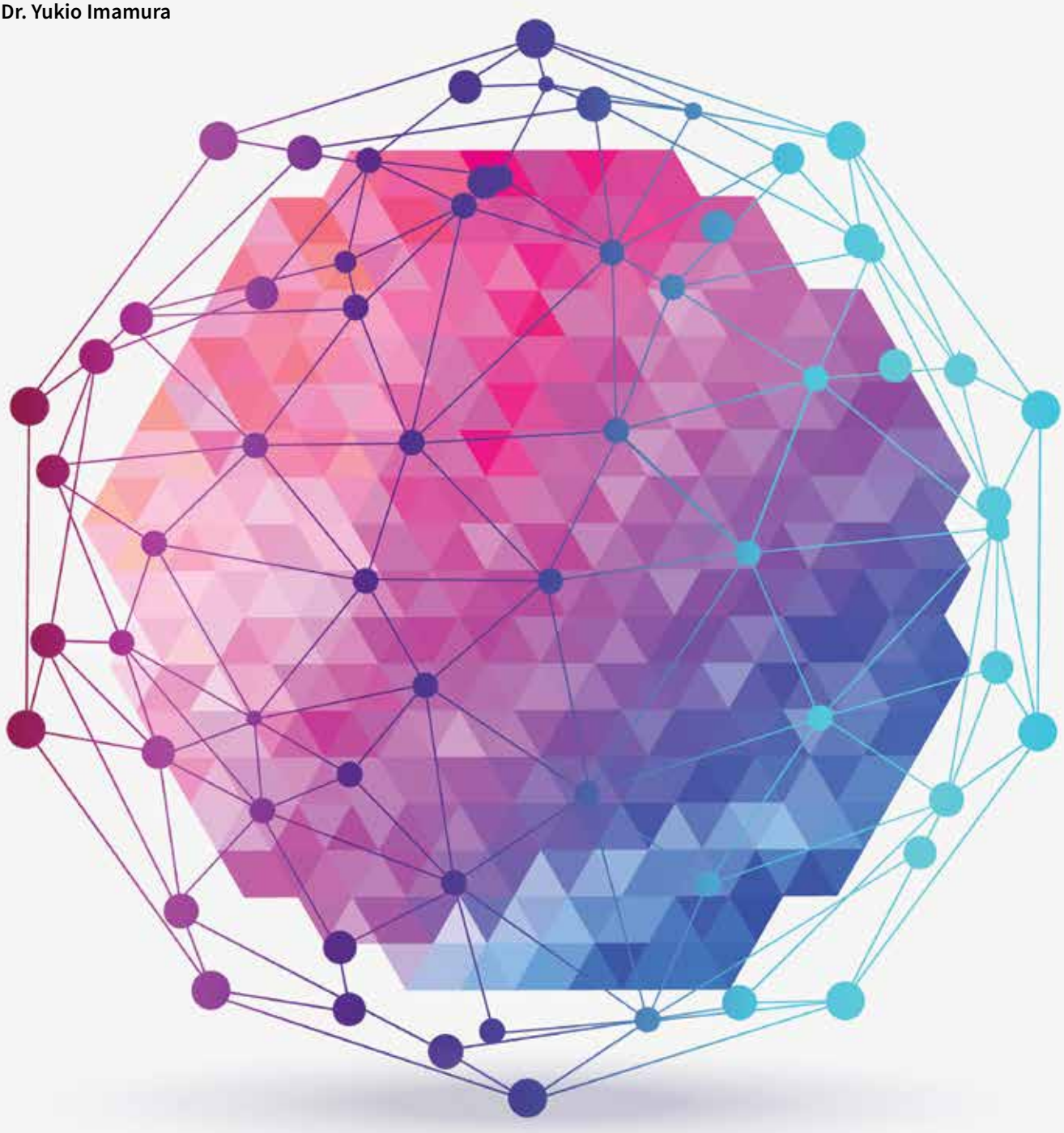
Challenges and opportunities for understanding septic encephalopathy

Dr. Yukio Imamura



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Dr. Yukio Imamura studies the molecular mechanisms of septic encephalopathy, enabling the development of better treatments and prevention.

