Mechanism of oncogenic signal activation by the novel fusion kinase FGFR3-BAIAP2L1

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SUMMARY

Targeted cancer genome profiling studies have identified many novel genetic alterations, including rearranged fibroblast growth factor receptor (FGFR) family members. However, most fusion genes are functionally unknown and their oncogenic roles in vivo remain unclear. In a previous study, we investigated the recently discovered gene fusion between FGFR3 and BAIAP2L1, a novel FGFR3 fusion in Non-Hodgkin lymphoma (BAIL, BAILA). We identified 4 patients with bladder cancer and 2 with lung cancer harboring the fusion gene via next generation sequencing (NGS) and confirmed the activation of FGFR3 kinase activity in vitro and in vivo. The gene set revealed that FGFR3 kinase activity is critical for tumorigenic activity.

METHODS

Oncogenic potential of FGFR3-BAIAP2L1

Classification of 327 cell lines

Purification of total RNA at the normal culture condition of 5% of cells

Scheme of pathway analysis

Pathway identification regulated by FGFR3-BAIAP2L1

RESULTS

Potential anti-tumor activity of CH518284/Debio 1347, a FGFR selective inhibitor against FGFR3-BAIAP2L1 tumors

Significant activation of MAPK pathway and suppression of tumor suppressive pathway by FGFR3-BAIAP2L1

ACKNOWLEDGEMENTS

CLINICAL TRIAL

REFERENCES


CONCLUSION

- FGFR3-BAIAP2L1 fusion was identified in patients and showed potent tumorigenic potential by dimerization via the BAR domain of BAIAP2L1.
- The selectively orally available FGFR inhibitor CH518284/Debio 1347, effectively inhibits in vivo tumor growth of cells harboring FGFR3-BAIAP2L1.
- FGFR3-BAIAP2L1 could activate MAPK pathway and attenuate tumor suppressive pathways. (ex. TP53)

In summary, targeting harboring FGFR gene fusions such as FGFR3-BAIAP2L1 for FGFR selective therapy as Debio 1347/CH518284/Debio 1347 could be a promising approach not only for FGFR fusion carrying tumors but also for FGFR transcriptionally activated tumors. A combination therapy with MAPK pathway inhibitor would be considered as a vertical pathway inhibition approach.