センター内アセット

作成日　2017/10/31

課題名	DNA 複製ストレス抵抗機構を標的とする新規抗がん剤の開発
研究代表者と所属	塩谷文章（細胞情報学分野）
共同研究者と所属	

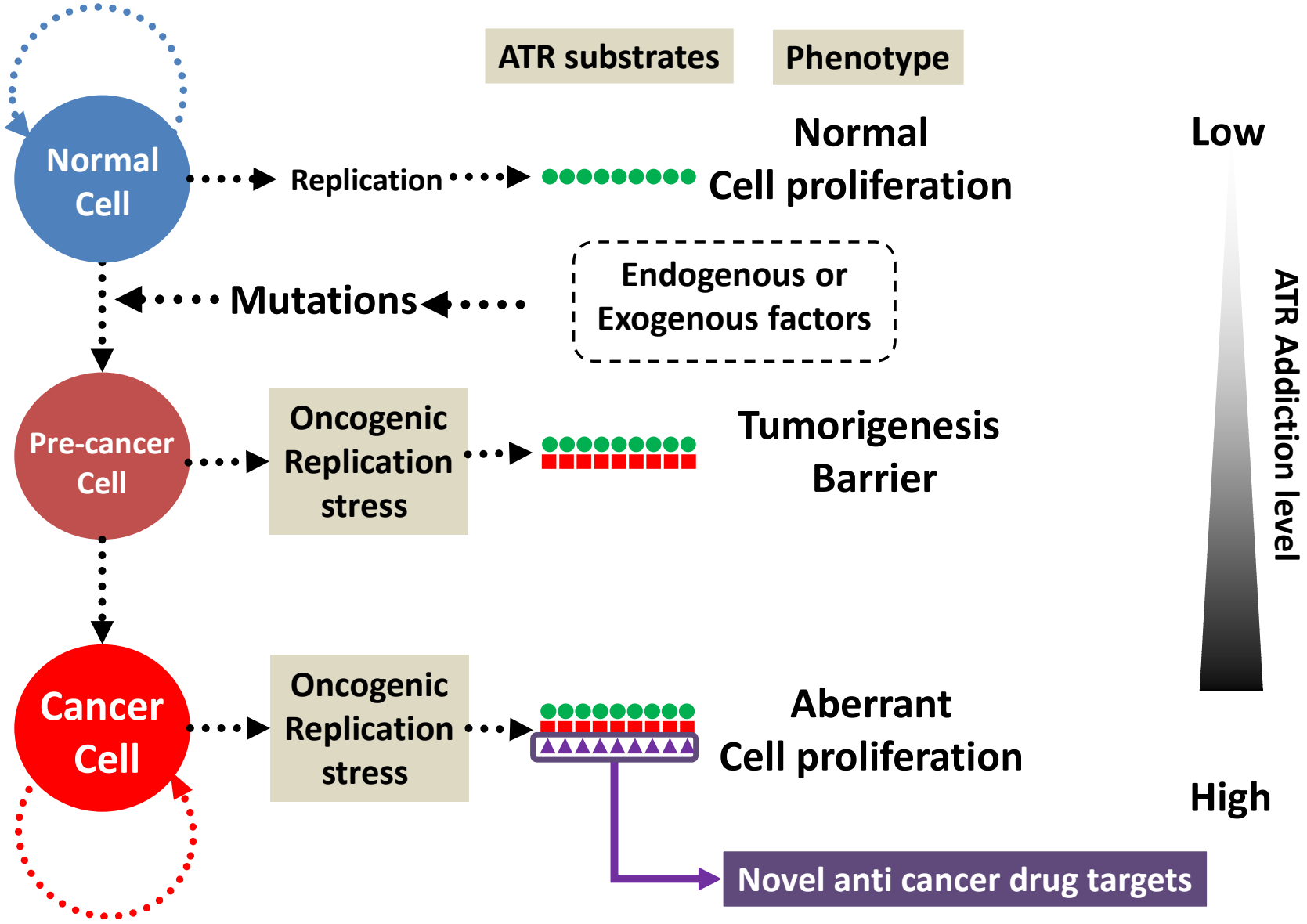
	Novelty	Speed	Capacity	Versatility	Cost	Human sample
Evaluation methods & systems						
Novel original cell lines						
New target identification	◎	×		○	×	
Platform technologies						
Compounds, Antibody, etc						

