Battling Bone Diseases: The Intriguing Roles of the Dendritic Cell Immunoreceptor

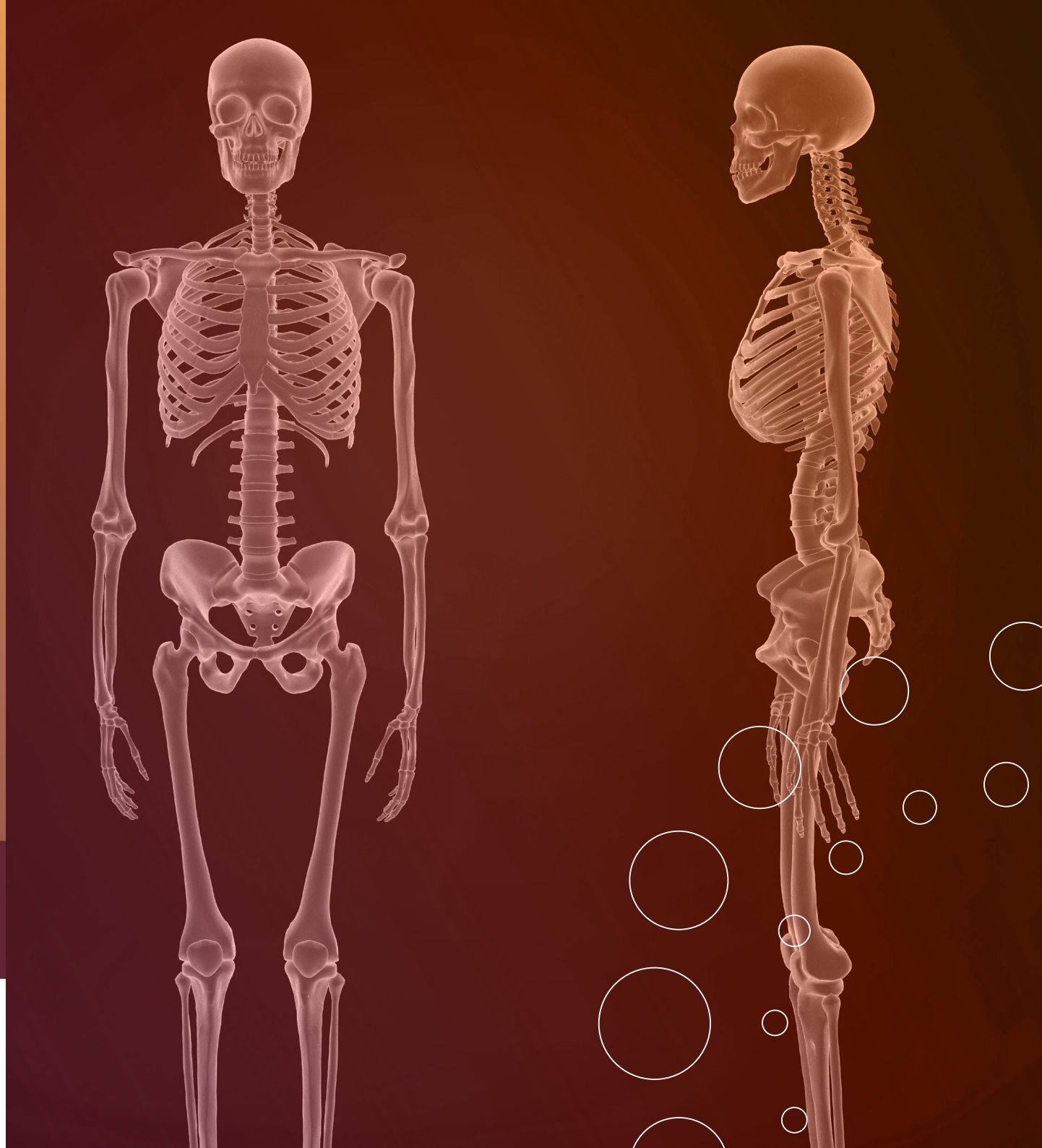
Dr Tomonori Kaifu

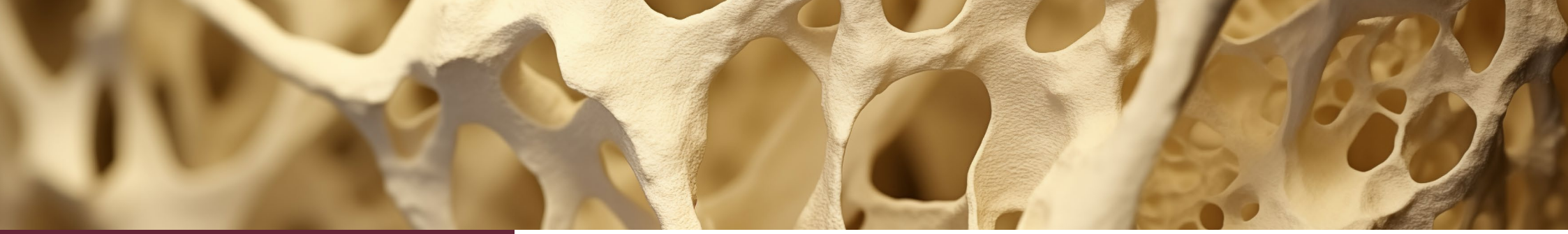
JANUARY 2025

doi.org/10.33548/SCIENTIA1161

MEDICAL & HEALTH SCIENCES

Scientia





Battling Bone Diseases: The Intriguing Roles of the Dendritic Cell Immunoreceptor

