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Targeting the humoral immune system of patients with rheumatoid arthritis

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Chapter 12

Anticyclic citrullinated peptide
antibodies: the footprint of autoreactive
plasma cells in synovium?

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Abstract

The presence of circulating anticyclic citrullinated protein antibodies (ACPAs) is a very specific finding in patients with rheumatoid arthritis (RA). A key question is whether ACPAs are pathogenic autoantibodies or merely bystander products. While studies have demonstrated local production of ACPAs in inflamed tissues, it has not yet convincingly been shown that ACPAs are indeed pathogenic autoantibodies, especially not when put in perspective of other known pathogenic autoantibodies. Autoantibodies are produced by plasma cells and it has long been known that plasma cell infiltration in synovium is commonly found in RA patients. In this review we summarize the evidence that (autoreactive) plasma cells may be involved in RA. A better understanding of the biology of plasma cells in RA may open new avenues for treating RA.

Introduction

Autoimmune diseases are chronic inflammatory illnesses of unknown etiology, commonly accompanied by the presence of circulating autoantibodies¹. A returning subject of many investigations is the question whether autoantibodies are pathogenic or merely bystander products of an abnormal immune response. Criteria have been proposed to determine whether an autoantibody is pathogenic². First, a plausible mechanism of action is required for autoantibodies to be called pathogenic. Second, pathogenic autoantibodies should be capable of causing the lesions attributed to autoimmune disease. Third, immunization should lead to the production of similar autoantibodies and eventually to a similar disease process. Fourth, pathogenic autoantibodies should be found along with the putative autoantigen at the site of tissue inflammation. Fifth, autoantibody levels and disease activity should correlate. And last, the removal of the autoantibodies, when possible, should ameliorate the disease process.

In the present review, the significance of autoantibodies directed against citrullinated proteins (ACPs) in patients with rheumatoid arthritis (RA) is discussed in the context of the criteria mentioned above. We particularly focus on a possible pathogenic role for autoreactive plasma cells in RA as the cellular origins of autoantibodies, viewed in a wider context of autoantibody-mediated conditions.

Scope on pathogenic autoantibodies

RA is a systemic autoimmune disease characterized by symmetrical joint involvement due to synovial inflammation, leading to joint erosions and deformities¹. Since the identification of citrullinated epitopes³ as a target for several autoantibodies found in RA patients, many reports have demonstrated that ACPs are a specific finding in RA patients⁴⁻⁸. The biological and immunological relevance of ACPA remains to be determined, however. In this regard, it is useful to briefly consider other autoantibodies that are generally accepted to be involved in disease pathogenesis. Examples of pathogenic autoantibodies are summarized in Table 1. Below, we briefly expand on anti-epidermal antibodies in pemphigus, an organ-specific autoimmune disease characterized by generalized blistering of the skin⁹, and autoantibodies against double-stranded DNA in

systemic lupus erythematoses (SLE)¹⁰. These autoantibodies were chosen to illustrate current concepts about their pathogenicity in view of the previously described criteria.

In pemphigus (foliaceus and vulgaris types), autoantibodies against desmoglein play a major role in the induction of the blistering of skin and mucous membranes through the loss of intracellular adhesion¹¹. Studies using direct immunofluorescence have shown that immunoglobulins are bound to the epidermal cell surface in virtually all patients⁹. Passive transfer of serum from patients led to acantholysis in epidermal cell cultures and transfer to neonatal mice reproduced blistering disease, clinically, histologically and immunologically^{12,13}. The observation that disease could also be passively transferred by Fab-fragments of anti-epidermal antibodies indicated that the mere binding of the autoantibodies to the desmoglein target was sufficient for induction of disease¹⁴. Moreover, children of mothers with pemphigus may develop transient disease due to maternal antibodies crossing the placenta^{15,16}. The level of antidesmoglein antibodies correlates with disease activity¹⁷ and the removal of these antibodies by plasmapheresis leads to clinical improvement¹⁸. Additionally, newer therapies, such as treatment with anti-CD20 monoclonal antibodies, have recently been shown to be clinically effective and reduce antidesmoglein autoantibody levels^{19,20}. Altogether, there is convincing evidence that antidesmoglein antibodies are the pathogenic source of pemphigus disease, even though it is controversial whether antidesmoglein autoantibodies in themselves directly cause the loss of adhesion⁹.