To begin, could you describe your research background and how you became interested in studying the molecular mechanisms of the brain?

When I was Master's student in engineering I was engaged in biological chemistry. I was particularly interested in how living organisms are controlled by a lot of molecules. At this time (around 1995), since molecular neuroscience contained a large mystery and was becoming a major topic worldwide I was strongly interested in the molecular mechanisms and started the research.

How did you come to study septic encephalopathy in particular?

Although I moved labs in Japan and Canada, when I went to the brain science institute, RIKEN, one of my colleagues (Dr. Matsumoto, Osaka Univ.) had a strong interest in my research background. He is a physician and neuroanatomist at Osaka University Hospital in Japan. He introduced me to septic encephalopathy as a very important topic in the medical intervention field including intensive and critical care. Especially the brain dysfunction that follows sepsis (i.e. septic encephalopathy) still remained obscure and he thought my research background should be useful to tackle the molecular mechanisms behind it.

Why do you think progress has been relatively slow regarding understanding the molecular causes of septic encephalopathy?

Patients of septic encephalopathy often showed coma, delirium and cognitive dysfunction. Clinical studies and preclinical research using animal models have been challenged to uncover the pathophysiological mechanisms and therapeutic potentials. Although a large variety of pathological molecules and physiological conditions affect the outcome of septic encephalopathy, their individual dynamics are not totally clear. Therefore, many candidate pathophysiological molecules associated with septic encephalopathy have been tested for their association with a better outcome for septic encephalopathy without success.

You discovered that sepsis causes an increase in interleukin-1ß(IL-1ß) in the brain resulting in decreased synaptic function and that inhibiting IL-1ß alleviated this effect. Could IL-1ß be a potential target for therapeutic development? What challenges might that pose?

IL-1ß will be a therapeutic target for septic encephalopathy. In fact, increased IL-1RN, an inhibitor of the IL-1 ß receptor, was linked with a better outcome for septic patients. However, septic encephalopathy sometimes shows complicated symptoms including vascular dysfunctions that lead to ischemia and edema. Therefore, in addition to molecular targeting therapy, morphological alteration should be carefully considered.

Quantum dots are an exciting new tool with potential uses in biomedical imaging. How can quantum dots be used to better understand septic encephalopathy?

Quantum dots show fluorescent intensity and employ a higher signal to noise ratio than the conventional fluorescent probes. In addition, we are currently working on developing a novel quantum dot in the second near-infra red wavelength (900-1300nm). The light in this wavelength shows highly permeability and less absorbance by the body. If this novel technology is successfully applied, the understanding of septic encephalopathy will be better.

Could quantum dots be used for therapeutic delivery in addition to imaging?

Q-dots can be useful for the delivery of drugs. Of course, to do so, Q-dots have to be coated with a hydrophilic polymer. Our research group is currently trying to produce novel Q-dot probes for drug delivery.

You mention vagus nerve stimulation as a potential method for mitigating sepsis. How long before we might see something like this in the clinic? What are the current barriers to its use?

Currently, pre-clinical research groups stimulate the vagus nerve with electrical stimuli directly. This process includes surgical operation. I think that the surgical operation is hard on patients with severe sepsis. Therefore, we are currently working on developing a novel method for non-invasive stimulation of the vagus nerve without surgical operation.

How will your findings inform and shape future studies or treatment of septic encephalopathy? Where should future work on septic encephalopathy focus?

Although our research studies were performed using a rodent model of septic encephalopathy, these lines of research suggest two potential therapeutic approaches for future development. First is the development of novel therapeutics targeting the antagonist of molecules involved in inflammation (e.g. interleukins, matrix metalloproteinases etc.) and neuronal function (e.g. neuronal synaptic plasticity, population activities of neurons). Second is the possibility of vagus nerve stimulation. To apply these methods to human patients we should very carefully test the validity and potential side effects in humans. Therefore, future works of septic encephalopathy will be needed to tackle these issues.

