様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

科学研究費助成事業　　研究成果報告書

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研究課題名（和文）Molecular basis of immortality-to-mortality switch in the life cycle of Cnidaria

研究課題名（英文）Molecular basis of immortality-to-mortality switch in the life cycle of Cnidaria

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研究成果の概要（和文）：動物の大多数は寿命が限られており、老化のために死にます。 ただし、淡水ポリープHydraや植民地時代のハイドロイドTurritopsisなどの生物学的に不死の生物の例があります。ミズクラゲでは、ポリプは不死であり、クラゲの段階は数ヶ月生きることができます。 このユニークな機能は、無制限の寿命を可能にする（または許可しない）遺伝的メカニズムを分析する機会を与えてくれます。
不死から死への切り替えの分子基盤を理解するために、転写変化、ヒストン修飾のゲノム全体のダイナミクス、およびポリープからクラゲへの移行中のDNAメチル化のパターンを分析しました。

研究成果の学術的意義や社会的意義
In this project we identified genes which might be responsible for the maintenance of unlimited proliferation of Aurelia cells during a polyp stage and the areas of the genome silenced during the switch to mortal jellyfish stage.
Data are available to public at http://compagen.unit.oist.jp/aurelia/

研究成果の概要（英文）：The majority of animals have a limited life span and die due to senescence. However, there are examples of biologically immortal organisms such as fresh water polyp Hydra and a colonial hydroid Turritopsis. In Aurelia jellyfish, similar to that in Hydra, polyps proliferate by budding and are immortal, while during metamorphosis the polyps transform into jellyfishes which survive for just several months. Hence, the same "individual" in Aurelia can be immortal or mortal depending on the stage of the life cycle. This unique feature gives us an opportunity to analyze the genetic mechanisms which allow (or disallow) unlimited life span in Aurelia and potentially in other animals.

In order to understand the molecular basis of immortality-to-mortality switch we analyzed transcriptional changes, genome-wide dynamics of histone modifications and patterns of DNA methylation during polyp-to-jellyfish transition.

研究分野：遺伝学

キーワード：life cycle　Aurelia　polyp　jellyfish　immortality

様　式　C－１９、F－１９－１、Z－１９（共通）

１．研究開始当初の背景

Scientific background

The majority of animals have a limited life span and ultimately die due to senescence. However, there are well described examples of biologically immortal organisms such as fresh water polyp *Hydra* (Martinez, 1998, Exp. Gerontol. 33(3):217-225) and a colonial hydroid *Turritopsis* (Piraino et al., 1996, Biol.Bull, 190:302-312; Kubota, 2011, Biogeography, 13:101-103).

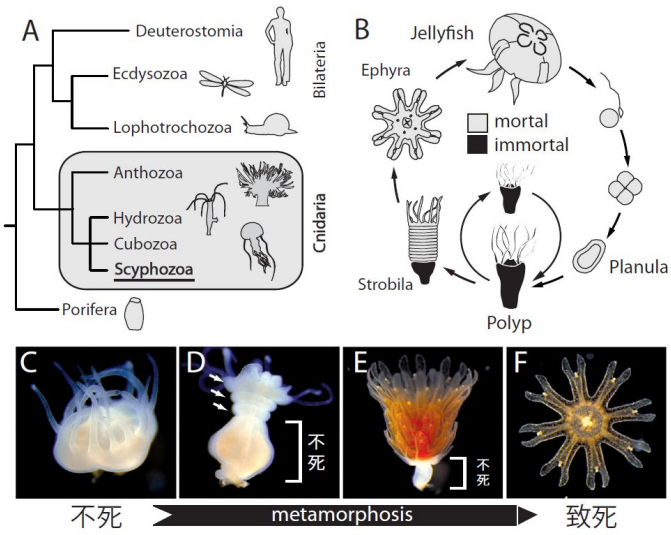

Figure 1: (A) The phylum Cnidaria is a sister group to all bilaterian animals. *Aurelia* is a scyphozoan jellyfish. (B) Life cycle of *Aurelia aurita*. black - immortal stages; grey - mortal stages (C-F) Polyp to jellyfish transition in *Aurelia*. Polyp (C) is divided into multiple segments (D) which develop into young jellyfishes (E,F).White arrows, segments. C, polyp; D, strobila, E, late stage of strobilation; F, ephyra; white bracket, "immortal" polyp tissue retained during metamorphosis.

In scyphozoan *Aurelia aurita* there are two alternating generations - polyps and jellyfishes (see Fig.1A-B). *Aurelia* polyps, similar to that in *Hydra*, proliferate asexually by budding and are immortal while during metamorphosis they transform via strobila stage into jellyfishes which can only survive for several months. In contrast to *Turritopsis*, adult *Aurelia* jellyfishes can not reverse back into polyp stage and their "mortal" state, therefore, seems to be fixed. Hence, the same "individual" in *Aurelia* can be immortal or mortal depending on the stage of the life cycle (Fig.1C-F). This unique feature gives us an opportunity to analyze the genetic mechanisms which allow (or disallow) unlimited life span in *Aurelia* and potentially in other animals.

２．研究の目的

Purpose of the project

Molecular basis for immortality in *Hydra*, *Turritopsis* and *Aurelia* is unknown. One possible reason for extraordinary longevity in these species might be the unlimited self-renewal and proliferation capacity of their stem cells. Such an unusual feature would allow perpetual tissue repair in the organism and the absence of senescence as a consequence. When *Aurelia* polyps metamorphose into jellyfishes they lose their immortal state. The main propose was to search for the mechanisms of this phenomenon in *Aurelia*.