In SLE, generally viewed as the prototype systemic autoimmune disease, there is supporting evidence for a pathogenic role of several autoantibodies, including anti-DNA autoantibodies, anti-Ro antibodies and antiphospholipid antibodies. Recent studies have demonstrated the arrhythmogenic potential of anti-Ro autoantibodies²¹⁻²³. Also, the close epidemiologic association between antiphospholipid autoantibodies and thrombosis²⁴ has been experimentally corroborated showing that these autoantibodies were associated with a significant increase in thrombus size and a delay in thrombus dissolution²⁵. However, the largest body of evidence has been produced on autoantibodies against double-stranded DNA (anti-dsDNA antibodies) based on the correlation of circulating levels of anti-dsDNA autoantibodies with disease activity^{26,27}. Furthermore, the

Table 1 Overview of systemic and organ-specific autoimmune diseases and their pathogenic autoantibodies*

Autoimmune Diseases	Target Organ(s)	Target(s) of pathogenic autoantibody*
Rheumatoid arthritis	Joints	Citrullinated proteins, Rheumatoid factor
Systemic lupus erythematosus	Systemic	Double stranded DNA, nuclear residues: SSA/Ro, SSA/La, phospholipids
Sjogren's syndrome	Salivary gland	Nuclear residues: SSA/Ro, SSA/La
ANCA-associated vasculitis	Vasculature	Myeloperoxidase (MPO) and proteinase 3 (PR3)
Antiphospholipid syndrome	Vasculature	Phospholipids
Idiopathic thrombocytopenia	Platelets	Platelets
Guillain-Barre syndrome	Peripheral nervous system	Myelin, monosialogangliosides
Autoimmune thyroiditis	Thyroid gland	Thyroid-stimulating hormone (TSH) receptor
Pemphigus vulgaris	Skin, mucous membranes	Desmoglein
Myasthenia gravis	Skeletal muscle	Acetylcholine receptor
Type I diabetes	Pancreatic islet cells	Pancreatic islets of Langerhans
Addison's disease	Adrenal gland	21-hydroxylase enzyme
Goodpasture's syndrome	Lung, kidney	Glomerular basal membrane (GBM)
Pernicious anaemia	Stomach	Parietal cells, intrinsic factor
Primary biliary cirrhosis	Liver	Mitochondrial autoantigens
Dermatomyositis-polymyositis	Skeletal muscle, skin	Aminoacyl tRNA synthetase, signal recognition particle (SRP), nuclear helicase (Mi-2)
Celiac disease	Small intestine	Gliadin, endomysium (tissue transglutaminase)

* Autoantibodies that are currently considered to associate with the etiology of their corresponding disease but not necessarily fulfill all the criteria for pathogenicity.

ANCA: Antineutrophil cytoplasmic antibody; tRNA: Transfer-reactive nitrogen species.

combination of high anti-dsDNA levels and consumption of complement factors are diagnostic for SLE¹⁰. In addition, anti-dsDNA autoantibodies were demonstrated to bind directly to the glomerular basement membrane of the kidneys²⁸, linking these autoantibodies to the pathogenesis of lupus nephritis. However, it is unclear whether the anti-dsDNA autoantibodies bind directly to the glomerular membrane or are deposited in the membrane through immune complex formation. Passive transfer of lymphocytes from lupus patients to severe combined immune-deficient (SCID) mice did not induce glomerulonephritis, although antinuclear antibodies and deposition of IgG and complement in the kidney could be detected^{29,30}. Importantly, the clinical outcome in SLE patients with severe nephritis did not improve after plasmapheresis^{31,32}. The merit of B-cell depleting therapies is currently being investigated^{33,34}. Recently, Anolik *et al.* reported that rituximab treatment did not eliminate anti-dsDNA autoantibodies in all SLE patients³⁵. Overall, it can be concluded that anti-dsDNA autoantibodies are related to nephritis in SLE patients, but may not in themselves explain all SLE-related symptoms.

In summary, only a limited number of autoantibodies will meet the criteria for being pathogenic, of which the antidesmoglein autoantibody in pemphigus seems to fulfill most criteria. In systemic autoimmune diseases in particular, autoantibodies alone do not explain all clinical symptoms.

