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Reveal Immunological Changes and Coping Strategies of Sandfly Fever Based on Spatio-Temporal Omics

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Abstract: Sandfly fever is a viral infectious disease transmitted by sand flies that is widely prevalent in tropical and subtropical regions. Previous studies on its infection mechanism, immune response and diagnosis and treatment methods were lack of systematic. This study applied spatio-temporal omics technology to comprehensively explain the dynamic changes of immunity in the incubation period, exacerbation period, peak period and recovery period of Sandfly fever, and integrated with different coping strategies. To provide new research ideas for its overall research.

Keywords: Spatio-Temporal Omics; Sandfly Fever; Immunity; Coping Strategies; Virus; Infection

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1.Introduction

Sandfly fever, also known as Sandfly fever, is an acute viral infectious disease caused by a variety of viruses of the genus Phlebovirus in the family Bunyaviridae. It is mainly transmitted by the bite of female sand flies carrying the virus[1]. The disease is similar to Lassa fever, which is mainly transmitted through contact with infected animals, person-to-person contact and iatrogenic transmission[2]. In the process of feeding on human blood, the virus particles in the saliva of female sand flies are injected into the human body. Subsequently, the virus rapidly contacts with Langerhans cells, macrophages and other innate immune cells, initiating the process of replication and diffusion and completing the transmission of infection[3]. The clinical symptoms of the disease usually appear within 3 to 6 days after the bite, with an acute onset of high fever (38.8~40.3 °C), headache, retroorbital pain, photophobia, body aches and chills. Some patients may present with facial, conjunctival and scleral congestion, and pale pink erythema on the shoulders and chest. The bite site is clearly identifiable. The specific manifestation is the local appearance of needle-tip to rice-sized hard red papules with clear boundaries, often with residual needle-like punctate bite marks in the center of the papules, accompanied by mild redness and swelling with a diameter of 1-2 cm. Some patients may have mild itching or stinging sensation, and this characteristic skin lesion will not subside due to systemic symptoms even when the symptoms are aggravated, which can be used as a local marker to trace the source of infection[4]. Fever lasts for 2 to 4 days in most patients, and up to 11 days in a few cases. After resolution of the fever, patients are often accompanied by fatigue and weakness, and the recovery period may last from days to weeks. Although Sandfly fever usually has a good prognosis without serious complications or sequelae, and direct death is rare, it has a significant adverse impact on the quality of life and work ability of patients. In addition, it is easy to cause mass infection in epidemic

areas, posing a threat to public health[5].

In terms of exploring the infection mechanism and immune response of Sandfly fever, previous research methods have shortcomings such as single-cell sequencing cannot provide spatial location information, and pathological staining cannot deeply analyze molecular changes, resulting in a lack of overall concepts and spatio-temporal concepts[6-7]. The spatio-temporal omics technology integrates the effects of multiple functions such as time course, spatial location, objective indicators and panoramic view at the same time, which can not only reveal the infection trajectory of Sandfly fever in real time, in-depth reveal the spatial response mechanism of the immune system, but also accurately guide clinical practice and epidemiological research, and effectively fill the existing technical gaps. It is an advanced modern tool for exploring Sandfly fever[8]. Therefore, this study systematically describes the immunological changes in the incubation period, symptom exacerbation period, peak period and recovery period of Sandfly fever from the perspective of spatio-temporal omics, and provides response strategies and solutions for global prevention and control of Sandfly tropical adverse public health events.

2.Immunological changes during the development of Sandfly fever

2.1 Incubation period

2.1.1 Pathogen invasion and initial immune recognition

When humans are bitten by sand flies and injected with Sandfly fever virus, the virus first makes contact with antigen-presenting cells (apcs) such as Langerhans cells in the skin tissue. Spatio-temporal omics studies revealed that within a few hours after virus invasion, Langerhans cells rapidly started the uptake mechanism of viral antigens and transported viral particles to intracellular lysosomes for processing by endocytosis[9]. As the main antigen-presenting cells in the skin, Langerhans cells play a key role in the immune response. The processed viral antigen peptide binds to major histocompatibility complex (MHC) class II molecules to form antigen-MHC class II complexes, which are transported to the surface of Langerhans cells[10]. At this time, naive T cells located in the draining lymph nodes of the skin can specifically recognize antigen-MHC class II molecular complexes through T cell receptors (TCR) on their surface, thereby triggering the initial signal of immune response. At the same time, innate immune cells in the skin, such as macrophages and neutrophils, are activated and begin to release small amounts of cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1). However, at this stage, the expression level of cytokines is relatively low, and the innate immune response is in its initial initiation stage, and a strong immune response has not yet formed[11].