Tackling sepsis head on

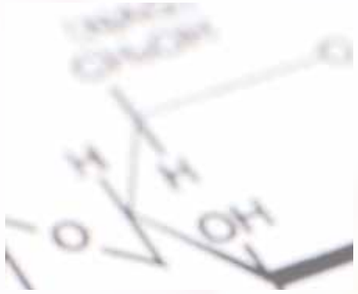
Systemic inflammation caused by some bacterial infections often leads to lasting brain damage. Dr. Yukio Imamura is working to figure out how this happens on a molecular level and how it can be prevented.

TOO MUCH OF A GOOD THING

In general, the inflammatory response is a good thing; it is the body's way of protecting itself from excessive cellular damage. Upon pathogen infection, or other forms of cellular wounding, the body mounts a coordinated response that involves a multitude of cellular players and signals. Typically, the inflammation is localized to the site of infection or injury and is relatively short-lived, resolving itself without need for serious intervention. However in the case of widespread infection, a systemic inflammatory response can be triggered. This condition, known as sepsis, is an over activation of the innate immune system. The response overwhelms the body and if left unchecked can lead to organ failure, neurological dysfunction and death. Sepsis affects millions of people each year and is one of the leading causes of death in intensive care units. Between 28 and 50 percent of patients admitted with sepsis will die.

For a condition that affects so many, surprisingly little is known about how sepsis-induced brain damage occurs.

While the immunological cascade leading to sepsis is well characterized, efforts to halt the overactive immune response have been largely unsuccessful. As such, treatment of sepsis primarily focuses on clearing the responsible infection from the body by administering antibiotics, and preserving organ function by managing symptoms such as fever and low blood pressure. Unfortunately, early symptoms of sepsis are easy to mistake for other, less deadly diseases such as the flu and treatment may not be sought until sepsis has done severe damage to the body. Even for patients who undergo successful treatment, sepsis can have lasting effects including impaired liver, kidney and brain function.



SEPTIC ENCEPHALOPATHY

The brain is especially sensitive to the effects of sepsis. Septic encephalopathy, brain damage caused by sepsis, is one of the most common complications of sepsis and is the leading predictor of death. Despite the critical role that septic encephalopathy plays in determining outcomes of sepsis, little is understood about how it arises in septic patients. There are no conclusive molecular markers of septic encephalopathy. A diagnosis is usually made by testing cognitive function. Without a more complete understanding of the pathophysiology of septic encephalopathy, successful treatments and preventative measures will be difficult to develop.

Dr. Yukio Imamura, a researcher in the laboratory of nano-bio probes, quantitative biology center, RIKEN, is working to elucidate the molecular mechanisms of septic encephalopathy. With a multidisciplinary research background that includes chemical electronics, biochemistry, and molecular oncology, Dr. Imamura is well poised to tackle this multifaceted problem. Using animal models of sepsis, in combination with biochemical assays and electrophysiological techniques, Dr. Imamura has identified several key factors in the development of septic encephalopathy, as well as some promising approaches for prevention and treatment.

MOUSE MODELS: TOWARDS A MOLECULAR MECHANISM

Postmortem examination of the brain following sepsis shows brain swelling, bleeding, and

cell death due to lack of oxygen. It is known that during sepsis the blood brain barrier is disrupted. This allows chemical substances to access the brain that would normally be excluded. Inflammatory cytokines, for example, are released during sepsis and are known to alter synaptic function by inhibiting the expression of excitatory receptors and enhancing the expression of inhibitory neurotransmitters. Other data suggests that sepsis might alter brain function in part by altering the abundance of several amino acids that function as neurotransmitters. These findings are consistent with the observation that septic encephalopathy disrupts neurotransmission, but there is still a lot that is unknown about the interactions of these molecules and others, and how they are involved in the progression of septic encephalopathy.

