Research area in Strategic Objective “Elucidation of biological system of extracellular fine particles”

6.2.2 Function and control of fine particles in a living body

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Overview

This research area will promote elucidation of dynamics and functions of fine particles in a living body and R&D on their control. We will address essential problems of biological phenomena caused by fine particles through this program.

In recent years, effects of various fine particles from environment (exogenous fine particles) to a living body and functions of fine particles generated in a living body (endogenous fine particles) have been focused. For example, relationship between diseases and exogenous particles such as PM2.5 and carbon nanotubes etc. has been studied, and many novel diagnostic techniques based on *in vivo* dynamics of endogenous particles like exosomes have been reported.

However, the processes of uptake, distribution and localization of exogenous fine particles in a living body are still unknown. On the other hand, it is still necessary to elucidate the generation process inside cells and the extracellular dynamics and biological significance of endogenous fine particles. This is an intrinsic problem on development of diagnostic and therapeutic technologies for diseases caused by these fine particles. In addition, due to variation of particle size and lack of good observation techniques, the quantitative analysis and understanding of the dynamics of these particles in a living body have not been elucidated sufficiently and accurately.

To repeat, this research area will promote the elucidation of dynamics and functions of fine particles in a living body and R&D aimed at their control. More specifically, we will pursue the elucidation of biological systems to deal with extracellular fine particles, the development of practical methods based on new techniques to analyze *in vivo* dynamics of fine particles, and the development of new technologies that can contribute to our health based on the methods to control fine particles through identifying their biological significance. Then we will be able to contribute to various solutions of environmental and health problems.

Research Supervisor’s Policy on Call for Application, Selection, and Management of the Research Area

There are various fine particles that affect a living body, including exogenous fine particles such as

PM2.5 and endogenous fine particles formed by cells. Mechanisms of their formation and their effects on a living body are very diverse. Therefore this research area can be studied from various aspects.

In recent years, great attention has been paid to exosomes, which are vesicles released from cells. However, the formation and transmission processes of exosomes have not been fully understood. Originally, a process that signal molecules are released from cells has been studied as “secretion”. In addition, novel secretion mechanisms different from conventional one (unconventional secretion) came to be known recently. There may be mechanisms that we do not know yet through which cells form and release “fine particles”. Novel approaches based on provocative ideas are encouraged to solve these questions.

It is a very important issue how a living body and cells respond to exogenous and endogenous fine particles. There are various exogenous fine particles around us that threaten our health. However, the biological response mechanisms against various exogenous fine particles are not well understood yet unlike against pathogens. There are still many problems to address such as invasion pathways into a body, response mechanisms at a cellular level, and molecular mechanisms for initiation of immune responses, etc. Although exosomes have been highlighted in recent research and the roles of exosomal miRNAs are receiving close attention, effects of exosomes are not exerted by miRNA alone. Many aspects such as identification of signalling molecules, possible concentration processes of molecules into exosomes, and possible mechanisms of targeting exosomes need to be addressed. Steady basic research is required. As described above, it is likely that endogenous fine particles other than exosomes are also released from cells. We are seeking ideas free from conventional dogmas on secretion.

Another important element is development of basic technologies that support and accelerate current research. Because fine particles cannot be observed by our own eyes, technologies for detection, observation, purification, separation, analysis and quantification of various parameters are indispensable to extract precise information about fine particles. Moreover, different approaches are necessary for different kinds of fine particles. Observations of *in vivo* dynamics of fine particles will need some advanced technologies such as super-resolution live imaging. We therefore welcome proposals that pioneer new technologies from various viewpoints.

Understanding of intracellular membrane traffic and cellular immune responses seems to be maturing as a result of active research over past many years. However, much of this understanding is still based on uncertain hypotheses. Paradigm is never unchangeable. We are therefore seeking novel proposals from young researchers who will proactively challenge a paradigm shift.

Specifically, we invite proposals aimed at tackling novel and challenging research by individuals in

the following areas:

(1) Cellular and biological response to exogenous and endogenous fine particles

Proposals for elucidating biological response mechanisms at various levels of cell, tissue, organ, and individual involving fine particles, for example, focus on specific components, sizes, and shapes of exogenous fine particles and issues on immune mechanisms caused by these particles, focus on specific endogenous fine particles and issues on signal transmission mechanisms of biological responses that they cause, or focus on specific biological responses and issues on relationships between various fine particles.

(2) *in vivo* dynamics of exogenous and endogenous fine particles

Issues on the uptake dynamics of exogenous fine particles from environment and processes for their removal by immune system or their accumulation, consequent issues on breakthroughs for measures to eliminate the effects of exogenous fine particles, the dynamic process from the formation of fine particles to functional expression to decomposition of endogenous fine particles, and further, issues to link the above findings to applications such as drug delivery.

(3) Formation mechanism of endogenous fine particles

For example, focus on specific extracellular vesicles and extracellular granules, and issues on the mechanisms underlying their formation and secretion, and, further, issues on their biological significance.

(4) Structure and function of endogenous fine particles

Focus on specific extracellular vesicles or granules and issues on their structures and quantitative determination of nucleic acids and proteins, and, further, issues on the structures and functions of these fine particles themselves and their contents.

(5) Quantitative analysis of fine particles and development and research on basic technology to analyze their dynamics

Technology to separate, detect, and quantify exogenous fine particles of different sizes, shapes, or surface conditions, technology to detect/quantify particles incorporated into a living body, and

technology to observe and trace their *in vivo* dynamics

The issues described above are only “examples”. We would welcome original proposals from unique viewpoints other than these examples.
It would not be appropriate to strictly define or determine a relevant range of “extracellular fine particles” discussed in this research area. Exogenous fine particles may include pollens, spores, bacteria, and viruses, which are of biological origin, although it is desirable for a proposal to specify “a research subject that behaves as a fine particle”. And any organism, not only animals but also plants or microorganisms, should be subject to a living body that responds to exogenous fine particles.

In promoting this research area, we will not only collaborate with the “CREST” research area on fine particles, which is pursued under the same strategic objectives, but also attempt to promote collaboration with other PRESTO areas and related academic associations and research organizations in Japan and overseas for synergy in research development.