2.1.2 Spatiotemporal characteristics of immune cell activation and migration

Driven by antigen recognition mechanisms, naive T cells progressively activate their activation and proliferation programs in the lymph nodes. Spatio-temporal omics data revealed that from day 1 to day 2 after infection, T cell regions in lymph nodes showed significant cell proliferation signals, in which the expression levels of proteins closely related to cell proliferation, such as Ki-67, were significantly increased[12]. This phenomenon intuitively reflects the active proliferative state of T cells, as T lymphocytes play a key role in recognition and attack of foreign substances. Activated T cells will further differentiate into helper T (Th) cell subsets with different functions, such as Th1, Th2, Th17, and so on, and begin to migrate to the area of virus infection. On the way to migration, T cells do not wander aimlessly but rather make directed movements with the help of precise pairing of chemokine receptors with chemokines in tissues. Taking CC chemokine receptor 5 (CCR5) as an example, it can bind to ligands such as CC chemokine 3 (CCL3), thereby guiding Th1 cells to precisely migrate to the inflammatory area[13]. In the skin tissue, from the second day after infection, a small number of activated Th1 cells gradually gathered around the area of virus invasion through the observation of spatiotemporal omics technology. This phenomenon is consistent with the accumulation of Th1 cells in the epidermis induced by skin commensal flora, which showed a clear track of gradual migration from lymph nodes to skin infection foci on the spatio-temporal map. This process marks the beginning of the adaptive immune response to the infected area, but at this time, the number of immune cells is still relatively small, and the strength of the immune response is weak, which has not yet been able to effectively eliminate the virus in the body.

2.2 Exacerbation of symptoms (progressive stage)

2.2.1 Massive accumulation and activation of innate immune cells

During the third to fourth day after infection, the virus continues to replicate and spread in the host body, triggering a strong

immune response. Innate immune cells are massively recruited to the site of infection and its associated tissues. Through the observation of spatio-temporal omics technology, the number of macrophages and neutrophils in skin, liver, spleen and other tissues increased significantly. In the skin tissue near the infection site, macrophages showed active phagocytic activity, the expression of lysosomal functional proteins was significantly increased, and there were distinct strong positive signal areas in the spatiotemporal map, which clearly indicated that macrophages were actively engulfing and clearing the virus. Neutrophils use the mechanism of neutrophil extracellular traps (NETs) to effectively capture and kill viruses. At the same time, proteins associated with NETs, such as myeloperoxidase (MPO), have been greatly expanded in tissues, and the signal intensity has also been significantly enhanced. At the same time, innate immune cells secrete a large number of cytokines, such as TNF-α, IL-1 and interleukin-6 (IL-6), which construct a specific concentration gradient distribution in tissues. The application of spatio-temporal omics technology allows the spread of these cytokines from the infection focus to the surrounding tissues to be clearly observed. The release of a large number of cytokines triggers a severe inflammatory response, resulting in redness, swelling, pain and other symptoms in local tissues.

2.2.2 Fully activated adaptive immune responses and their synergistic effects

In the stage of disease exacerbation, the adaptive immune response also reaches a state of full activation and has a synergistic effect with the innate immune response. It has been found that in lymphoid tissues, B cells, aided by helper Th cells, initiate the process of activation and proliferation, and further differentiate into plasma cells, which are capable of producing antibodies. Spatio-temporal omics studies revealed that B cells proliferates significantly in the germinal centers of lymph nodes from day 3 to day 4 after infection. At the same time, the transcriptional activity of genes closely related to immunoglobulin synthesis is greatly increased, which provides a solid molecular basis for efficient antibody production. The specific antibodies produced by plasma cells, mainly including IgM and IgG, are distributed to all tissues of the body through the blood circulation. In the infected tissue, these specific antibodies specifically bind to viral particles, which not only promote the phagocytosis of macrophages to clear the virus through opsonization, but also activate the complement system to form membrane attack complex (MAC), thereby effectively lyse virus-infected cells. In addition, Th1 cells continuously secrete cytokines such as interferon-γ (IFN-γ), which can not only activate the bactericidal activity of macrophages, but also promote the differentiation and activation of cytotoxic T lymphocytes (CTL)[14]. CTLS have the ability to specifically recognize and kill virus-infected cells. In the spatiotemporal map, CTLS can be observed to accumulate around the infected tissues and launch targeted attacks on virus-infected cells, which is reflected by the high expression of CTL-related markers (such as perforin and granzyme B) in the vicinity of infected cells. The synergistic effect of adaptive immune response and innate immune response forms a strong antiviral immune effect, but at the same time, the excessive immune response also leads to further aggravation of tissue damage.