Unravelling the complex communication pathways between cells is vital to identifying new therapeutic targets for certain bone diseases. Dr Tomonori Kaifu is based at the Tohoku Medical and Pharmaceutical University in Japan. Over the years, his research has focused on cell signalling via the dendritic cell immunoreceptor. He works to understand the various roles of this receptor in regulating the immune system and metabolism of the bones, with the aim of developing novel therapies for metabolic bone diseases and autoimmune conditions.

Receptors and Ligands

Cells communicate with each other in a process called cell signalling. These are complex chain reactions of events resulting in a particular outcome, such as a change in the production of a certain chemical in the body or behaviour of a particular type of cell. Cells produce and release various molecules which then link to other cells using receptors, stimulating a cascade of responses within. Revealing and understanding these cell signalling pathways and the receptors involved can help identify potential targets for new therapies.

Dr Tomonori Kaifu carries out his vital work in the Division of Immunology at the Tohoku Medical and Pharmaceutical University. His ground-breaking research focuses on the dendritic cell immunoreceptor (DCIR). In his earlier investigations, he found that clinical symptoms of certain autoimmune diseases could be eased by increasing the levels of the ligands – the specific molecules that bind to the DCIR. He also found that DCIR helps to regulate certain functions and the activation of particular genes in a group of bone cells called osteoclasts. His current research aims to decipher the interactions of DCIR and its ligands with a view to understanding their impact on immune responses and bone metabolism.

The Specialists: Osteoclasts and Dendritic Cells

Osteoclasts have a vital role in the remodelling of the skeleton and metabolism of bone tissues, taking the form of specialised cells in the bones. They break down and resorb damaged and older bone using enzymes to make way for another type of bone cell, called osteoblasts, to create new and healthy bone tissues. Through this process, the skeleton is continually being broken down and replaced.

Dendritic cells are another type of specialised cell. As part of the immune system, they hold a vital role in enabling other immune cells to recognise and target unwanted foreign bodies such as bacteria or viruses. DCIR has been linked to various metabolic bone diseases and abnormalities, inflammation and numerous autoimmune conditions, where the immune system turns against the body, such as rheumatoid arthritis and multiple sclerosis. Understanding the interactions of DCIR and its ligands, and the resulting impacts on the osteoclasts, could be used to develop novel therapies which target cell signalling pathways involving the DCIR. Dr Kaifu describes DCIR as an inhibitory C-type lectin receptor, adding that it acts as a negative regulator in the immune system and bone metabolism, helping to maintain the delicate balance in the response of the immune system.

Understanding Osteoclastogenesis

Dr Kaifu's previous work revealed that a deficiency in DCIR enhanced osteoclastogenesis – the multistep process resulting in the production of new osteoclasts. He highlights that DCIR deficiency also affects antigen presentation of the dendritic cells, impacting how they interact with the other immune cells. In addition, the team identified a ligand for DCIR called asialo-biantennary N-glycan (NA2).

Dr Kaifu explains that the osteoclasts begin as myeloid progenitor cells, which then change into osteoclasts in the presence of a substance called macrophage colony stimulation factor, M-CSF, and the receptor activator of nuclear factor-kB ligand, RANKL. He says that M-CSF also promotes the growth, survival, and mobility of certain types of immune cells, and RANKL is responsible for gene expression (the activation of particular genes) required for osteoclastogenesis.

> Osteoclasts have a vital role in the remodelling of the skeleton and metabolism of bone tissues, taking the form of specialised cells in the bones.

The team's research in mouse and human cells found that NA2 binding to the DCIR resulted in the suppression of osteoclastogenesis occurring in the presence of M-CSF and RANKL. Dr Kaifu highlights that the DCIR-NA2 pathway clearly plays an important role in regulating osteoclastogenesis but currently, the underlying mechanisms at play are unclear.