A pathogenic role for ACPAs in RA?

ACPAs are directed against the citrulline residue of citrullinated proteins. Citrulline is an amino acid that is not incorporated into proteins during mRNA translation but can be generated by post-translational modification of arginine residues by peptidylarginine deaminase (PAD-)enzymes³⁶. Therefore, an intrinsic characteristic of ACPAs is the recognition of different peptides containing citrulline, such as citrullinated fibrinogen (i.e. antiperinuclear factor [APF] and antikeratin autoantibodies [AKA], collectively named anti-fibrinogen autoantibodies)³⁷ and citrullinated vimentin (anti-Sa)³⁸. Citrullination of extracellular proteins such as fibrin, which is commonly present in chronically inflamed joints, can occur when PAD-enzymes are released from cells that undergo apoptosis, also a common process in inflamed synovium³⁹. Several studies have reported

the presence of citrulline residues and ACPAs in synovium^{5,40}. Moreover, two studies demonstrated the production of ACPAs in synovial explants^{41,42} while other reports showed higher levels of ACPAs in synovial fluid as compared with serum^{39,43-45}. Collectively, these studies clearly indicate that ACPAs are present at the site of inflammation in RA patients (although not excluding other sources) and that they are targeted against antigens generated through a plausible mechanism.

However, whether ACPAs themselves can cause tissue inflammation and erosive disease in RA patients remains to be determined. It has been demonstrated in several studies that RA patients with ACPAs had a more progressive disease⁴⁶⁻⁴⁹, at least suggesting a role of ACPAs in joint destruction. A recent study showed a moderate correlation between ACPA levels and radiological erosion scores⁵⁰, but an association between ACPA levels and disease activity has not yet been found⁵¹. Additionally, elimination of ACPA by plasmapheresis has not been reported. Still, it is intriguing that the presence of ACPAs was demonstrated years before symptoms of joint inflammation became clinically overt^{52,53}. Also, in a collagen-induced arthritis model, ACPAs were demonstrated before the development of experimental arthritis and induction of tolerance for citrulline was associated with lower disease severity⁵⁴. These reports indicate that the presence of ACPAs in serum is intrinsically related to clinical symptoms of arthritis.

Further support for the pathogenic role of ACPAs in RA can be deduced from studies evaluating ACPA levels in effectively treated RA patients. Of special interest is the recent introduction of B-cell depleting therapies in RA. Treatment with rituximab, an anti-CD20 monoclonal antibody, was shown to be clinically effective in RA⁵⁵⁻⁵⁷ and increasing in ACPA levels after treatment preceded clinical relapse⁵⁸. However, several reports demonstrated only moderate effects on ACPA levels despite good clinical effect^{59,60}. Along the same lines, TNF-blocking agents resulted in significant improvements of disease activity but, although controversial, the majority of studies did not show large reductions of circulating ACPA autoantibodies^{8,61-64}. Also for conventional DMARD treatment, reduction in levels of circulating ACPAs were modest albeit statistically significant⁶⁵. Taken together, these studies show that a reduction or eradication

of ACPAs is not a prerequisite for clinical improvement of RA, it remains unknown whether ACPAs are responsible for the chronicity of RA symptoms.

In summary, there is ample evidence that ACPAs can be detected and are produced at the site of joint inflammation in RA patients. ACPAs are specific for RA and are associated with disease progression and worse outcome. However, firm evidence that ACPAs themselves are pathogenic agents in the disease processes of RA patients still needs to be provided. As a consequence, it is evident that the cellular origin of autoantibodies, for instance, autoreactive plasma cells, needs closer attention, especially because the production of ACPAs remains a very specific finding in RA patients.

Synovial plasma cell infiltration is related to disease activity in rheumatoid arthritis

Because ACPAs are produced by (autoreactive) plasma cells, it is logical to assume that plasma cells have a role in RA pathogenesis. Although no study has yet reported the existence of ACPA-specific producing plasma cells (probably due to technical limitations), several studies independently reported that plasma cells are a specific finding in the synovium of RA patients. The presence of plasma cells in synovial biopsies of arthritic patients was observed to have a specificity of 72% for RA diagnosis⁴⁰ and a high degree of plasma cell infiltration was able to correctly diagnose RA in approximately 85% of patients with early arthritis^{66,67}. Moreover, RA synovium showed a gradual increase in plasma cell infiltration when developing from an acute to subacute and finally chronic synovitis⁶⁸. Overall, these data indicate that plasma cell infiltration is a very specific finding for RA, notably in chronic, longstanding disease. It is therefore worthwhile to consider the body of evidence concerning the role of plasma cells in the pathogenesis of RA, as summarized below.