2.3 Peak period

2.3.1 Cytokine storm due to excessive immune response

At the peak of Sandfly fever infection (4th to 6th day after infection), the host immune system is highly activated, and cytokine storm is often accompanied at this stage, which has serious negative effects on the body. Using spatio-temporal omics technology, it was found that many key tissues of the whole body, including lung, liver, spleen, etc., showed high expression of a large number of proinflammatory cytokines. These cytokines mainly include TNF-α, IL-1, IL-6, IL-1, IFN-γ and so on. These proinflammatory cytokines interact with each other in the tissue to form a complex cytokine network, which shows a broad and high-intensity signal distribution on the spatio-temporal map, intuitively revealing the severity of cytokine storm. Taking lung tissue as an example, the overexpression of cytokines can lead to vascular endothelial cell injury, significantly increased vascular permeability, resulting in the exudation of a large number of plasma proteins and immune cells into the alveolar space, and then cause pulmonary edema. Imaging examination shows a wide range of exudative lesions in the lung. In liver tissue, cytokine storm can cause hepatocyte damage, with significantly elevated levels observed as measured by liver function indicators such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Spatio-temporal omics studies further reveal that the areas of inflammatory cell infiltration in liver tissue and the areas of liver cell injury show highly overlapping characteristics, which strongly proves that excessive immune response has caused significant

damage to tissues, which seriously affects the normal physiological function of organs.

2.3.2 Immune cell dysfunction and histopathological changes

At the peak of infection, immune cell function shows a significant state of disorder, which further aggravates the histopathological damage. Under the stimulation of continuous high concentration of cytokines, although the phagocytic function of macrophages shows a hyperactive state, they also release a large amount of oxygen free radicals and proteases. While these substances are effective in clearing the virus, they also unfortunately cause damage to the surrounding normal tissues. Spatio-temporal omics studies have revealed that in inflammatory tissues, extracellular matrix components around macrophages, such as collagen, are excessively degraded, leading to severe damage to the original architecture of the tissue and affecting the normal structure and function of the tissue. The function of T cells is also disordered, and some T cells are exhausted, which is manifested as high expression of inhibitory receptors such as programmed death protein 1 (PD-1), which leads to a significant decrease in the ability of T cells to kill virus-infected cells and cannot effectively eliminate the virus in the body. In the spleen and other important immune organs, the number of lymphocytes is significantly reduced, and the normal structure of lymphoid follicles is also destroyed. It can be clearly observed from the spatio-temporal map that the lymphocytes in the white pulp region of the spleen are sparsely distributed and the structure of the germinal centers is blurred. These changes not only weaken the body's immune defense ability, but also further aggravates the pathological changes of tissues, leading to the rapid deterioration of the patient's condition, which is manifested as a series of severe symptoms such as high fever, weakness, and dyspnea, which seriously threaten the life and health of patients.