Dr. Imamura uses an animal model of sepsis to study the molecular mechanisms of septic encephalopathy. Septic conditions are stimulated in the mouse using a surgical procedure known as "cecal ligation and puncture" (CLP), wherein the cecum of the large intestine is closed off, punctured, and then returned to the abdomen. This allows a large amount of bacteria to be released into the body, triggering systemic inflammation very similar to that seen in septic humans. To study what happens in the brain following sepsis, the mice are sacrificed and very thin brain slices are prepared. Abundance and localization of specific protein can then be performed by immunohistochemistry. In one such assay, Dr. Imamura found that occludin, a marker of the blood brain barrier, was significantly reduced in mice that underwent CLP. He also found that the proinflammatory cytokine interleukin-1ß(IL-1ß) accumulated in microglial cells that its receptor was upregulated on neurons. These results are consistent with the pathology of septic encephalopathy and known mechanisms of the inflammatory response.

To enable better treatments of septic encephalopathy, it is important to understand how molecular changes in the brain lead to impaired brain function. To measure changes in brain function Dr. Imamura uses an electrophysiological technique known as field excitatory post-synaptic potential (fEPSPs) recording. In this method, an electrical pulse is applied to a brain slice, stimulating neuronal activity and the amount of time the neurons remain active following stimulation, termed long-term potentiation (LTP), is recorded. If neurons are damaged or inhibited, LTP will be short or nonexistent. Indeed, Dr. Imamura found that LTP could not be induced in brain slices from septic mice. This was consistent with his finding that IL-1ß was increased in the brain of septic mice, as previous research has suggested that IL-1ß inhibits LTP. To test whether this was the case, Dr. Imamura preincubated the brain slices with an antagonist of the IL-1ß receptor before performing fEPSPs recording. Remarkably, LTP was restored. These results suggest that during sepsis, increased IL-1ß in the brain disrupts normal neurotransmission. It also raises the possibility that the IL-1ß receptor may serve as a target for mitigating the effects of sepsis on the brain.

NEW TREATMENTS AND TECHNOLOGIES

Inhibition of neuronal activity caused by sepsis also plays a role in the body's ability to quell the systemic inflammation. The vagus nerve, part of the autonomic nervous system, is a modulator of the innate immune response. During sepsis, the vagus nerve is weakened and fails to signal to the brain to suppress the overactive immune response. However, researchers have found that electrical stimulation of the vagus nerve during sepsis activates the cholinergic anti-inflammatory pathway, inhibiting the immune response and preventing organ damage in the lungs, gut and spleen. Currently, stimulation of the vagus nerve is done directly and requires a surgical procedure. However, such a procedure would be hard on patients already suffering from the symptoms of sepsis. Therefore, to bring the promising treatment to septic patients, Dr. Imamura and colleagues are working on developing a noninvasive method of vagus nerve stimulation.

There is still a lot to be learned about septic encephalopathy. Only a handful of molecular players contributing to the pathophysiology of septic encephalopathy have been identified and their effects have only been studied in a small region of the post-mortem brain. Quantum-dots (Q-dots) are a novel technology for single molecule imaging that show potential for tracking molecules in the living brain with high spatial and temporal resolution. In the future, Q-dots may even be used for drug delivery. Currently, Dr. Imamura and his colleagues on working on developing novel Q-dots for just such purposes. If they are successful, our understanding of septic encephalopathy will be greatly increased.

Researcher Profile

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Dr. Yukio Imamura has a multidisciplinary research background. He holds a B.A. in Chemical Electronics and an M.S. in Biochemistry from Tohoku University in Japan, and most recently a Ph.D. in Molecular Oncology from Kyoto University, Japan. Dr. Imamura has held research positions at the Mitsubishi Kagaku Institute of Life Sciences, Ottawa Health Research Institute, Okinawa Institute of Science and Technology, the RIKEN Brain Science Institute, Department of Human Health Sciences, Unit for Liveable Cities at the Kyoto University Graduate School of Medicine. Currently he is a research scientist in the laboratory of nano-bio probes, quantitative biology center, RIKEN. His research has focused primarily on synaptic transmission and the pathophysiology of the brain. His current work focuses understanding and developing treatments for septic encephalopathy.

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