Delving into Mechanisms

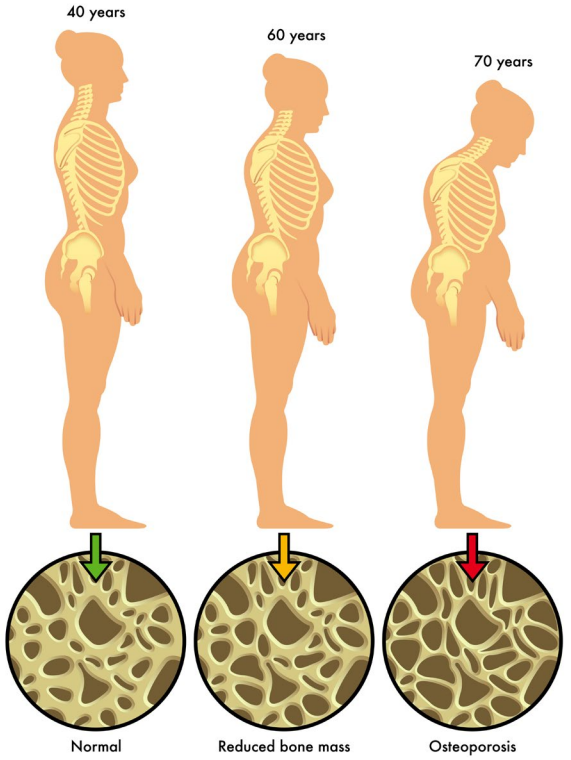
Dr Kaifu and his team investigated these mechanisms using genetically altered mouse immune cells with the DCIR removed and compared them with normal (also known as wild-type) mouse immune cells. They found that the altered immune cells showed a greater response in terms of growth and differentiation to M-CSF and RANKL. They also explored genetically altered osteoclasts, reporting an increase in bone resorptive activity in these DCIR-deficient bone cells compared to the wild-type cells.

Dr Kaifu explains that DCIR deficiency clearly affects gene expression patterns in osteoclasts, adding they also found that the expression of a substance called neuraminidase 4 was increased in the genetically altered cells. In terms of the DCIR-NA2 interaction, the team found altered responses to M-CSF and RANKL in the different types of cells, noting a decrease in the process called phosphorylation, where a phosphate group is added onto a protein involved in cell signalling cascades in wild-type cells.

A Unique Receptor

Dr Kaifu and his team have made significant progress in deepening our understanding of the role of DCIR. He highlights that their data suggest that DCIR regulates osteoclastogenesis by downregulating the signalling from M-CSF and RANKL. He notes that DCIR-mediated signalling might also contribute to the modification of particular molecules called oligosaccharides, by controlling the production of the enzymes involved. He adds that further studies are needed to investigate these other metabolic processes, which are mediated by DCIR signalling.

Metabolic bone diseases encompass various abnormalities of the bones resulting from a wide range of disorders. They can be caused by a variety of issues. For example, a simple dietary calcium and vitamin D deficiency can result in rickets and falling hormone levels in menopause are linked to osteoporosis. There can also be genetic problems impacting specific cell signalling pathways in the bone tissues. Dr Kaifu says that their findings suggest that DCIR is a unique receptor that negatively regulates M-CSF and RANKL, adding that the DCIR-NA2 axis is a potential target for treating metabolic bone diseases linked to the action of osteoclasts. DCIR agonists, drugs which act on the DCIR in a specific way, could be a valuable therapeutic strategy for numerous bone diseases, bringing fresh hope to patients with these life-changing conditions.



MEET THE RESEARCHER

Dr Tomonori Kaifu
Tohoku Medical and Pharmaceutical University, Sendai Miyagi, Japan

Dr Tomonori Kaifu completed his PhD at the Institute of Development, Aging and Cancer, Tohoku University, where he discovered that a signal adaptor protein in the immune system functioned in the central nervous system. In 2007, he held the position of Postdoctoral Fellow at the Centre d'Immunology de Marseille-Luminy in France, focusing his work on an activation receptor involved in the regulation of human immune cells. Later, in 2009, he started his research on the dendritic cell immunoreceptor under Professor Iwakura at the Institution of Medical Science, University of Tokyo. Here, he made several breakthroughs in understanding the dendritic cell immunoreceptor. Dr Kaifu currently holds the position of Associate Professor at the Tohoku Medical and Pharmaceutical University, where he continues to explore the functions of the dendritic cell immunoreceptor, and how it regulates the immune system and bone metabolism. He also works to develop new therapies for autoimmune diseases.

CONTACT

kaifu@tohoku-mpu.ac.jp
https://www.tohoku-mpu.ac.jp/medicine/lab/immunology/

TOHOKU MEDICAL AND PHARMACEUTICAL UNIVERSITY

KEY COLLABORATORS

Professor Yoichiro Iwakura, Department of Biomedical Science, Graduate School of Agricultural and Life Sciences, University of Tokyo

FUNDING

The Core Research for Evolutionary Science and Technology (CREST) program of the Japan Science and Technology Agency (105100000222)

A Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (24220011)

A grant from the Japan Agency for Medical Research and Development (16809407)

A Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (23500489)

FURTHER READING

T Kaifu, T Maruhashi, S Chung, *et al.*, DCIR suppresses osteoclastic proliferation and resorption by downregulating M-CSF and RANKL signaling, *Frontiers in Immunology*, 2023, 14, 1159058, DOI: https://doi.org/10.3389/fimmu.2023.1159058