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Review

Towards personalized medicine for patients with autoimmune diseases: Opportunities and challenges

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ABSTRACT

There is generally no cure for autoimmune disorders, but the symptoms can be managed. Currently available drugs/treatments are more potent than those in the past decades. However, finding the right drug and right patients has remained a serious problem. We should revise our diagnosis criteria to more accurate ones. During the recent years, personalized medicine has attracted much attention. However, it needs to be well-explained for autoimmune diseases. Personalized medicine aims to find the most optimum drugs for a patient. Hence, recognizing the drugs based on genetics and molecular profile of patients, needs a comprehensive protocol. This study attempted to discuss the most practical and effective ways for identifying right patient and right drug. Patients should be divided into subpopulations. According to the last diagnosis criteria and therapeutic options, it was attempted to highlight the gaps or contradictions in current understanding and suggest what the future of research in this area may hold. Various factors could be considered, including genes variants, genes expression, epigenetic alterations, immune responses, and also basic and obvious characteristics (sex, age, ethnic, etc.). Moreover, advantages, disadvantages, obstacles, and opportunities during the personalized medicine for autoimmune diseases have been discussed in great detail. Finally, creation of a global library that covers all the aspects of personalized medicines for different types of autoimmune disease was suggested. In conclusion, revising diagnosis and treatments of autoimmune diseases toward personalized medicine could be the revolutionary step for having more effective and safer therapeutic options.

1. Introduction

Every day, millions of people are taking medications that seem to be helpful, but will not help them. It is also possible that those drugs lead into development of serious new conditions, which make the previous disease more complicated. These tragedies occur more severely in patients with autoimmune diseases. Indeed, because of heterogeneity of these diseases, there is no universal consensus associated with the treatment. There are more than 80 autoimmune conditions, which could not be cured, while the symptoms can be well-managed in the presence of efficient treatment protocol. Despite the fact that one treatment does not fit all, majority of patients with autoimmune diseases are managed with the same limited immunosuppressants. Following emergence of different biological drugs that target some specific signaling pathways such as monoclonal antibodies, most of the patients are receiving these drugs in a relatively blind way. Indeed, almost no reliable predictor of treatment response has been identified that could be considered before initiation of treatment for autoimmune diseases. This has led to contradictory results associated with drugs efficacy. Tumor necrosis factor-α (TNF-α) inhibitors are the examples, which have been reported to be associated with inadequate response or intolerance in some patients with certain types of autoimmune diseases [1]. Moreover, it was demonstrated that psoriatic lesions can be induced by anti-TNF drugs in some of patients with inflammatory bowel disease [2]. One of the other widely used biological drugs is rituximab, an anti-CD20 monoclonal antibody, which is used in different autoimmune conditions, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and pemphigus [3]. Although rituximab depletes B cells in nearly all the patients, not all of them respond to this drug [72]. Moreover, exacerbation of disease has been reported in patients with pemphigus, once they received rituximab [4,5]. These contradictory results in patients with the same diagnosis of disease may be a confirmation for heterogeneity of autoimmune diseases, which are probably different in the governing signaling pathways. In most of the autoimmune diseases, some clinical manifestations, serum autoantibodies, and pathology findings are used to categorize disease into

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different variants. However, that is not the whole story. In fact, those who seem to meet similar criteria, based on the mentioned approaches do not essentially fall into a same variant. Indeed, they may have completely different signaling pathways underlying the disease, which lead to same outcome. On this condition, it is not surprising that patients do not respond to treatments equally. Hence, our criteria for determining variants of autoimmune diseases should be revised toward more specific ones.

In order to avoid finding the optimum treatment in a trial, it is essential to have some biomarkers as the predictor of response to treatment to consider for selecting the optimum drug for the patients. Personalized medicine was defined by the personalized medicine coalition (PMC) as an evolving field to use diagnostic tests to determine which medical treatments will work best for each patient. Indeed, it aims recognizing environmental and immunological background, and epigenetic ecology as well as genetic and molecular landscape effects on the treatment response. Accordingly, more effective treatments could be employed. These approaches could be used in a wide range of diseases, including cancers, transplantation, allergic diseases, and autoimmune diseases. However, this study has focused on approaches for defining new autoimmune diseases variants as well as proper biomarkers to find the optimum treatment with highest efficacy and least side effects for these diseases.

