

## The Distinct Characteristics of Gastric Cancers with CLDN18-ARHGAP Fusion Gene

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The presence of CLDN18-ARHGAP fusion gene in Gastric Cancer (GC) has been recently highlighted [1-5], and it was indeed a pleasure to read the article by Nakayama, et al. [1], who nicely performed a study on 146 Early-Onset Gastric Cancer (EOGC) patients to investigate the molecular traits, and concluded that the CLDN18-ARHGAP fusion gene is enriched in EOGC, which could contribute to their aggressive features and poor prognosis. In fact, we also conducted some research about the CLDN18-ARHGAP fusion gene using thousands of patients, and some results were largely consistent with this study, despite that we were concerned about Signet-Ring Cell Gastric Cancer (SRGC) [2] whereas Nakayama focused on EOGC.

In addition to the reported fusion pattern of CLDN18-ARHGAP26 in TCGA, [3] a couple of rare unreported types of ARHGAP fusion with CLDN18, namely ARHGAP42/exon7 or ARHGAP10/exon8 were found in Nakayama's cohort [1]. Meanwhile, an unprecedented case of CLDN18/exon4-ARHGAP26/exon11 has been identified in our patient cohort [2]. All of these ARHGAP genes were found to be fused to CLDN18 in an in-frame manner, and an expression of chimeric protein with the GAP activity is retained and whole region of the most conserved domain of CLDN18 has been retained among these ARHGAP or CLDN18 subtypes, indicating the similar features and roles of such fusion pattern as others.

Notably, some distinct characteristics exist in gastric cancer patients with CLDN18-ARHGAP fusion gene. Firstly, from the molecular and cellular level, the frequency of this fusion is enriched in the GS (genomically stable) subgroup stratified by TCGA, which is mutually exclusive with RHOA and CDH1 somatic mutations [6]. Besides, it also plays a key role in cell migration and motility in vitro, and exhibits resistance to 5Fu-based chemotherapy, indicating its aggressive biological behavior

and unsatisfactory outcome towards chemotherapy. Moreover, from the clinical aspect, the prevalence of this fusion gene is significantly associated with younger age, signet-ring cell content, diffused type, advanced stage, demonstrating a poor clinical course, which are all related to an unfavorable prognosis. Lastly, patients with CLDN18-ARHGAP tend to show a worse survival than those who are without, no matter for SRGC or EOGC.

Whether SRGC or EOGC, they share something in common because of their disadvantageous clinicopathologic features and detrimental survival [7]. The fusion gene, CLDN18-ARHGAP, is enriched in these subtypes of gastric cancer, which is in accordance to the distinct clinical characteristics and treatment outcomes. As we know, there is no robust evidence to address how its expression would affect cellular process and biological function, and whether the fusion protein could be the target to improve gastric cancers' sensitivity towards chemotherapy. Therefore, further studies on its detailed molecular mechanism are needed in the near future to gain better insight about CLDN18-ARHGAP fusion gene.

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