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

6.1.1 "Elucidation of biological mechanism of extracellular fine particles and the control system"

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Overview

This research area aims to elucidate biological mechanism of extracellular fine particles and the control system.

There are various extracellular fine particles ranging from nano-sized to micro-sized particles in the living body. They can be classified into two large groups: exogenous fine particles such as PM2.5 and nanomaterials, and endogenous fine particles of in vivo origins, such as extracellular vesicles including microvesicles and exosomes.So far, research on exogenous fine particles has mainly included improvements or safety evaluations of existing materials. Hence, the mechanisms underlying biological responses to these particles and their dynamics have not been fully elucidated. On the other hand, extracellular vesicles, which are endogenous fine particles, have recently been found to play important roles in intercellular communication and be related to many diseases including cancers and cognitive impairments. However, their physiological processes and physiological significance have not been elucidated in detail so far.

Considering the above-described background, this research area combines findings about recognition mechanisms, action principles, and biological responses to approach the elucidation of new biological phenomena caused by extracellular fine particles and to develop base technologies for their control.

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

1. Direction of this research area and profile of solicited research and development themes

A feature of this research area is the fusion of two research communities: one working on exogenous fine particles and the other working on endogenous fine particles. Biological responses elicited by

extracellular fine particles are the result of a series of processes: ❶ uptake of the particle into the body or formation, ❷ addition of functions or inclusion of functional substances, ❸ transportation to a tissue or to cells, ❹ dynamics of immunological response or their avoidance, ❺ uptake into cells, ❻ recovery and decomposition. Processes ❸-❺ are common for exogenous and endogenous fine particles. As for the measurement technologies for fine particles, for example, it is possible to successfully develop useful compound techniques for the separation and analysis in combination with a physical technique mainly for exogenous nanoparticles and a surface recognition technique for biotechnologies. However, considering the present state where the two research communities have shared very few overlapping areas in the past, they do not seem ready to merge hastily. Therefore, although we do not request that the two communities merge into a team for a single research and development objective from the beginning, we would like for the two communities to start sharing their findings and issues in thisresearch area, develop an interdisciplinary and collective research area that has not existed so far, and, as a consequence, elucidate new biological phenomena and develop and create innovative technology.

Based on the above described purposes, we will set the following three pillars for this research area to promote research and development: (1) uptake of extracellular fine particles into the living body and elucidation of biological mechanisms based on the understanding of in vivo dynamics, (2) creating and upgrading base technologies for the detection, separation, measurement, and analysis of extracellular fine particles, and (3) development of the created base technologies for controlling in vivo dynamics of extracellular fine particles.

(1) Uptake of extracellular fine particles into the living body and elucidation of biological mechanisms based on the understanding of in vivo dynamics

① Exogenous fine particles

Although safety evaluation for hazard (source of danger) identification with regard to exogenous fine particles have seen good progress, the actual state of exposure, uptake into the living body, and in vivo dynamics have not been elucidated sufficiently. Neither their accumulation in the living body nor their influence over generations can be said to have been fully studied. Extremely small particles of 0.1 μm in size involved in PM2.5 are known to exert particularly large effects on health. It is reasonable to assume that the different small particles have different effects on the body because they have different origins such as metals and organic substances. In order to elucidate the

mechanisms underlying biological responses to exogenous fine particles, it is important to pay attention not only to their quantities and properties but also to forms of their existence such as coagulation and ionization after they are incorporated into the body.

Therefore, we would welcome proposals focused on the elucidation of biological response mechanisms based on the understanding of the dynamics of fine particles, including recognition mechanisms at the tissue and cell levels and accumulation and decomposition of exogenous fine particles, thus proceeding beyond simple hazard identification of exogenous fine particles.

② Endogenous fine particles

In recent years, it is expected to utilize exosome, one of the extracellular vesicles, for innovative drug development and diagnosis. However, the actual processes that endogenous fine particles undergo and their in vivo dynamics in extracellular vesicles have not been elucidated. Secreted vesicles are currently distinguished by "particle size." One major issue may be the elucidation of its formation mechanism or the identification of factors that control its secretion. Furthermore, because xtracellular vesicles have been confirmed to exist in different species of organisms, the elucidation of their physiological roles is believed to be very significant for basic biology.

Therefore, we would welcome proposals with an emphasis on the elucidation of the formation mechanisms of extracellular vesicles and those aimed at elucidating their physiological significance.

(2) Creating and upgrading base technologies for the detection, separation, measurement, and analysis of extracellular fine particles

It is essential to develop and upgrade new base technologies including technologies to efficiently separate and purify extracellular fine particles in order to promote research for elucidation of biological mechanisms of extracellular fine particles. Because there are practical limitations to in vivo measurements, in particular it seems necessary to utilize simulation technologies, artificial intelligence, and the like in the future for this purpose.

When these base technologies are streamlined to become "usable" technologies, they would become truly meaningful and acquire the status of a global standard. Therefore, we request that a research team working on research and development issues with an emphasis on base technologies creates a developing technology not only for the research team itself but also for other teams in the research

area in a timely manner and receives feedback in order to actively undertake information exchange and joint research.

Furthermore, business firms would need to participate at some point in time to develop a base technology for practical use as a universal technology in the future. Their participation is not necessarily requested at the beginning, but it is recommended that their participation be considered at a proper stage of the research to build a system of cooperation and teamwork with business firms.

(3) Development of the created base technologies for controlling the in vivo dynamics of extracellular fine particles

Extracellular fine particles go through a series of processes: ① uptake into the body or formation, ② addition of functions or inclusion of functional substances, ③ transportation to a tissue or to cells, ④ dynamics of immunological responses or their avoidance, ⑤ uptake into cells, and ⑥ recovery and decomposition to result in various functions or biological responses. Understanding the mechanisms underlying biological responses to fine particles through the above processes is expected to lead to not only the elucidation of biological system but also the control of biological functions including in vivo dynamics.

Therefore, this research area approaches themes based on the control of fine particles, thus aiming to build a technology base that contributes to solution of societal problem including healthy life longevity, safety, and security. Following are specific examples, but not limited to them:

- Basic research on drugs, food, etc. with functions associated with fine particles or on those that contain functional molecules to substantially upgrade the actions and effects on the living body (development of in vivo targeting technologies and the like of functional molecules by developing new materials)
- Basic research that contributes to the development of nanomaterials with safety (development of new functional materials with high applicability to the living body, such as cosmetics)
- Utilization of the immune system to develop technologies to remove harmful fine particles

2. Research team composition

A team of researchers from various areas that incorporates at least two of the aforementioned three pillars is recommended.

3. Points to be noted while writing a proposal

- When writing a proposal for the elucidation of biological mechanism, clearly describe the technical problems that are bottlenecks of existing technologies; also mention how resolving these problems would be milestones and describe the practical possibility of success and the predicted results of preliminary studies. Be aware that it is desirable to not only mention the main technical problems in the development of the base technology but also list up clearly the expected key points at each step of technology development and the expected problems with regard to the application target in the process to be verified.
- Research and development does not necessarily proceed according to the initial plan. Therefore, it entirely possible that the course of research would need to be altered as it progresses. Writing a back-up plan would help realize the technological development that had been initially aimed for.