News Release

Title

Developing analysis methods to classify the evolution of cancer with regard to treatment resistance
- towards the establishment of new treatment methods and treatment strategies tailored to the cancer evolution of individual patients

Key Points

○ Develop methods to classify the patients of different treatment backgrounds by quantifying similarities in the evolution structure of the cancers within a patient

○ Through an analysis of lung cancer and kidney cancer, identify evolution structures related to recurrence and drug sensitivity

○ Expected that this will form the basis of treatment strategies that predict the evolution of an individual patient's cancer, working towards personalized medicine.

Summary

Designated Assistant Professor Yusuke Matsui and Designated Associate Professor Teppei Shimamura at the Nagoya University Graduate School of Medicine (Dean Kenji Kadomatsu), department of systems biology, cooperated with Professor Satoru Miyano of the Human Genome Center at the University of Tokyo's Institute of Medical Science to develop a statistical scientific approach of inferring and classifying the evolutionary structure of each cancer patient's cancer (Note 1). They demonstrated that the evolutionary principles of cancer in lung and renal cancers differ from one another and that there is a connection between the evolutionary structures of cancer in each patient and their recurrence and resistance to treatment.

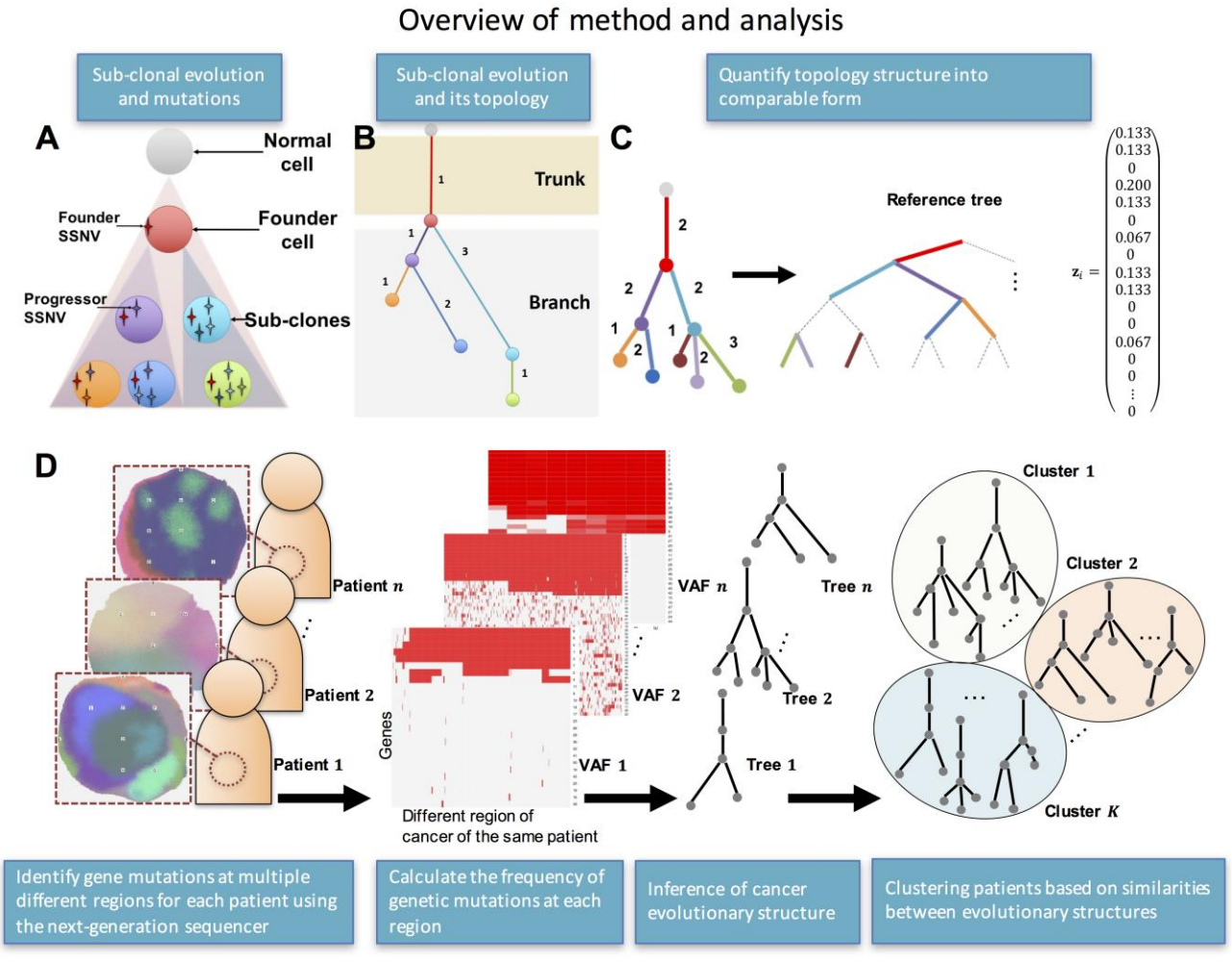
Cancer is thought to occur when a normal cell evolves as it accumulates genetic mutations that lead to abnormal proliferation. The combinations of such genetic mutations differ according to the patient (intertumor heterogeneity), and it is also known that even within a single patient there are cell populations called subclones (Note 2) containing different combinations of genetic mutations (intratumor heterogeneity).

