論文 / 著書情報
Article / Book Information

題目(和文)	天然化合物による細胞内microRNAとAnnexin A2による細胞外microRNA調節機構の解明
Title(English)	Regulation of intracellular microRNA by natural products and extracellular microRNA by Annexin A2.
著者(和文)	萩原啓太郎
Author(English)	Keitaro Hagiwara
出典(和文)	学位:博士（理学）, 学位授与機関:東京工業大学, 報告番号:甲第9956号, 授与年月日:2015年9月25日, 学位の種別:課程博士, 審査員:黒川　顕,徳永　万喜洋,川上　厚志,立花　和則,中島　信孝
Citation(English)	Degree:Doctor (Science), Conferring organization: Tokyo Institute of Technology, Report number:甲第9956号, Conferred date:2015/9/25, Degree Type:Course doctor, Examiner:,,,,
学位種別(和文)	博士論文
Category(English)	Doctoral Thesis
種別(和文)	要約
Type(English)	Outline

平成 27 年度　学位論文

Regulation of intracellular microRNA by natural products and extracellular microRNA by Annexin A2.

(天然化合物による細胞内 microRNA と Annexin A2 による細胞外 microRNA 調節機構の解明)

生命理工学研究科　生命情報専攻
黒川・中島・山田研究室
博士 3 年
萩原　啓太郎

指導教官　黒川　顕教授

Thesis Outline

Therapeutic strategies are essential for curing human cancer [1]. Therefore, a continuous search for new approaches to tackle human diseases is important. Indeed, I previously describe a novel and important function of RPN2-mediated CD63 glycosylation, which regulates MDR1 localization and cancer malignancy, including drug resistance and invasion (Fig. 1).

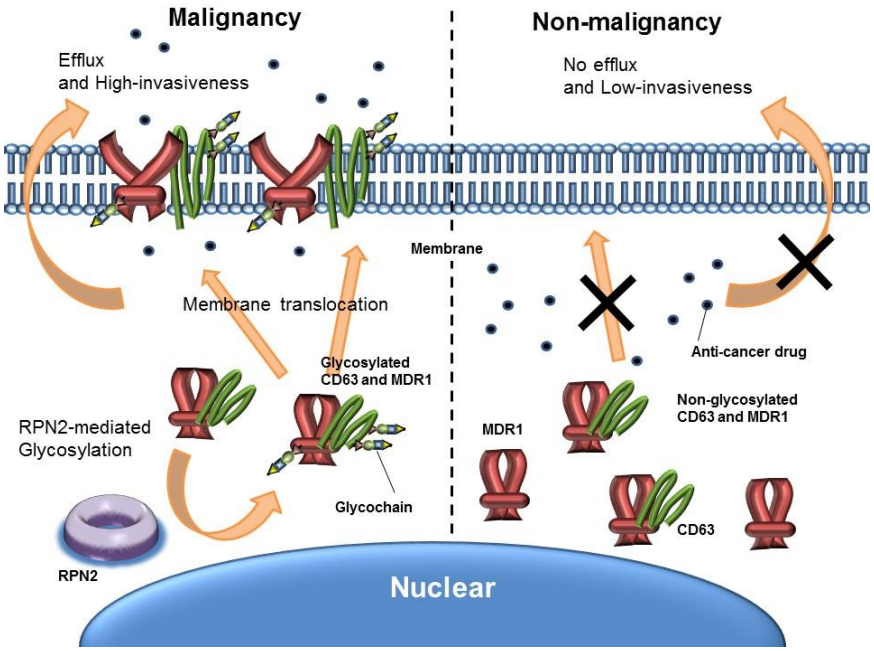

Figure 1 | The mechanism of RPN2-mediated CD63/MDR1 glycosylation pathway in breast cancer cells

The discovery of RNA interference (RNAi), which is mainly performed microRNAs (miRNAs) that attenuate translation, for target-specific gene silencing has rapidly created a powerful tool for the exploration of pathogenesis of human cancer [2-4]. miRNAs have been identified as a fine-tuner of a wide range of biological processes, including development, organogenesis, metabolism, and homeostasis (Fig. 2).