３．研究の方法

Research method

In *Aurelia* we can compare immortal polyps, polyps during metamorphosis (they are gradually losing their immortal state) and jellyfishes of different age which live for just several months (see Fig.1B). Moreover, foot part of a polyp does not undergo metamorphosis and retains full capacity for unlimited life span (see Fig.1E). Hence, *Aurelia* is convenient and informative model to study molecular mechanisms of immortality-to-mortality transition which takes place during ontogeny. In one individual we have tissues (body areas) which are immortal or have a life span limited to several months. Thus, we can compare various molecular features associated with these distinct states. In order to understand the molecular basis of immortality-to-mortality switch we analyzed transcriptional changes, genome-wide dynamics of histone H3 modifications and patterns of DNA methylation during polyp-to-jellyfish transition.

４．研究成果

Research outcomes

In the course of the project the reference genome assembly of *Aurelia* was drastically improved by using NanoPore / PacBio data and reached N50 = 5Mbp with 50% of the genome in just 57 scaffolds. This resulted in the refinement of gene models and allowed considerable simplification of downstream analysis of RNAseq and epigenetic data.

According to the original research plan the detailed analysis of differential gene expression during polyp-to-jellyfish transition with the special focus on the comparison of immortal and mortal tissues of strobila has been performed. Patterns of DNA modifications at the various stages of the life cycle were analyzed by PacBio and NanoPore sequencing.

Preliminary analysis of the results shows that there might be considerable differences in DNA methylation not only between the life stages, but also among the cells belonging to different lineages within each stage. For example, epithelial cells in the ectodermal and entodermal tissue layers have different methylation patterns in multiple loci. This finding is important for the interpretation of the results and data processing. It indicates that the analysis of genome modifications in the specific cellular populations that undergo trans-differentiation during metamorphosis (for example, ectodermal cells of sub-umbrella region which give rise to striated muscle cells) might provide much better view of epigenetic mechanisms that regulate jellyfish life cycle progression. In the initial "whole-body" approach the differences between cell types may to some extent obscure the differences between the stages and these differences should be taken care of in the course of data analysis. Integration of RNAseq and epigenetic data is in progress.

Transcriptomic and genomic data generated by this project were integrated into web resources and utilized as reference datasets in several publications. These recourses from *Aurelia* created at Marine Genomics Unit at OIST can be accessed at http://compagen.unit.oist.jp/aurelia/. In order to download data which are already publicly available or to perform BLAST searches please use the following credentials (Login: guest Password: welcome).

５．主な発表論文等

〔雑誌論文〕　計4件（うち査読付論文　4件／うち国際共著　4件／うちオープンアクセス　4件）

１．著者名 Khalturin K, Billas IML, Chebaro Y, Reitzel AM, Tarrant AM, Laudet V, Markov GV	４．巻 184
２．論文標題 NR3E receptors in cnidarians: A new family of steroid receptor relatives extends the possible mechanisms for ligand binding	５．発行年 2018年
３．雑誌名 J Steroid Biochem Mol Biol	６．最初と最後の頁 11-19
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.jsbmb.2018.06.014	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

１．著者名 Khalturin K, Shinzato C, Khalturina M, Hamada M, Fujie M, Koyanagi 5, Kanda M, Goto H, Anton-Erxleben F, Toyokawa M, Toshino S, Satoh N	４．巻 3(5)
２．論文標題 Medusozoan genomes inform the evolution of the jellyfish body plan	５．発行年 2019年
３．雑誌名 Nature Ecology and Evolution	６．最初と最後の頁 811-822
掲載論文のDOI（デジタルオブジェクト識別子） 10.1038/s41559-019-0853-y	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

１．著者名 Hamada M, Satoh N, Khalturin K	４．巻 10(11)
２．論文標題 A Reference Genome from the Symbiotic Hydrozoan, Hydra viridissima.	５．発行年 2020年
３．雑誌名 G3 (Bethesda)	６．最初と最後の頁 3883-3895
掲載論文のDOI（デジタルオブジェクト識別子） 10.1534/g3.120.401411	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

１．著者名 Shinzato C, Khalturin K, Inoue J, Zayasu Y, Kanda M, Kawamitsu M, Yoshioka Y, Yamashita H, Suzuki G, Satoh N	４．巻 38(1)
２．論文標題 Eighteen Coral Genomes Reveal the Evolutionary Origin of Acropora Strategies to Accommodate Environmental Changes	５．発行年 2021年
３．雑誌名 Mol Biol Evol	６．最初と最後の頁 16-30
掲載論文のDOI（デジタルオブジェクト識別子） 10.1093/molbev/msaa216	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

〔学会発表〕　計2件（うち招待講演　1件／うち国際学会　0件）

1．発表者名 Konstantin Khalturin
2．発表標題 Genetic basis of a jellyfish body plan
3．学会等名 13-th NCB (The Nippon Cnidarian Biologists) Meeting
4．発表年 2017年

1．発表者名 Konstantin Khalturin
2．発表標題 Genomes of Aurelia and Morbakka jellyfishes
3．学会等名 我が国の刺胞動物研究の発展（東京大学大気海洋研究所）（招待講演）
4．発表年 2017年

〔図書〕　計0件

〔産業財産権〕

〔その他〕

Aurelia aurita Genome Browser https://marinegenomics.oist.jp/aurelia_aurita/viewer/info?project_id=69 Genomic and transcriptomic resources for Cnidaria http://compagen.unit.oist.jp/aurelia/

6．研究組織

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考

7．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

８．本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関