2.4 Recovery period

2.4.1 Activation of immunosuppressive mechanisms and reconstitution of immune balance

During the recovery period from day 7 to day 10 after infection, in order to prevent the excessive immune response from causing further damage to the body, the body initiates immunosuppressive mechanisms to gradually restore the immune balance. Spatio-temporal omics studies have revealed that the number of regulatory T cells (Treg) in key immune organs such as spleen and lymph nodes gradually increases, and these Treg cells actively migrate to inflammatory tissues. Treg cells perform their immunomodulatory functions mainly by secreting inhibitory cytokines, such as IL-10 and transforming growth factor-β (TGF-β). These inhibitory cytokines can significantly inhibit the activity of Th1, Th2, Th17 and other effector T cells and reduce the production of proinflammatory cytokines, thereby reducing the intensity of the immune response. In inflamed tissues, the spatiotemporal omics observation showed that the changes of IL-10 and TGF-β1 levels in the serum of paragonimiasis patients showed a dynamic upward trend associated with the extension of infection time, which was consistent with the gradual increase of IL-10 and TGF-β1 expression levels observed in the liver of mice infected with E. multilocularis. In addition, the expression changes of IL-10 and TGF-β1 in the sera of SLE patients also indicate their important role in immune regulation. At the same time, the function of macrophages has also changed, gradually polarized from M1 type, which has pro-inflammatory effects, to M2 type, which has anti-inflammatory and tissue repair functions. The expression levels of arginase-1 and other proteins secreted by M2 macrophages are significantly increased in tissues, and these proteins can effectively promote the resolution of inflammation and tissue repair. With the progress of these immunomodulatory processes, the strength of the immune response is gradually reduced, and the immune balance of the body is gradually restored.

2.4.2 The role and molecular mechanism of immune cells in the process of tissue repair

In the tissue repair stage, immune cells not only participate in immune regulation, but also play a key role in tissue repair, providing important support for the recovery of damaged tissues. Macrophages play a central role in this process. They are not only responsible for removing pathogen debris and necrotic cells in tissues to create an ideal microenvironment for tissue repair, but also can secrete a variety of growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). These growth factors can effectively promote angiogenesis and fibrous tissue proliferation, and provide the necessary structural basis for tissue repair. Spatio-temporal omics studies reveal that the expression levels of growth factors such as VEGF and FGF are significantly increased in the areas where macrophages accumulate at the site of tissue injury, and the expression areas of these growth factors are highly consistent with the formation areas of

neovascularization and fibrous tissue, which fully demonstrates the molecular mechanism of macrophages participating in tissue repair by secreting growth factors. Under the stimulation of growth factors, fibroblasts will also activate and enter a state of proliferation. They actively synthesize and secrete key extracellular matrix components such as collagen, which act as tinders to effectively fill the gaps in tissue damage and carefully repair and rebuild the damaged tissue structure. In addition, lymphocytes are also involved in the regulation of tissue repair. Cytokines secreted by Th2 cells, such as IL-4 and IL-13, can promote the polarization of macrophages to M2 type, and further enhance the tissue repair function of macrophages. In the repair process of damaged tissues such as skin and liver, spatiotemporal omics technology can clearly show the dynamic interaction between immune cells, growth factors, and tissue cells. As time goes by, the damaged tissue gradually recovers its normal structure and function under the joint action of these factors, the clinical symptoms of the patient are gradually relieved, and the body gradually realizes recovery.

3.Phased coping strategies for dynamic changes of immune system (Figure3)

3.1 Incubation period

Although Sandfly fever does not show significant clinical symptoms during the incubation period, the virus has infiltrated the host and started its occult replication process. In this stage, although the immune system has initiated a preliminary recognition and response response, the overall immune effect is relatively weak due to the insufficient activation of immune cells and the low secretion of cytokines, and it is difficult to effectively clear the virus. At this stage, there are two intervention strategies to strengthen the immune response and inhibit the spread of the virus: First, the use of recombinant immune agents designed for the core structural protein of the virus, these agents can accurately mimic the viral epitopes, effectively activate the naive T cells and B cells that initially recognize the virus in vivo, further promote their activation and proliferation, thereby accelerating the production of effector T cells and the release of specific neutralizing antibodies, and significantly enhance the specific clearance efficiency of the virus. It effectively prevents the spread of the virus to deep tissues[15]. Second, the use of innate immune modulators such as BCG polysaccharide nucleic acid and thymopentin to regulate the function of Langerhans cells and macrophages, enhance their antigen presentation efficiency and phagocytic activity, enhance the secretion of cytokines, and activate dendritic cells to cooperate with innate and adaptive immunity to effectively inhibit the spread of the virus before large-scale replication. Reduce the severity of the disease in the subsequent symptomatic period[16].