When addressing plasma cell biology, it is important to realize that the immunobiology of life-long humoral immunity against pathogens in man is still subject of continuous debate^{69,70}. Two concepts are currently competing, but not mutually exclusive: in the first model, memory is mediated through polyclonal bystander activation of memory B-cells leading to maintenance of serum antibody

concentrations of various antigen specificities⁷⁰. In the second model, memory depends on the continuous competition for survival niches between newly formed plasma cells and ‘older’, resident plasma cells⁶⁹. The concept of survival niches is supported by a vast array of studies showing that the survival and function of plasma cells is dependent upon their environment⁷¹⁻⁷⁴. Nevertheless, our understanding of the physiological processes that govern the homeostasis of plasma cells is still poor and, consequently, their role in autoimmune disease is even less well-defined. Therefore, in order to clarify the possible relationship between synovial plasma cell infiltration and RA pathogenesis, we approached this issue by answering the following pivotal questions: a) is inflamed synovium an adequate survival niche for plasma cells? b) as plasma cells can specifically be found in RA patients, can plasma cells either be generated locally or migrate into inflamed synovium? and c) does adequate, immunosuppressive treatment for RA also have detrimental effects on synovial plasma cells?

First, to demonstrate that inflamed synovium is an adequate survival niche, it is important to know that there is a wide array of studies showing that several signals, alone or in synergism, can support the survival of plasma cells in bone marrow^{72,75,76}. These signals include, among many more, chemokine receptor-ligand-12 (CXCL-12), TNF, IL-5, IL-6, B-lymphocyte activating factor (BAFF) and a proliferation-inducing ligand (APRIL), all produced in high concentrations in inflamed tissues. Not surprisingly, plasma cells can be found at a high degree in inflamed synovium of RA patients^{40,66}. It has been reported that the immune response against recall antigens elicited by lymphocytes from inflamed synovial tissue is limited when compared with the lymphocytes in peripheral blood^{77,78}, suggesting that cellular infiltrates are composed of a selected population of, including possibly autoreactive, plasma cells. Overall, it is well-established that inflamed synovium of RA provides a survival niche for autoreactive plasma cells⁷⁹.

Second, an important issue in unraveling the pathogenic contribution of synovial plasma cells in RA is to determine whether these plasma cells have been generated locally, in inflamed synovium, or have migrated from lymphoid organs to the site of inflammation, or both. In mice, autoreactive plasma cells were shown to survive in virtually every lymphoid organ, including spleen, bone marrow and inflamed tissue. In NZB/W mice, a model for SLE, long-lived

(nondividing) as well as short-lived (dividing) autoreactive plasma cells could be observed in spleen, inflamed kidney and bone marrow of these mice⁸⁰. In collagen-induced arthritis, production of anticollagen autoantibodies was demonstrated in lymph nodes, bone marrow as well as arthritic paws⁸¹. In humans, several studies have demonstrated the formation of large T-cell B-cell aggregates with incidental co-localization of CD21L+ follicular dendritic cells in inflamed synovial tissue⁸²⁻⁸⁵, resembling germinal center-like structures. Because the differentiation to the stage of plasma cell is dependent upon CD70/CD27 interactions^{86,87}, the close interaction between T-cells and B-cells support the hypothesis that plasma cells can be locally formed. Moreover, memory B-cells can be locally generated through the close interaction with T-cells via CD40-CD154 interactions^{88,89}. Both mechanisms create the possibility for local, most likely autoantigen-driven, generation and differentiation of plasma cells. Arguments against the local formation of autoreactive plasma cells in synovium came from studies suggesting that CXCR4 expression on early plasma cells is important for the migration of these cells from lymphoid organs to bone marrow and inflamed tissue⁹⁰⁻⁹², supporting the view that early plasma cells migrate to the site of inflammation. However, it has not yet been shown that terminally differentiated plasma cells also migrate towards inflamed synovium. In this regard, a recent study described the penetration of the cortical barrier by synovial inflammatory at the junction zone (i.e., the insertion site of the synovial membrane into the articular cartilage and periosteum)⁹³. This finding raised the possibility that terminally differentiated plasma cells are able to migrate directly from bone marrow to the inflamed synovium or vice versa. Indeed, this study showed that mature B-cells were the predominant cell type of these periosteal cell infiltrates and found that plasma cells were enriched in this region⁹³, but they were unable to determine whether terminally differentiated plasma cells actually migrated into the synovium. On the whole, the issue of the origin of synovial plasma cells remains unresolved.

