Discussing how his studies on Sjögren’s syndrome are forging new insights into its initiation and progression, rheumatologist Professor Takashi Fujimoto reveals how he foresees his research developing in the future.

Sjögren’s syndrome (SS) is an autoimmune disease characterised by exocrine gland dysfunction. To begin, can you explain how it manifests itself and discuss what treatments are currently available?

SS is a chronic inflammatory disease that affects the exocrine glands, particularly the salivary and lacrimal glands. It is characterised by the presence of a variety of autoantibodies directed against organ and non-organ-specific autoantigens. Focal, mononuclear cell infiltrates surround the ducts and replace the secretory units. Xerostomia is an important clinical concern in oral health and is known to induce various problems, including dental and denture issues, periodontitis, mastication and swallowing problems, burning sensations and dysgeusia. Although muscarinic agonist medications such as pilocarpine and cevimeline induce salivary secretion from the residual functional tissue, these medications provide only temporary relief from the symptoms and have a limited effect on the recovery of damaged tissues. Accordingly, the development of a novel treatment to restore or regenerate damaged salivary gland tissues is eagerly awaited.

Could you introduce your professional background and explain why you chose to focus your research on SS?

I am a rheumatologist with a background in clinical immunology and molecular biology. I obtained my medical degree from Kobe University, and PhD from Nara Medical University in Japan, where I studied the structure and function of renal involvements in patients with SS. I identified a variety of organ involvements in SS and my research interests have since been focused on the pathogenesis of this disease. During my postdoctoral studies at the University of Cambridge in the UK, I studied molecular mechanisms in the pathogenesis of vasculitis syndrome using cutting-edge molecular biology techniques. This was further extended into research projects that involved the isolation of autoantigens, which were recognised in the sera of patients with SS, and the mechanisms of autoimmunity in the pathogenesis of the disease. Succeeding in our goals requires a collective research effort bringing together biochemists. Professor Shin Takasawa is a key collaborator who actively promotes our pathophysiological investigations on SS.

The importance of epithelial cells to the progression of SS has been identified in recent years. What role do they play?

During the past 15 years, the importance of the epithelial cells in the pathogenesis and evolution of SS has been highlighted and has prompted the use of the term ‘autoimmune epithelitis’ as an alternative name for the disease. Immunologically-activated or apoptotic glandular epithelial cells that expose autoantigens in genetically predisposed individuals might drive autoimmune-mediated tissue injury. Indeed, the upregulation of adhesion molecules and production of chemokines and cytokines are known to be critical to the initiation and perpetuation of the SS pathogenesis. Together, these processes promote the migration of lymphocytes and dendritic cells into the glands, maintaining their cycle of homing.

Why are women more likely to develop the condition than men?

Most SS patients are indeed women. It therefore seems reasonable to speculate that sex steroids play a fundamental role in the pathogenesis of the disease. The usual age of onset is between 40 and 50 years, concomitant with the meno- and adrenopause. Estrogens favour autoimmunity and, therefore, the ceasing function of the ovaries should protect women from SS rather than predisposing them to the condition. However, androgens protect from autoimmune diseases and it seems more likely that the loss of this protection is an important predisposing factor. Furthermore, patients with SS have low serum dehydroepiandrosterone (DHEA) concentrations.

Finally, what conclusions have you been able to draw from your research, and can you discuss your aims for the future?

Our research to date has clearly shown that the causes of hypofunction in the salivary glands of patients with SS are highly complex. Looking to the future, the challenge will be to distinguish non-immunologic mechanisms from immunologic mechanisms in the target organs of this unique disease. We are also eager to identify the genes responsible for non-immune pathogenesis using gene-targeting models. Finally, the creation of an integrated model that can account for the hypofunction of salivary and lacrimal glands would be ideal.
Researchers at Nara Medical University, Japan, are investigating the pathophysiology behind Sjögren’s syndrome; an autoimmune disorder characterised by exocrine gland dysfunction.

AS THE SECOND most common autoimmune disorder after rheumatoid arthritis, Sjögren’s syndrome (SS) is a condition where the body’s immune system attacks the glands that secrete fluid. This leads to the onset of uncomfortable symptoms such as xerostomia (dry mouth) and xerophthalmia (dry eyes), along with lymphocytic infiltration of the glands. Eventually, this inflammatory process damages or destroys the glands. SS is generally categorised into one of two groups: primary SS, when the condition develops by itself and not as a result of another condition, and secondary SS, when the condition develops concurrently with another autoimmune condition such as rheumatoid arthritis or systemic lupus erythematous.