2. Possible signaling pathways associated with autoimmunity

Before suggesting any potent treatments or therapeutic approaches, it is essential to uncover the signaling pathways involved in the disease. This is even more critical in highly heterogeneous diseases, such as autoimmune diseases and cancer. Generally, it has been accepted that autoimmune diseases are developed following breaking of central tolerance and peripheral tolerance [6]. Thus, it is expected that several players, from the primary lymphatic organs to several other organs and tissues be involved in the autoimmunity. Those T cell and B clones that may escape negative selection are essential for autoimmunity. Thereby, an error during expression of tissue-specific self-antigens by autoimmune regulator (AIRE) could initiate autoimmunity [7,8]. For example, a mutation in AIRE gene is followed by dysfunction of this critical protein and leads to the multi-organ syndrome [9]. However, escape of auto-reactive T cells and B cells during the negative selection does not necessarily result in autoimmunity. In fact, some other factors are needed for development of autoimmune disease. Various studies have shown that auto-antibodies could be detected in serum of normal individuals with no clinical manifestation of autoimmunity [10,11]. This paradox could be easily explained by the peripheral tolerance, which supress the auto-reactive cells. Peripheral tolerance prevents autoimmunity through different mechanisms, including direct inactivation of effector T cells, conversion to regulatory T cells (Tregs) or induction of anergy [12]. Accordingly, even in presence of auto-reactive lymphocytes, an effective alteration mechanism is available.

Several factors could determine the efficacy of peripheral tolerance, including different cytokines, transcription factors, co-stimulatory/co-inhibitory molecules, and microRNAs. For example, TGF-β, IL-10, and IL-35 are well-known cytokines, which cause development and protection of regulatory T cells [13]. FoxP3 or CTLA-4 and PD-1 are well-known examples of transcription factors and surface molecules which are associated with regulatory responses [13]. Clearly, any dysfunction in these factors could be a risk of autoimmunity. Additionally, over expression of some miRNAs, which cause silencing and post-transcriptional regulation of expression of any genes associated with mentioned proteins, may lead to breaking of peripheral tolerance. Down-regulation or up-regulation of regulatory inducers or effector players, respectively, which may be due to different reasons, such as mutation of over-active effector cells, and inflammatory responses, could interfere with peripheral tolerance. It is also possible that a mutation in genes associated with self-antigens, or molecular mimicry, where a foreign antigen shares sequence or structural similarities with self-antigens causes the self-antigens to be recognized as foreign by immune cells [14]. Ross [15] has hypothesized that immune responses against the proteins whose DNA sequence mutates somatically could be involved in development of several autoimmune diseases. The bad news regarding treatment of autoimmune disease is that no practical solution is available for restoring the central tolerance or mutation in self-antigen until now. However, the encouraging one is that lost peripheral tolerance could be restored relatively through different signaling pathways, which were discussed by the author, such as inducing regulatory responses [16–20] or inhibiting responsible immune cells [21–25]. However, it is important firstly to recognize responsible players to be reversed. For example, if one of the cytokines, (e.g. IL-12) is being overproduced and is identified as a possible reason for breaking peripheral tolerance, targeting this cytokine via a proper treatment, (e.g. ustekinumab) may be effective in restoration of immune tolerance. Unfortunately, it seems than even if one factor is the first initiator of aberrant immune responses; several other signatures of the immune response could be detected, which is confusing. Interestingly, from the therapeutic experiences, it could be learned that inhibiting the majority of these signature could mitigate disease. However, recently, I have proposed that targeting the dominant response may not necessarily improve the alopecia areata, which may be true for other autoimmune conditions [24]. In order to find the main responsible factor and employ the most proper therapy, some other approaches could be suggested, all of which will be discussed in the rest of the manuscript.

3. Patients with autoimmune diseases do not respond to treatments equally: what can be learned?

Because autoimmune diseases are considered as the heterogeneous diseases, it is not surprising that patients do not respond to the treatments uniformly. The most commonly used drugs in treatment of those with autoimmune diseases is corticosteroids, which have been shown a very promising therapy, but are associated with several serious adverse events. Hence, some patients may not tolerate corticosteroids therapy. Additionally, there are several types of adjuvants, the efficacy and safety of which varies in a wide range from person to person [26,27]. This is also true for some new biological treatments that act in a very specific way [28–31]. From these data some lessons could be learned. Firstly, these different rates of responses may be due to various signaling pathways involved in tolerance breakage as well as numerous governed responses in different patients. In fact, a certain autoimmune disease may have different underlying molecular signaling pathways, which lead to the same phenotype. Secondly, an effective approach of treatment is not necessarily beneficial for other patients. On the other words, one drug/treatment does not fit all.

According to the current approaches, the best treatment for every patient is usually recognized through trial and error observation. Unfortunately, these methods need a very long time to reach a fairy reasonable conclusion, while patients do not receive optimal treatments. Moreover, patients probably experience several adverse events or even develop different other life-threating diseases, such as other autoimmune diseases (e.g. psoriasis) [2], neoplastic diseases (with prolonged use) [32,33], and even exacerbation of the current disease (e.g. pemphigus) [34]. Accordingly, it is important to distinguish patients, based on prediction of drug responses through more intelligent approaches. Although there are some pharmacogenomics (PGx) studies associated with predicting response to therapy in different autoimmune diseases [35–38], it is essential to employ those results to create a global database, which covers all the aspects of personalized medicine and suggests the most optimum drug(s).