Strongest point=◎　Strong point=○　Weak point=×

対象疾患	悪性腫瘍：現在は肺腺がんを対象にしているが将来的には臓器横断的な治療を提案。
アセットの概要	● がん細胞に共通する DNA 複製ストレス抵抗性を制御する ATR キナーゼの特異的基質を分子標的として同定。 ● ドライバー遺伝子に依存しない治療が可能 ● 様々な臓器由来の腫瘍を対象としうる。 ● 将来的な超早期治療（がん予防）薬としての可能性
関連する研究費 （申請中を含む）	国立がん研究センター研究開発費（シーズ選定課題） 応募中：科研費基盤研究 B、科研費挑戦的萌芽研究、がん研究振興財団、高松宮妃がん研究基金
論文、特許、共同研究、grant	(1) *Shiotani B and *Zou L. Signaling of DNA Replication Stress through the ATR Checkpoint. In Hanaoka F. and Sugasawa K. (ed.) ***DNA Replication, Recombination and Repair - Molecular Mechanisms and Pathology***, Springer, 405-428, 2016 ***These are co-corresponding.** (2) Shiotani B, *Zou L. Single-Stranded DNA as an ATM-to-ATR Switch at DNA Breaks. ***Mol. Cell***, 33: 547-558; 2009. (3) Liu S[1], Shiotani B[1], Lahiri M, Maréchal A, Tse A, Yang XH, and *Zou L**,** ATR Autophosphorylation as a Molecular Switch for Checkpoint Activation**. *Mol. Cell*,** 43: 192-202; 2011 **[1]These authors are equally contributed.** (4) *Shiotain B., Nguyen H.D., Håkansson P., Maréchal A, Tse A., Tahara H., and *Zou L, Two Distinct Modes of ATR Activation Orchestrated by Rad17 and Nbs1. ***Cell Reports***, 3: 1651-1662; 2013 ***These are co-corresponding.**

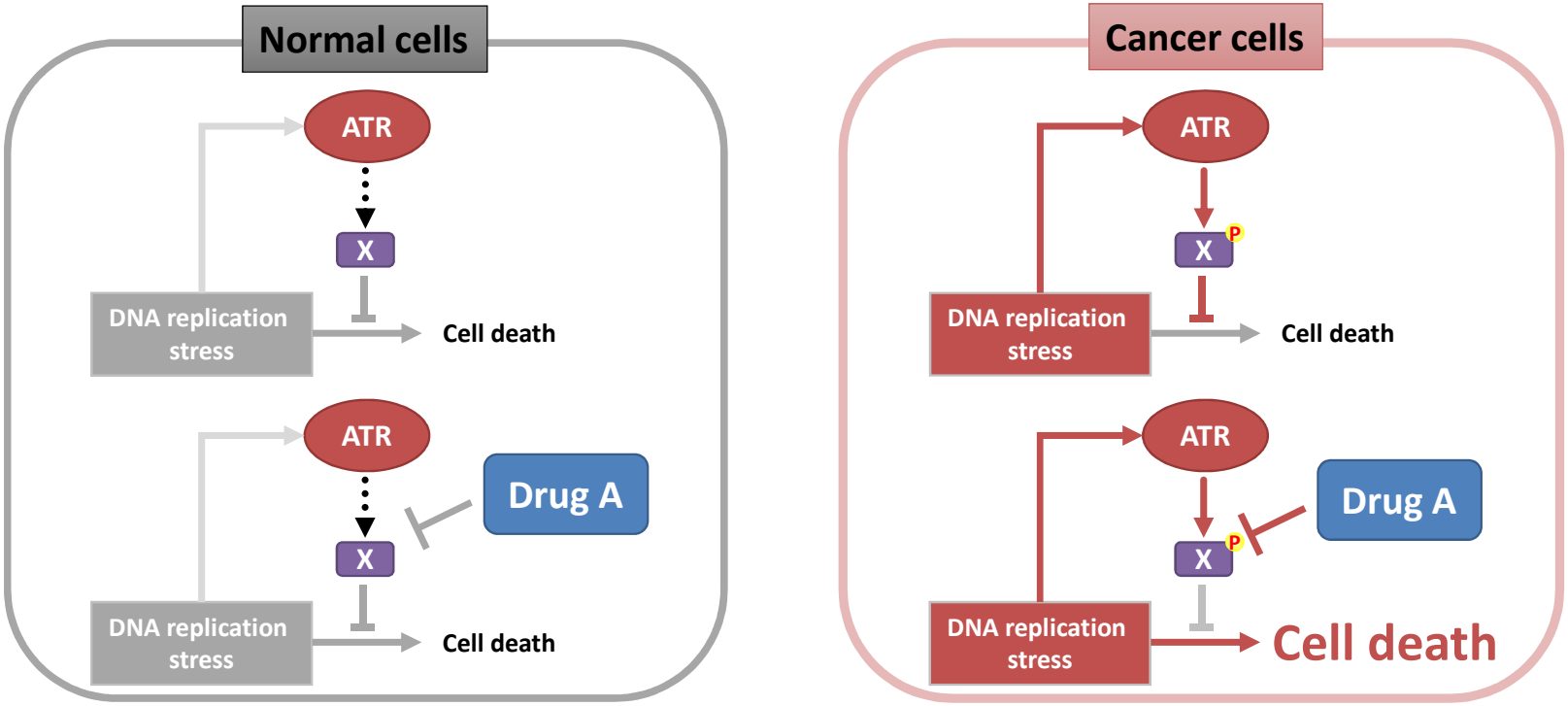
	(5) Hirokawa T., **Shiotani. B**, Shimada M., Murata K., Johmura Y., Haruta M., Tahara H., Takeyama H., and *Nakanishi M., CBP-93872 is an inhibitor of NBS1-mediated ATR activation that abrogates maintenance of the DNA-double-stranded break-specific G2 checkpoint. ***Cancer Res***., 74: 3880-3889, 2014

