

Zinc signalling: a revolutionary platform for drug targeting

Professor Dr Toshiyuki Fukada from Tokushima Bunri University uncovers the innovative and prominent role of zinc signalling in the physiological homeostasis and disease status, and discusses the potential impact of zinc signalling pathways and zinc transporters as drug targets



What is zinc signalling and why is this research important?

Let me start by saying that zinc is an essential trace

element for human life; indeed, not only the human body but also for animals, plants and even bacteria. It is a very important trace element that plays a fundamental role in various biological processes such as growth, immunity and metabolism in both humans and animals. Recent research findings have demonstrated that zinc behaves like a signalling factor or a second messenger, and it is capable of facilitating signalling cascades stemming from external stimuli. Furthermore, and as highlighted from the research performed in my group, zinc transporter-mediated zinc signals are of the utmost importance for maintaining physiological homeostasis, thus ensuring normal cellular function. Notably, each zinc transporter-mediated zinc signal has distinct biological roles, which means each zinc signalling has selectivity to control molecular events and cellular fates that we call 'zinc signal axis'.

Therefore, zinc can highly influence a wide range of biological pathways, and potential zinc dysregulations – such as zinc deficiency or zinc overload – can compromise the homeostatic system of individuals, and hence favour the development of various

diseases. My research focuses on zinc signalling performed at the molecular level, and our target is to investigate these signalling networks using disease models and human trials to eventually evaluate its effectiveness as a drug target.

Part of your work involves investigating zinc signalling in cancers and cancer cachexia. What are you hoping to learn?

Cancer and cancer cachexia are prominent examples of our research objectives. The long-term focus of our research involves drug development for various diseases that are related to zinc signalling associated diseases. In particular, cancers and cancer cachexia are wasting syndromes, a complication if you will, that typically promotes anorexia, anaemia, and frailty, and cancer cachexia is responsible for around 20 per cent of cancer deaths. Previously, we found that the zinc ion importer ZIP10 (Zrt- and Irt-like protein - ZIP) is highly expressed in human leukaemia and melanoma, published in 2014. In 2018, it was shown that ZIP14 is increased in skeletal muscle cells by inflammatory cytokines secreted from migrated cancer cells, and ZIP14-mediated zinc signal represses skeletal muscle formation, leading to cachexia. Since zinc transporters are essentially the gatekeepers of zinc signalling, we focus on investigating the means to control the transporting function but also the expression of these transporters. Eventually, we aim at implicating these transporters

as a therapeutic target for the treatment of these degenerative diseases. This further justifies the primary target of our research which is to use zinc transporters and zinc signalling pathways as potent drug targets for zinc-related diseases.

You are organising the 6th Meeting of the International Society for Zinc Biology in Kyoto in September (ISZB-2019). Can you tell us a little about the purpose of this meeting?

Despite the fact that our findings are novel and clearly indicate that there is a distinct relationship between zinc transporters and related diseases, zinc signalling is still an emerging field in life sciences. Therefore, since the International Society for Zinc Biology (ISZB) was established in 2007, we have kept holding a biannual international conference to share updated information of this field. The conference we are organising (ISZB-2019) intends to disseminate recent findings to other groups, thus enhancing our international collaborations but also allowing young scientists from other countries – and from Japan, of course – to acquire proper education and training on this field. One of our ambitious purposes is to establish the potential of the "Zinc Biomedical Life Science" field. After all, and given the rapid pace of recent advances, it is becoming clear that zinc rival calcium in their importance for cell biology as a signalling mediator. So, we must get together in Kyoto and 'Think Zinc' in ISZB-2019! ●