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Commentary

Novel gene fusions found in cervical cancer

Yiwei Ling [a,b], Shujiro Okuda [a,*]

[a] Division of Bioinformatics, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
[b] Division of Cancer Genome Informatics, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Over the last decade, modern medicine has always concentrated on the exploration of relationships between somatic mutations, abnormal chromosome structures and various illnesses which are difficult to cure, in the hope of capturing something crucial for gene therapies [1]. Among the various types of chromosome abnormalities, chimeric fusions have proved to be a potential critical therapeutic target of cervical cancer [2]. However, how to highlight the frequent fusions and discriminate significant ones for clinical therapy has been an ongoing issue since the start. In view of this, the method to certify clinically relevant gene fusions is particularly worthy to discuss and to be examined in practice. To solve these problems, a novel and innovative attempt was performed in a study inf this issue in EBioMedicine [3] by Wu Peng and colleagues, who have continued to examine the mechanism of cervical carcinogenesis [4]. In this paper, the authors concentrated on the exploration of cervical cancer relative chimeric fusions which are produced by inter-genic splicing. They combined bioinformatics analysis and experimental validation, which involved both public secondary data from The Cancer Genome Atlas (TCGA) (201 cases) [5] and their primary data of clinical cases from affiliated university hospitals (11 cases). This experiment-assistant analysis is a considerable contribution that could cast off possible bias produced by simplex informatics analysis, and would supply the necessary experimental foundation for further verification and application in future research.

Their computational approach to chimeric fusions was remarkable. As it is well known, there are many interference factors that must be considered while investigating chromosomal rearrangements, such as parental exon relative junction positions, parental genetic chromosomal locations, reading frames corresponding to the 3′ and 5′ genes [3], etc. In addition, as the authors noted, different criteria such as the combination of exon or intron boundaries, parental gene positions, or frame-shifts in different strands must also be considered. The subsequent gene ontology analysis verified prior experiences for selecting the features of viral processing or symbiosis in different carcinomas, which reflected the effectiveness of this multi-dimension/multi-level observation method.

Finally, two new cervical cancer relative chimeric fusions, which were likely to become potential biomarkers, were discovered by taking advantage of a frequency-based enrichment method. One of these could occur in early tumorigenesis in a subclass of cervical cancer, which was concluded based on sufficient clinical statistics. The other one could regulate cellular proliferation but its parental genes could not, which was validated by wet-experiments such as qRT-PCR. These two fusions make potential sense in clinical diagnosis, prognosis and treatment using the former one, and the latter one was shown to be potentially involved in the carcinoma mechanism. The mechanism verification and therapeutics development should be conducted in future studies since these novel fusions have been validated by clinical data in Wu Peng et al.'s study [3].

Some unresolved problems are worthy to address in the future. First of all, we need to explore how to deal with low frequent fusions and to interpret them. As we know, when we call somatic mutations or other abnormalities by comparing sequencing data between carcinoma and normal tissues, low frequent variants/abnormalities are a controversial issue. The reason for this is that, low frequent variants/abnormalities always occupy an overwhelming proportion, but in mostcases they are omitted because of low statistical power and meaningless non-representatives. However, some researchers have attempted to rescue low frequent variants/abnormalities by various kinds of computational algorithms, considering the possibility that even low frequent ones might hold great potential in cancer therapy or present opportunities for personalized medicine [6,7]. Thus, computational methods to disambiguate the low frequent fusions from a great number of candidates such as the frequency-based fusion enrichment method developed by Wu Peng et al. [3] are also crucial and challengeable. In general, low probable repeatability is an unavoidable characteristic in cervical cancer gene fusions, which was indirectly proven by the low frequent significant fusions (≤3%) reported in previous research.

Secondly, elucidation of the signaling mechanism of chimeric fusion *SLC2A11-MIF*, whose function was suggested to relate to *CDKN1A* pathway, is still expected. Many fusion-oriented treatments have been challenged so far, and the signaling mechanisms were gradually ascertained. Therein, some treatments have enhanced gene expression in the *CDKN1A* pathway and some other cyclin-related pathways related to therapy-targeted fusions [8]. In this respect, any follow-up study could also be anticipated based on the discovery about fusion *SLC2A11-MIF*.

Disclosure

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* Corresponding author.
E-mail address: okd@med.niigata-u.ac.jp (S. Okuda).

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Author contributions

YL and SO wrote the manuscript.

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