ATR function could be different between normal and cancer cells

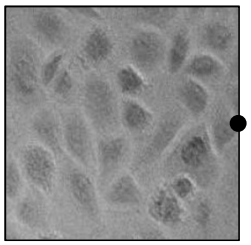


Goal:

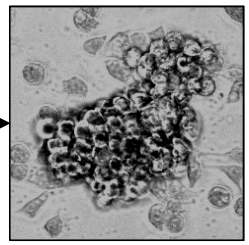
By analyzing the ATR signaling pathway that regulates the DNA replication stress resistance which is a hallmark of cancer cells, we will identify a druggable signaling pathway and establish a molecular basis for future novel molecular targeted drug development



Our Strategy to identify specific ATR substrates in transformed cell



Oncogene activation



Normal cells

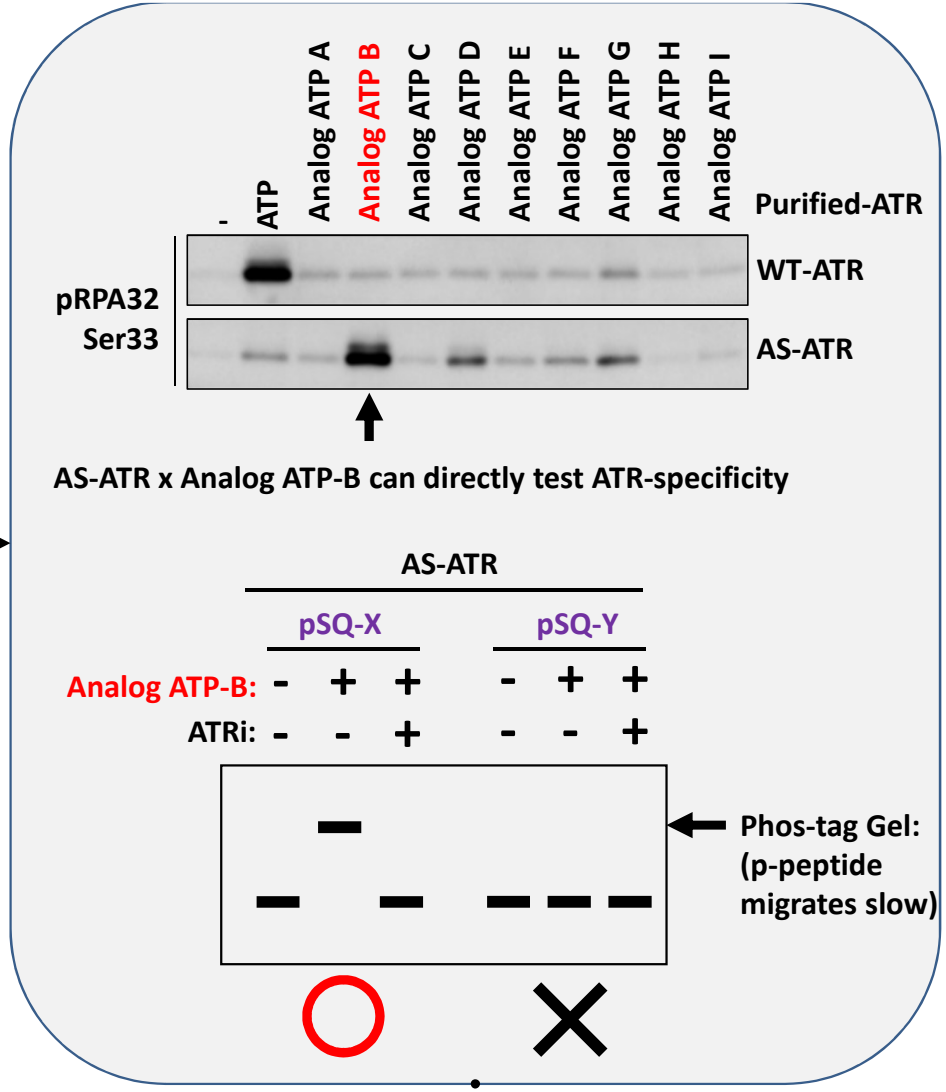
Transformed cells

Quantitative Phosphoproteomics
(Total p-site: 5572)

pSQ/pTQ (ATR consensus site: 90)

pSQ/pTQ sites
Higher in Transformed cell (15)