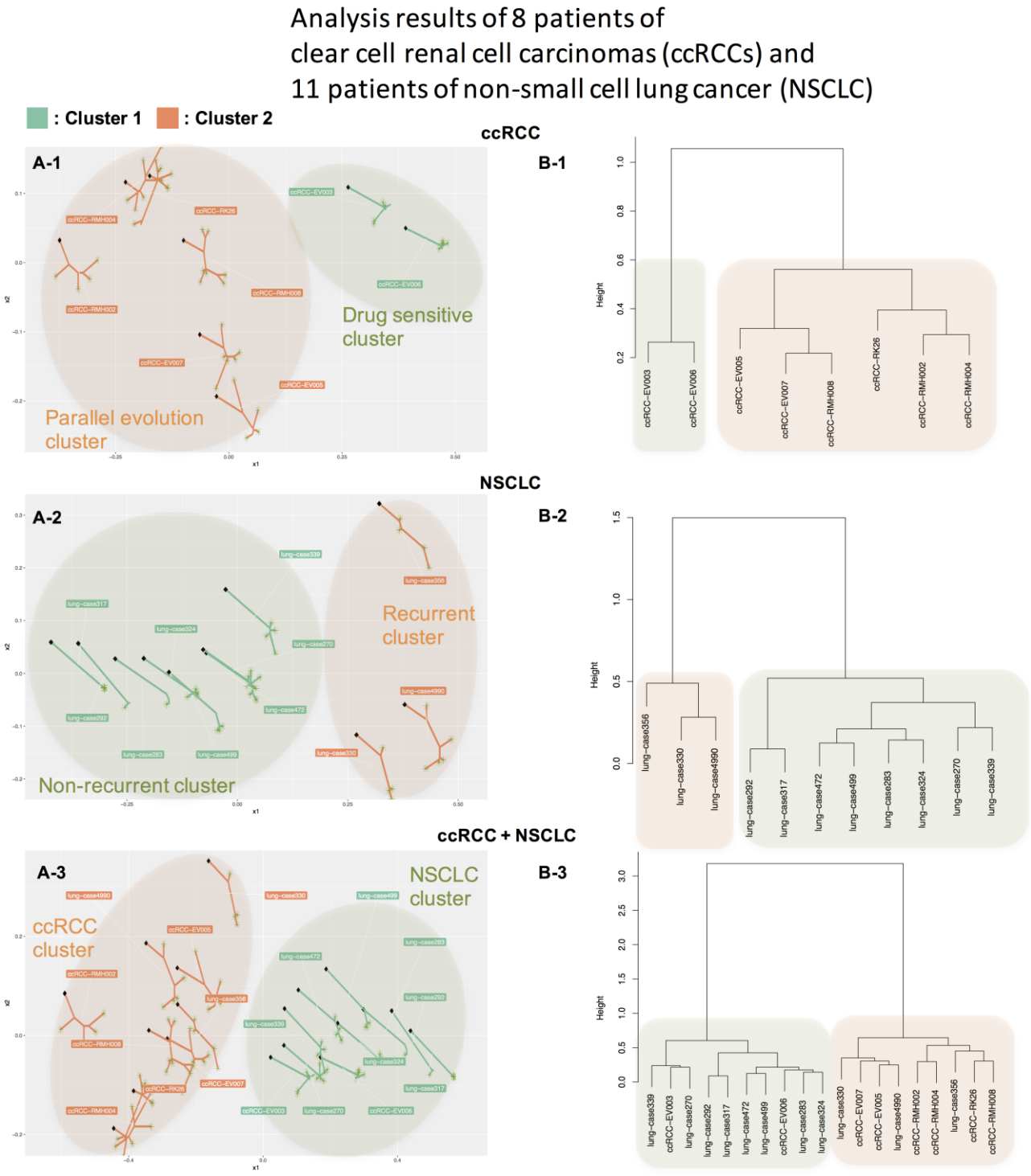
One factor explaining cancer's resistance to treatment and its recurrence are subclones, which indicate a given resistance contained inside a cancer. It is thought that resistant subclones that are originally few in number acquire greater resistance by evolving and proliferating in order to adapt to the environmental change introduced by medication treatment. Therefore, understanding how the evolutionary structure of subclones differs in patients with different treatment backgrounds is important to cancer treatment.