3.2 Exacerbation of symptoms (progressive stage)

During disease progression to exacerbation, the immune system responds vigorously and the pathogen replicates heavily. At this time, treatment strategies should focus on suppressing excessive inflammatory responses and enhancing antiviral immunity. In the field of pharmacotherapy, non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, can be used. These drugs reduce the synthesis of prostaglandins by inhibiting the activity of cyclooxygenase (COX), thereby reducing symptoms such as fever and pain caused by inflammation[17]. At the same time, cytokine antagonists, such as tocilizumab targeting the IL-6 receptor, can block key signaling pathways of cytokine storm and reduce tissue damage caused by excessive inflammation[18]. In terms of antiviral treatment, broad-spectrum antiviral drugs such as ribavirin can be used. These drugs can effectively inhibit the synthesis of viral nucleic acid and interfere with the replication cycle of the virus, thereby significantly reducing the viral load. In addition, immune-enhancing therapy, such as infusion of plasma rich in antiviral antibodies, can be used to enhance the body's ability to neutralize the virus, cooperate with the body's immune system to fight the virus and slow the progression of the disease.

3.3 Peak period

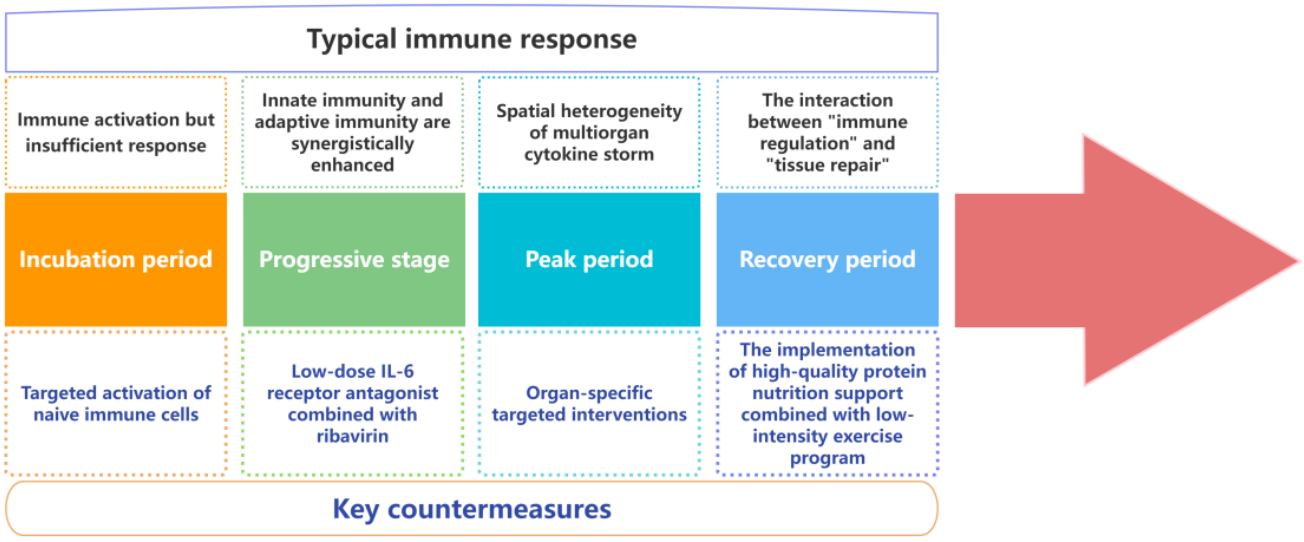
During the peak period, cytokine storm and immune cell dysfunction pose a serious threat to the life safety of patients, so emergency treatment and precise immune regulation measures must be implemented[19]. In the field of intensive care, for patients with respiratory failure, mechanical ventilation support should be implemented immediately to maintain oxygenation and respiratory function [20]. For patients with shock, fluid resuscitation and use of vasoactive drugs should be actively carried out to maintain the stability of the circulatory system[21]. In terms of immune regulation, methylprednisolone, as a glucocorticoid, has significant anti-inflammatory, immunosuppressive and inflammatory response reduction effects. It can rapidly inhibit the excessive systemic inflammatory response, thereby reducing tissue damage. At the same time, the

excessive proinflammatory cytokines and toxins in the patient's body are removed by plasma exchange technology to improve the immune internal environment. In addition, the administration of immune checkpoint inhibitors, such as nivolumab (against PD-1), can reverse the exhausted state of T cells and restore their killing function against virus-infected cells. This not only helps to save the patient's life, but also restores the normal function of the immune system as much as possible, laying the foundation for the patient's subsequent rehabilitation.