ATR specificity check by in vitro kinase assay

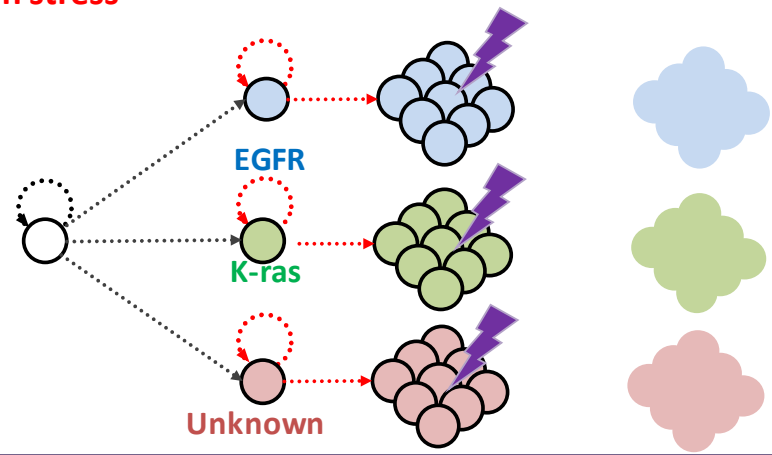


Functional analysis (Druggability)

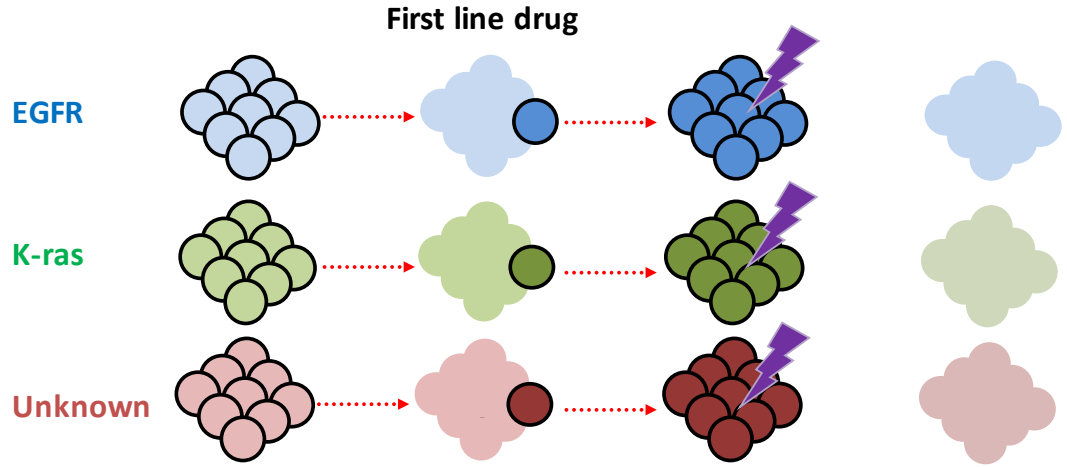
Possible applications of Drug A targeting ATR substrate X (Independent of driver mutations)

General risk factor ····▸

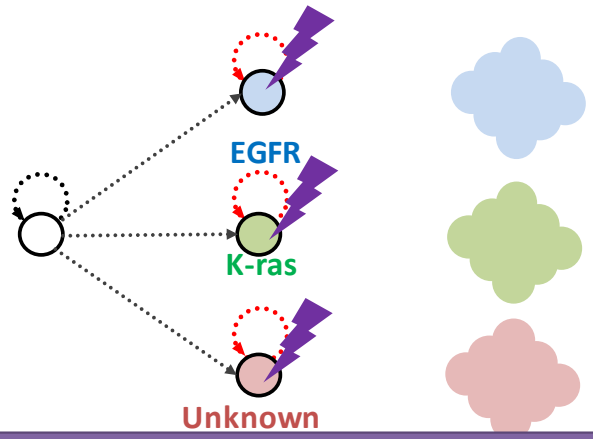
Replication stress ····▸



First line



Second line for drug resistant tumor



Ultra-early treatment: Cancer prevention

Other options

- Sensitize conventional chemotherapy and radiotherapy
- Work for tumor derived from a wide variety of organs
- p-X antibody as a predictive biomarker for ATR inhibitor