Third, our understanding of the pathologic contribution of plasma cells in RA has been augmented by recent data on the effects of immunosuppressive treatment on the infiltration of plasma cells in synovium. Importantly, local formation of plasma cells in inflamed synovium implies that these plasma cells are proliferating cells or dependent upon proliferating cells, making them more susceptible to immunosuppressive treatment than in case of migration of ma-

tured, terminally differentiating plasma cells. Several studies have reported the effects of different antirheumatic treatments on the cellular infiltration in synovium. One study reported on the clinical and biological effects of high-dose chemotherapy (HDC) followed by autologous hematopoietic stem cell transplantation (HSCT)⁹⁴. In the responders to HDC + HSCT, the intensive antiproliferative and immunosuppressive treatment led to reductions in all markers of the synovial cellular infiltrate, including synovial CD138+ plasma cells⁹⁴. Importantly, responsiveness to HDC + HSCT was associated with extensive synovial inflammation before treatment and significant reductions of low-avidity ACPA autoantibodies from the circulation⁹⁵. The latter suggested an association between reduction of synovial plasma cells and the reduction of ACPA autoantibodies. Similarly, TNF-blocking agents significantly reduced CD38+ plasma cells in synovium from patients, naïve or refractory to conventional DMARDs. In this study CD38+ CD138+ double-positive plasma cells were more susceptible to TNF-blocking therapy than activated T-cells that were double positive for CD38 and CD3⁹⁶. Another study evaluating the synovial effects of TNF-blocking agents versus placebo treatment confirmed reductions in CD38+ plasma cells, but also reported significant reductions in intimal macrophages⁹⁷. This was also reported by Gerlag *et al.* demonstrating that oral corticosteroids led to significant reductions not only of sublining macrophages but also of CD38+ cells, presumably plasma cells⁹⁸. These studies illustrate the close relationship between changes in plasma cells and disease activity brought about by immunosuppressive treatments.

It is noteworthy that the above mentioned treatments (DMARDs, corticosteroids, chemotherapy or TNF-blocking agents) not only target plasma cells, and consequently that the observed reductions could merely reflect broad suppression of inflammation. It has already been stated that the survival of plasma cells depends upon environmental conditions. The introduction of cell-targeted therapies with anti-CD20 monoclonal antibodies has recently provided intriguing findings with regard to synovial plasma cells. Two studies investigating the effects of anti-CD20 monoclonal antibodies (rituximab) in synovium demonstrated a reduction in synovial plasma cells after treatment. However, one of these studies showed that the reduction of synovial plasma cells was not a direct effect but a delayed result of local CD20+ B-cell depletion^{99,100}. Importantly, the infiltration of plasma cells, expressing CD79a+ but not CD20 or CD138, pre-

dicted the responsiveness to rituximab treatment in these patients⁵⁹. Collectively, these studies indicate that the survival of plasma cells in synovium, irrespective of them being produced locally or migrating into the synovium, is closely associated with the response to anti-rheumatic treatments.

ACPAs: the footprint of plasma cell activation in synovium

Currently, there is little evidence supporting a direct relationship between circulating ACPA levels and disease activity in RA patients. On the other hand, several studies have demonstrated that elimination of plasma cells in synovium is associated with improvement of disease activity. The latter has not been the case for ACPAs, as it is still unclear why antirheumatic therapies (DMARDs and biologicals) are unable to eliminate ACPA production despite the clinically observed improvements. Together with the observation that synovial infiltration of plasma cells is characteristic for RA patients argues in favor of the hypothesis that ACPA producing cells, not ACPA themselves, play a prominent role in RA.