In spite of concerted efforts to investigate the aetiology of SS in recent years, the molecular mechanisms that underpin its initiation and progression remain unclear. Indeed, at present SS is very difficult to diagnose because the characteristic dry eye and mouth symptoms are often mistaken for normal, age-related complications. There is not one specific diagnostic test for SS; rather, diagnosis is established through a series of tests, which can take a number of weeks. Additionally, while the symptoms of SS can be controlled, there is currently no cure. There is therefore an urgent need for robust studies to shed greater light on this autoimmune disease and pave the way for the development of improved diagnostic and therapeutic strategies.

Dr Takashi Fujimoto, Professor in the Centre for Rheumatic Diseases at Nara Medical University and a visiting scientist in the Department of Medical Chemistry at Kyoto University, Japan, is an eminent researcher in this area. With a strong track record of published research, Fujimoto has spent the past few decades investigating the pathophysiology of autoimmune diseases including SS, rheumatoid arthritis and systemic lupus erythematous. Working with his team of researchers, Fujimoto is primarily focusing on how salivary glands are damaged and regenerated and how salivary function deteriorates in SS.

THE REGENERATING GENE

One of Fujimoto’s main areas of research is the role of the regenerating gene (Reg) in the pathophysiology of SS. Reg was initially isolated as a growth factor from a cDNA library.
INTELLIGENCE
ELUCIDATION OF THE PLAYBACK MECHANISM AND SALIVARY GLAND DISORDER OF SJÖGREN’S SYNDROME

OBJECTIVE
To reveal a possible involvement of Reg in regeneration and destruction of salivary gland acinar and ductal cells in Sjögren’s syndrome (SS).

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of rat regenerating pancreatic islets – that is, tiny clusters of cells scattered throughout the pancreas. This was followed by subsequent studies that identified Reg-related proteins in humans and other animals, as well as Reg gene expression outside the pancreas: “The Reg gene family constitute a multi-gene family consisting of four subtypes,” discloses Fujimoto. “In humans, five functional REG genes – namely, REG Iα, REG IIα, REG IIIβ, HIP/PAP and REG IVβ – have been isolated. Reg family proteins are primarily involved in cell proliferation and differentiation, inflammation, diabetes and carcinogenesis.”

Importantly, a significant body of evidence suggests the Reg gene family could be a key candidate for restoring damaged pancreatic beta cells – the producers of insulin – in diabetes mellitus. This finding is highly relevant for Fujimoto’s research into SS because the structure of salivary gland cells is known to be similar to that of pancreatic beta cells, with both cells having secretion apparatus. Together, the researchers have investigated how salivary gland dysfunction in SS is initiated and how it can be regenerated or progressed by Reg proteins. To date, their findings have demonstrated that REG mRNA is expressed in the salivary glands of patients with SS and that the REG protein is expressed in the ductal epithelial cells of the salivary glands in SS patients.

Furthermore, antibodies against the REG protein (anti-REG) have been identified in some patients with SS, leading Fujimoto to explore the possible role of anti-REG in the progressive destruction of the salivary gland in patients with SS. He found that when the salivary gland is inflamed, the REG protein is induced in acinar progenitor cells to repair and recover the damaged cell mass. However, the presence of anti-REG hinders ductal epithelial cell regeneration in the salivary gland. “We have revealed clearly that saliva secretion was reduced in SS patients with anti-REG,” Fujimoto points out. “Furthermore, there was a correlation between the presence of anti-REG and REG protein expression in the ductal cells of the salivary gland.” The researchers therefore believe that autoimmunity to the REG protein has a major role to play in the regeneration of salivary gland ductal epithelial cells in SS.

FUTURE AIMS
To date, Fujimoto’s research group has made important progress in understanding how and why salivary glands are damaged or regenerated in patients with SS. The scientists have mapped the potential role of anti-REG in salivary gland degeneration and, looking ahead, plan to continue investigating the association between tissue injury in salivary glands and autoimmunity to Reg in some SS patients. Ultimately, Fujimoto and his team are aiming to build knowledge about the pathophysiology behind a range of autoimmune diseases, leading to the discovery of innovative new therapeutic strategies for devastating conditions like SS.