trigger abnormal immune activation, eventually leading to diabetes and other associated clinical manifestations.

2.3 PTPN22 Gene Polymorphism

The PTPN22 gene encodes lymphoid tyrosine phosphatase (LYP), which is mainly expressed in lymphoid tissues and is associated with the development of autoimmune diseases [7]. Studies have shown that the frequency of PTPN22 polymorphisms in MODY patients is similar to that in healthy controls, indicating that autoimmune-associated gene frequencies are not increased in MODY [7,8].

Nevertheless, certain PTPN22 variants may be more prevalent in specific regional populations, possibly owing to local environmental factors or genetic background. For instance, studies have reported that the frequency of the c.788G>A variant of PTPN22 is significantly increased in Czech and Brazilian MODY populations. Interestingly, this variant behaves as a loss-of-function mutation in T cells, thereby potentially protecting against autoimmune attack [11].

3. Diagnosis and Treatment of MODY

3.1 Importance of Genetic Testing

Genetic testing is the cornerstone of MODY diagnosis. Through next-generation sequencing (NGS), pathogenic variants in MODY-related genes can be identified, enabling early diagnosis and precision treatment [12]. Genetic testing not only allows accurate classification of the MODY subtype but also provides individualized therapeutic guidance.

For example, some MODY subtypes respond well to sulfonylureas, whereas others may require insulin therapy. By identifying the causative mutation, clinicians can better predict treatment response and choose the most appropriate management strategy.

3.2 Treatment Strategies

Treatment strategies for MODY vary according to the genetic subtype. Some forms of MODY respond favorably to sulfonylureas, whereas others may require insulin therapy.

For example, patients with GCK-MODY2 generally do not require insulin and instead control blood glucose through lifestyle modification [4,13]. In contrast, patients with HNF1A-MODY3 may require insulin because of severe pancreatic β-cell dysfunction. Moreover, in MODY patients with immune abnormalities, a more comprehensive treatment approach may be necessary, including immunomodulatory agents and lifestyle intervention. For example, patients with DNAJC3 mutations may require not only diabetes treatment but also therapy for neurodegenerative manifestations and hearing impairment [14].

4. Future Directions

4.1 Precision Medicine

Future studies will increasingly rely on laboratory testing and genetic analysis to achieve more accurate patient stratification and treatment. Through genetic testing and bioinformatics, the molecular mechanisms of MODY can be better understood, thereby supporting personalized treatment strategies.

For example, by analyzing genetic variants and metabolic features in MODY patients, therapies targeting specific mutations may be developed, improving treatment efficacy while reducing adverse effects. Precision medicine may also facilitate the identification of high-risk MODY populations, thereby enabling early intervention and prevention.

4.2 Research on Immune Mechanisms

Further studies are needed to investigate immune dysfunction in MODY patients and to clarify its relationship with diabetes pathogenesis. For example, it remains important to determine how DNAJC3 mutations affect immune system function and how this contributes to the development of diabetes.

A deeper understanding of the immune mechanisms involved in MODY may lead to the development of novel therapies, including immunomodulatory drugs and gene therapy. In addition, research on immune markers and inflammatory responses in MODY patients may help clinicians monitor disease progression and assess treatment efficacy more effectively.

5. Conclusion

MODY is a monogenic form of diabetes with diverse clinical manifestations and genetic backgrounds. Although MODY patients may show positive autoimmune markers, the appearance of these markers is usually considered coincidental rather than being caused by distinct genetic mechanisms. Genetic testing remains the key diagnostic tool for MODY and is essential for early diagnosis and precision treatment.

Future research will continue to explore the molecular basis of MODY and its associated immune abnormalities, thereby providing a stronger foundation for individualized treatment. Through these studies, we will gain a better understanding of MODY pathogenesis and develop more effective therapeutic approaches, ultimately improving the quality of life of patients with MODY.

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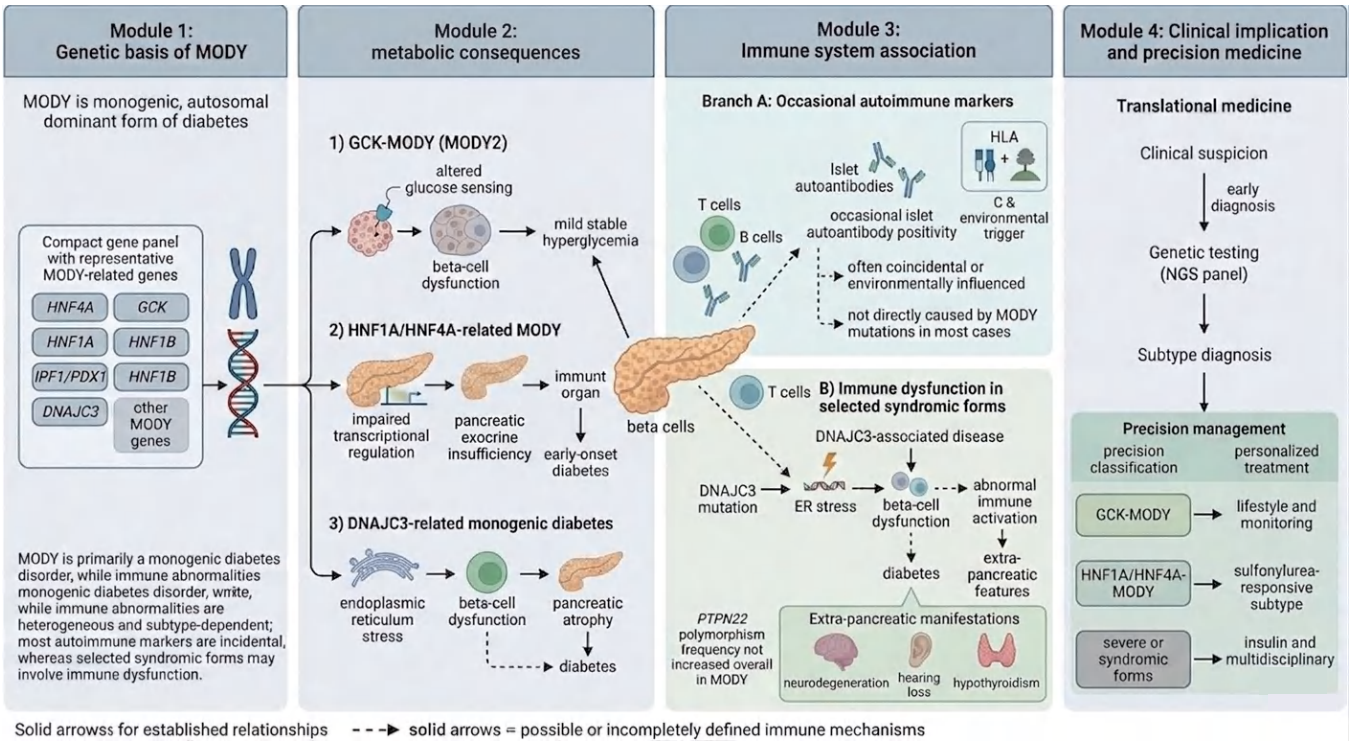

Figure 1. Schematic overview of SASP: sources of senescent cells, major SASP components, tissue heterogeneity, systemic propagation, and intervention strategies (senolytics/senomorphics). (Graphical Abstract)