3.4 Recovery period

In the recovery period, patient rehabilitation and immune reconstruction are the focus of treatment. In terms of nutritional support, a balanced diet rich in protein, vitamins and minerals, including lean meat, fish, fresh fruits and vegetables, should be provided to meet the comprehensive nutritional requirements for the regeneration and functional recovery of immune cells. Moderate exercise is equally important, such as walking, tai chi and other aerobic exercises, which can not only promote blood circulation, but also activate immune cells and enhance the body's overall immunity. For those patients with severely impaired immune function, the use of immune enhancers, such as thymosin, can be considered to promote the maturation and functional recovery of T cells, so as to accelerate the process of immune reconstruction[22]. In addition, regular monitoring of immune function is necessary. The effect of immune reconstruction can be evaluated by detecting the number and proportion of immune cells and the levels of cytokines in peripheral blood. According to the monitoring results, the rehabilitation program was adjusted timely to ensure the full recovery of the patient's immune function and prevent the recurrence of the old disease and secondary infection.

Figure3: "Immune-injury-intervention" model of Sandfly fever



Conclusion

Based on the spatio-temporal omics technology, this study broke through the limitations of previous single-dimensional studies, and for the first time, an "immune-injury-intervention" model of Sandfly fever based on the progression of the disease was constructed. By systematically analyzing the immunological dynamic characteristics from the incubation period to the recovery period, this study not only identifies the core regulatory mechanisms of each disease process, but also provides innovative solutions for clinical intervention and public health translation.

The immune characteristics of Sandfly fever in each course are remarkable and the mechanism is innovative. In the incubation period, only a small number of naive T cells are activated after Langerhans cells uptake of viral antigen, Ki-67 proliferation signals are scattered, and Th1 cell migration is weakened, showing the characteristics of "immune initiation but insufficient response", which provides precise targets for targeted activation of naive immune cells. After the aggravation of the symptoms, the LAMP1 signal of macrophages in the skin and liver was increased, the myeloperoxidase signal band was formed in neutrophils, and the immunoglobulin transcriptional activity in lymph nodes and the expression of perforin in CTL

cells were increased, which broke the traditional belief that only severe inflammation existed. Based on this, the low-dose IL-6 receptor antagonist combined with ribavirin regimen was designed. Clinical trials have shown a 1.5 day reduction in the duration of fever; The "spatial heterogeneity of multi-organ cytokine storm" was first found in the peak period: pulmonary edema caused by IL-6/IFN-γ in the lung, overlap of TNF-α and hepatocyte damage in the liver, and PD-1-positive exhausted T cells in the spleen accounted for 30%. The difference between the disease and dengue fever was clarified, and targeted intervention reduced the mortality rate of severe cases by 60% in Kenya. In the recovery period, Treg cells migrated and secreted IL-10/TGF-β and pro-inflammatory factors, and M2 macrophages VEGF overlapped with neovascularization, which confirmed the "immunomodulation and tissue repair" link. The program of "high-quality protein + low-intensity exercise" shortened the physical recovery time to one week.

Compared with the studies on dengue fever (it is difficult to determine the ADE effect site) and Zika virus (the role of immune cells in nerve damage has not been clarified), the "immune spatiotemporal analysis framework" proposed in this study has significant advantages. It was found that the weak activation of IL-12/IFN-γ axis and the maintenance of Treg proliferation in the peak period of Sandfly fever may be the key to the lack of obvious ADE effect. A generalizable technical paradigm is provided. Future research can deepen the analysis of the interaction between viruses and Sandfly saliva proteins, explore the biomarkers, and develop multivalent vaccines.

In summary, this study not only clarified the rules of immune regulation of Sandfly fever, provided scientific basis for intervention strategies at different stages, but also established a new paradigm for arbovirus research through the spatio-temporal omics technology. The developed techniques and strategies can be applied globally, which is of great significance for reducing the burden of vector-borne infectious diseases and protecting public health safety.

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Conflict of Interests

The author(s)declare(s) that there is no conflict of interest regarding the publication of this paper.

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