This hypothesis does not claim that autoreactive plasma cells are the causative cell population for RA. Obviously, the development of long-lived plasma cells is dependent upon T-cell dependent B-cell activation and plasma cell survival is largely dependent upon interaction with the local environment, through soluble factors (cytokines, chemokines) or cell-cell or cell-matrix contact. In a study by Tak *et al.* on the histological effects of anti-CD4 treatment (cM-T412), in patients whose CD4⁺ T-cells were eliminated (and thus also CD3⁺ T-cells), a simultaneous reduction of synovial CD38⁺ plasma cells could be seen¹⁰¹. These results strongly suggested that the survival of synovial plasma cells is T-cell dependent. This is in accordance with recent observations on plasma cells survival in human tonsils¹⁰². However, although plasma cells may not be the sole dysfunctional cell population in RA, it is well appreciated that they can play an important role in the perpetuation of autoimmune disease. Therefore, the assignment of a central role to autoreactive plasma cells in the disease process of RA patients leads to a shift in focus of ACPA-related investigations from questioning ACPA's pathogenicity to unraveling the mechanisms leading B-cells to differentiate into autoreactive, ACPA-producing plasma cells. Consequently,

the fate of these developed autoreactive plasma cells is of high interest. For example, it is as yet unknown whether ACPAs are produced in bone marrow and other lymphoid tissues of RA patients.

Thus, the role of autoreactive, ACPA-producing plasma cells in the pathogenesis of RA remains to be elucidated. It is known that TGF- β mRNA can be expressed by human bone marrow plasma cells¹⁰³, which is known to regulate proliferation, differentiation, and other functions in most cell types. Through the production of cytokines, such as TGF- β , plasma cells may exert some not yet recognized immunoregulatory functions. Also, plasma cells express and actively produce the proteolytic matrix metalloproteinases (MMPs), notably MMP-3 and MMP-9¹⁰⁴. Because MMPs play a pivotal role in tissue remodelling, local infiltrated plasma cells in synovium might be capable of mediating destructive processes characteristic for RA. Additionally, it was recently shown that plasma cells expressed Fc γ -receptor IIB (Fc γ RIIB), through which their survival is regulated. It was also reported that survival of autoreactive plasma cells was prolonged in a mouse model for SLE due to the loss of Fc γ RIIB expression¹⁰⁵. It is conceivable that similar mechanisms are operative in inflamed synovium of RA patients.

Future perspective

In conclusion, plasma cells may prove to have a more central role in RA pathogenesis than is currently appreciated. The pathologic mechanisms involved in the formation and survival of autoreactive plasma cells in RA are largely unknown. For example, while the isotype distribution and the avidity of circulating ACPAs can vary between patients, it is thus far unknown whether the underlying mechanisms for isotype switching and affinity maturation of ACPA-producing cells resemble those of regular antibody-producing cells. Further studies are needed to identify the immunobiology of autoreactive plasma cells. The results of such studies may lead to new and effective treatments to achieve long-lasting control of disease activity in RA.

Executive summary

The role of anticyclic citrullinated protein antibodies in rheumatoid arthritis

- Anticyclic citrullinated protein antibodies (ACPAs) are very specific for rheumatoid arthritis and produced at the site of joint inflammation.
- RA patients seropositive for ACPA have more severe RA.

ACPA in perspective

- When compared with other well-established autoantibody-mediated diseases (pemphigus, systemic lupus erythematoses) the current evidence in favour of ACPAs being pathogenic autoantibodies in RA is pending.

The emerging role of autoreactive plasma cells in RA

- Because ACPA production is a very specific finding in RA, their cellular origins, for instance, autoreactive plasma cells, are increasingly being considered as part of the pathologic processes involved in RA:
- Several studies have established a close relationship between synovial infiltration of plasma cells and disease severity in RA patients.

Conclusions

- Although our understanding of plasma cell biology is still developing, autoreactive plasma cells are potential key players in the maintenance and perpetuation of RA.
- ACPAs may prove to be the footprint of pathologic mechanisms sustaining autoreactive plasma cells in RA patients.

Future perspective

- Unraveling the difference in plasma cell biology between healthy individuals and RA patients will augment our understanding of disease processes in RA. This may lead to new therapeutic strategies.

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