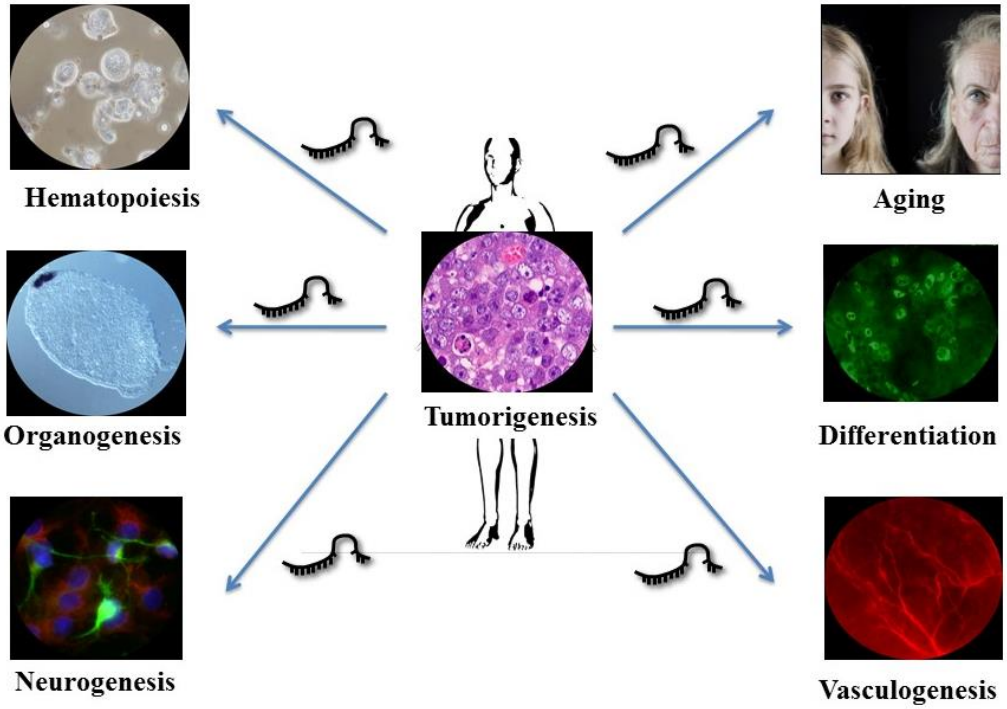

Figure 2 | miRNAs regulate many physiological process

Deregulation of miRNAs leads to the development of several types of diseases [5,6]. Indeed, more than 70 diseases have been reported to be associated with miRNA deregulation [7]. The identification of these remarkable molecular pathways has manifested a new field of gene therapy. For instance, we previously reported key miRNAs that were deregulated in a highly malignant CD133high population and found that miR-133a regulated the cell invasion that characterizes a lethal tumor phenotype. Silencing of miR-133a with locked nucleic acid (LNA) reduced cell invasion of this cell population, and systemic administration of LNA along with chemotherapy suppressed lung metastasis and prolonged the survival of osteosarcoma-bearing mice (Fig. 3).

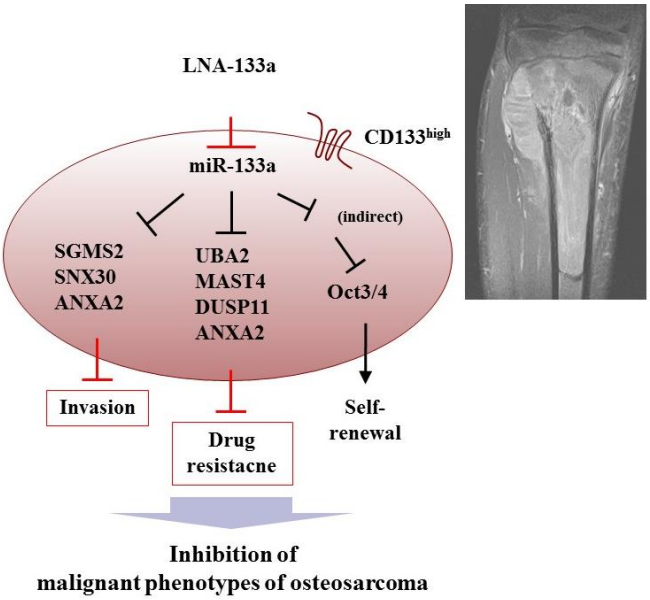

Figure 3 | The scheme of miR-133a pathway in osteosarcoma

In addition, we also identified a miR-197/CKS1B/STAT3-mediated PD-L1 network in chemoresistant non-small-cell lung cancer (NSCLC), independent of immunoinhibitory signals. miR-197 is downregulated in platinum-resistant NSCLC specimens, resulting in the promotion of chemoresistance, tumorigenicity, and pulmonary metastasis *in vitro* and *in vivo* (Fig. 4).

