2021年7月7日
7th July, 2021

大学院学生各位　To All Graduate Students

2021年度 基盤医学特論 開講通知 Information on Special Lecture Tokuron & Tokupro AY2021

特徴あるプログラム CIBoG オミクス解析学プログラム
CIBoG Omics Analysis Program

題目：全がん解析によるがん遺伝子における複数変異の全体像と意義の解明

Title ：Landscape and significance of multiple mutations in oncogenes

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日時：2021年8月23日（月）17：00～18：30　(Zoom)

Time and Date：23th August, 2021 17:00-18:30(Zoom Lecture)

使用言語：日本語　Language：Japanese

概説：Although sporadic reports have described cases possessing multiple driver mutations(MMs) in the same oncogene, their landscape and relevance remain elusive. Here weperformed a pan-cancer analysis of 60,638 samples, and evaluated the frequency of MMsin different oncogenes. Although several highly mutated oncogenes contained no or fewMMs, such as IDH1, MMs were frequently observed across a wide variety of oncogenes,including PIK3CA and EGFR. To identify genes recurrently affected by driver-driver MMs,we applied a permutation-based approach, and identified 14 oncogenes (hereafter MM+oncogenes) where MMs occur more frequently than expected (1-10% of mutated genes).Phasing from RNA sequencing and whole-exome/genome sequencing reads revealed thatMMs are preferentially present in cis in oncogenes. Importantly, the proportion of MMs incis was particularly high in MM+ oncogenes (89%), which was confirmed by long-readgenomic sequencing and cDNA Sanger sequencing of cell lines harboring oncogenic MMs.To evaluate the biological role of MMs, we transduced PIK3CA single or double mutantsinto several cell lines. Importantly, PIK3CA MM-transduced Ba/F3 cells showed markedlyenhanced viability and proliferation than those with single PIK3CA mutants, other thancombinations of mutations from the same functional domain. In subcutaneous mousexenograft model, PIK3CA MM-transduced MCF10A cells displayed significantly increasedtumor growth than those with single mutants. Consistent with this, PIK3CA double mutantsaugmented AKT phosphorylation more than single mutants. To understand the molecularmechanism of PIK3CA MMs, we finally performed a molecular dynamics (MD) simulationsof exemplary synergistic mutants (R88Q and H1047R). The simulation confirmed thepredicted single mutant-induced conformational changes: instability of the R88-D746 saltbridge between the ABD and kinase domains by R88Q and distorted orientation of thekinase domain by H1047R. Unexpectedly, R88Q-H1047R double mutant caused acleavage of the R38-D743 salt bridge, leading to further detachment of the ABD-kinasedomain interface, which can promote ABD domain movement and subsequent iSH2rotation. The coordinated (or amplified) structural alteration may underline the PIK3CA MM-enhanced downstream pathway activation. Together, our results suggest that oncogenicMMs in cis synergistically function and are a common driver event in human cancers.

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