In this research, a next generation sequencer (Note 3) was used to investigate several different regions of genetic mutations in the cancer of a single patient in order to infer the process by which subclones evolved within the patient. The differences in the evolution of

subclones obtained from many patients were quantified in order to develop an analytical method of clustering (Note 4) groups of patients according to the similarity of their subclone evolution. By investigating the connection between each group and their treatment background, it is also possible to investigate the relationship between subclone evolution and treatment response. As a result of actually using this method to analyze clear cell renal cell cancer in eight patients and non-small cell lung cancer in eleven patients, it was discovered that the identified subgroups shared characteristics of recurrence and drug susceptibility.

In the future, it is hoped that this research will provide a foundation for new treatment development and treatment strategies in personalized medicine based upon the evolutionary structure of subclones in each patient. We published the results of this research in the international science journal "PLoS Computational Biology."





Glossary

(1) The evolutionary structure of cancer: The process whereby a part of cancer cell populations proliferate while acquiring new mutations in order to adapt to environmental changes such as medication.

(2) Subclone: Cell populations that possess different combinations of genetic mutations. It is known that multiple subclones exist within a single patient's cancer and this is thought to be one factor behind treatment resistance.

(3) Next generation sequencer: A cutting edge machine capable of reading at once large

quantities of letter strings made up of 3 billion ATCG.

(4) Clustering: An analytical method for grouping together groups of entities according to their mutual similarities.

Research Background

Although cancer is a disease caused by genome mutation, the combination of mutations differs in each patient. Moreover, even in a single patient's cancer, there are cell populations called subclones, which have a combination of different mutations that are thought to have evolved while adapting to the environment, contributing to treatment-resistance. By developing statistical methods that classify and estimate the evolution structure of subclones in patients with varying treatment backgrounds, we identified the subclones' evolution structure in relation to treatment response.

Research Results

By developing statistical methods that classify and estimate the evolution structure of subclones in patients with varying treatment backgrounds, we identified the subclones' evolution structure in relation to treatment response.

Research Summary and Future Perspective

We hope that this will form the basis for the development of new treatment methods and treatment strategies that take into account the evolution of an individual patient's cancer.

Publication

Matsui Y, Niida A, Uchi R, Mimori K, Miyano S, Shimamura T (2017) phyC: Clustering cancer evolutionary trees. PLoS Comput Biol 13(5): e1005509. https://doi.org/10.1371/journal.pcbi.1005509

Japanese ver.

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