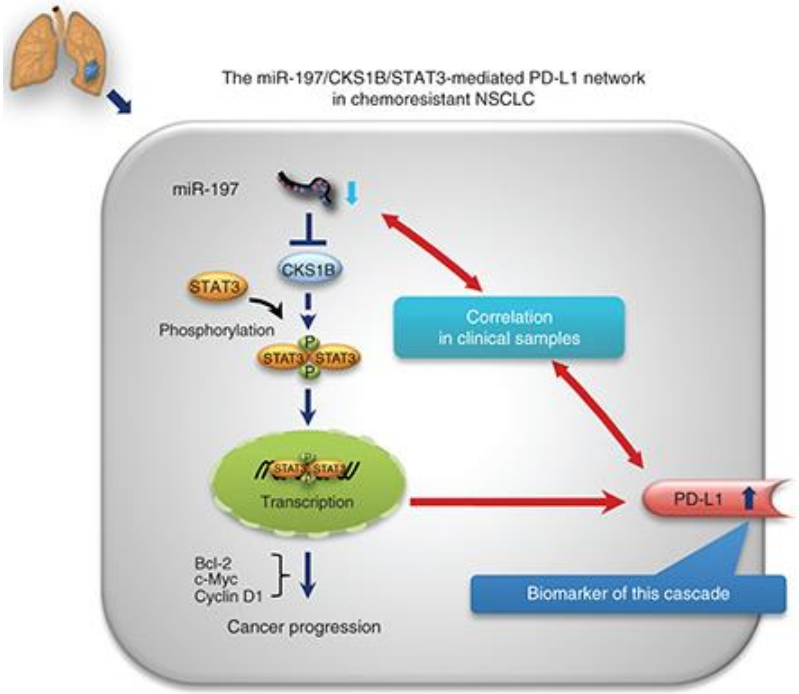

Figure 4 | The scheme of the miR-197/CKS1B/STAT3-mediated PD-L1 network in chemoresistant NSCLC

Moreover, two human clinical trials have assessed directed miRNA-targeting as therapeutics, according to ClinicalTrials.gov (http://clinicaltrials.gov). One staudy is anti-miR-122 therapy against chronic hepatitis C and another trial ismiR-34 mimics as a therapeutic against primary and metastatic liver cancer [8,9]. However, the clinical use of miRNA entails at least two critical steps: delivery of miRNA to the appropriate tissues and subsequent maintenance and expression. A key goal of target-specific RNAi-delivery technology for cancer is the development of delivery systems directed at the target tissues only. Currently, there are many types of drug delivery systems. However, these methods have several limitations such as the lack of delivery systems that are safe, efficient, tissue specific and that do not cause immune and inflammatory responses when they are used *in vivo*. In this thesis, I reported two approach to resolve these problems; miRNA-upregulation by using natural products in chapter 1, miRNA-based screening in chapter 2, and the mechanism of extracellular miRNAs in chapter 3. My goal is preemptive medicine that is new medical paradigm that identifies an individual's susceptibility to a disease at the earliest possible stage by using predictive diagnosis and precise medicine. It is well known that miRNAs as biomarkers are one of the basis for preemptive medicine and available for early diagnosis of several diseases. My study will have an important impact for future development of miRNA therapy for preemptive medicine (Fig. 5).

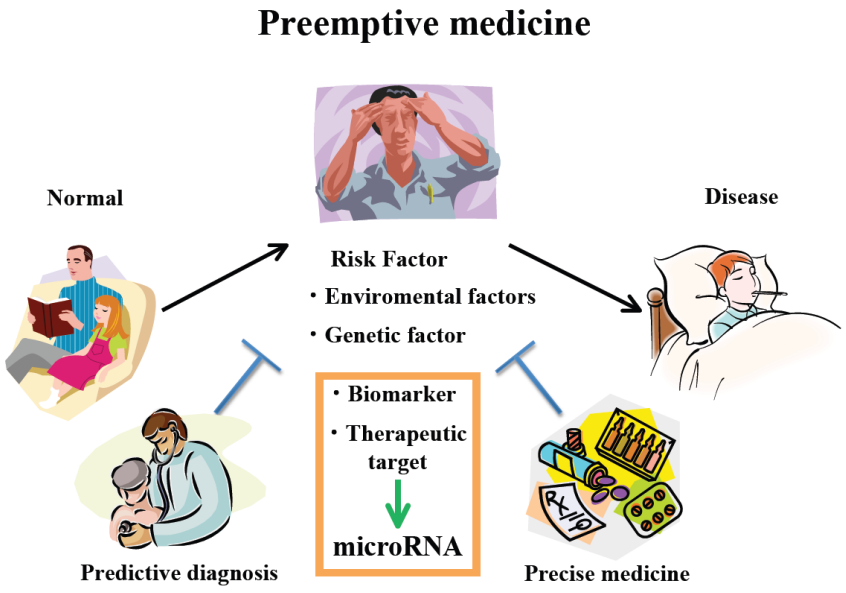

Figure 5 | The scheme of preemptive medicine