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Special Issue: Singularity Biology and Beyond

Commentary and Perspective (Invited)

Integration of single-cell manipulation, whole transcriptome analysis, and image-based deep learning for studying "Singularity Biology"

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Molecular identification of cell phenotype is important for the investigation of the role of cells and for their medical applications. For this identification, single-cell whole-transcriptome analysis by RNA sequencing is the gold standard approach. This data-driven approach is a powerful tool to characterize "singularity cells" as well, which are a small number of cells that have a significant impact on a living system [1]. However, this method basically kills the target cell, which prevents further investigation of the cell such as dynamics measurements that provide a crucial insight for understanding "singularity phenomena" [1]. To overcome this open problem, here, we developed a platform based on the integration of live imaging, cell manipulation, omics analysis, and AI (machine learning).

We first developed a multifunctional robot, the Automated Live imaging and cell Picking System (ALPS), that enables automated single-cell picking under an optical microscope and single-cell depositing into a tube or well. We used ALPS to isolate microscopically observed single cells (such as cell lines and peripheral blood mononuclear cells) into each well in a 96-well plate. Then, we performed single-cell RNA sequencing for these deposited cells using our developed protocol. This robotic approach provided the data that linked cell images and the whole transcriptome for more than 1,000 cells efficiently. Using the obtained datasets, we successfully predicted transcriptome-defined cell types among three cell lines with more than 0.8 accuracy from individual cell images using an image-based deep learning model [2]. We are working further to obtain higher accuracy, and currently, the accuracy is increased using other deep learning models.

This noninvasive approach by integrating robotic data acquisition and AI opens a new window to determine the live-cell whole transcriptome in real time. Moreover, this work, which is based on a data-driven approach, is a proof-of-concept for determining the transcriptome-defined (omics-based) phenotypes (i.e., not relying on specific genes) of any cell from cell images using a model trained on linked datasets. Using this approach, we may have an opportunity to identify the features of live "singularity cells", and may be able to understand molecular mechanism(s) behind the "singularity phenomena", e.g., the spontaneous generation of spiral wave in social amoeba operated by a small number of cells [3]. Moreover, controlling the expression of specific genes can be used to manipulate "singularity phenomena" in the future.

In addition, we improved our single-cell RNA sequencing method using our developed DNA molecular barcodes which provide the accurate measurement by removing amplification bias, noise, and sequencing errors [4]. The new protocol contributed to collaborative studies on, for example, immune and neuronal systems [5–8]. This improvement also advanced the collaboration within the Singularity Biology A01-3 group (Table 1) for studying tumor-related immune system and gut-related immunity [9,10].

In summary, A01-3 group in the Singularity Biology developed the measurement and analytical platform which contributes to Singularity Biology. Indeed, we have started multiple collaborations using our developed tools for making a new measurement system for further understanding of "singularity phenomena", including genomic characterization of "singularity cells".

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Table 1 A01-3 group composition and collaborators in the Singularity Biology

A01-3 group	
Principal Investigator	Katsuyuki Shiroguchi (RIKEN)
Collaborating Researcher (CR)	Eiryo Kawakami (Chiba University)
Collaborators in the Singularity Biology	
A03-4 PI	Taku Okazaki (University of Tokyo)

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