Commentary

Future perspectives of Sleeping Beauty transposon system in cancer research

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With the unsolved challenges to explore potential predictors of metastasis in colorectal cancer patients, Nicoloso and colleagues endeavored in this issue to combine a transposon-based forward genetic screen with the forced Single Cell Suspension assay (fSCS) to discover specific regulators of metastatic colorectal cancer [1]. They found that the fSCS was a simple and scalable in vitro assay to select cells with pro-metastatic traits. Meanwhile, the Sleeping Beauty transposon integration was proven to generate fSCS-resistant colorectal cancer cells. Also, its insertion in the 3'UTR of BTD7 disrupted miR-23b::BTBD7 interaction and contributed to metastasis. In addition, both miR-23b and Btbd7 protein show promising potential for prognostic biomarkers in colorectal cancer patients.

Colorectal cancer remains to be the second and third most prevalent cancers in 2019 among males and females, respectively [2]. Despite of the developments in diagnostic technologies and treatments, cancer metastasis is still a severe threat to patients’ survival. Searching for prognostic biomarkers and therapeutic targets will help developing efficient therapies and good outcomes of colorectal cancer patients.

Recently, liquid biopsy technique is increasingly adopted for evaluating diagnostic or prognostic biomarkers in various kinds of cancers. Sources for biomarker development can include circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), circulating cell-free RNA (cfRNA), circulating extracellular vesicles (EVs), tumor-educated platelets (TEPs), proteins or metabolites in patients' peripheral blood. All these have the potential to provide information about traits of primary tumors or metastases [3]. Besides, sensitivity and specificity of a single analyte should be verified by multiple preclinical studies before moving into clinical application of liquid biopsy assay. However, chemicals, radiation or viruses are used frequently in science with the intention to test the function of the potential biomarker associated with cancer metastasis. Biomarkers found under such conditions have a high potential to fail. The Sleeping Beauty transposon system demonstrates to be a more stable and better method for laboratory applications [4].

The Sleeping Beauty transposon system consists of the Sleeping Beauty transposase and a transposon which was found in the genome of salmonid fish in 1997 [5]. The Sleeping Beauty elements act to insert specific sequences of DNA into the genome of humans resulting in truncating the encoded proteins (inserting in a gene) or increasing the gene products (inserting near a gene) [6]. Therefore, advantages of Sleeping Beauty integration over other genetic tools rely on its location in the host genome which has no serious biases for any chromosomes [7]. For decades, researchers have already applied Sleeping Beauty the genetic system to identify altered genes in varieties of cancers [8,9]. While in colorectal cancer, the Sleeping Beauty method was only applied in a mice model to explore cancer-related genes by Starr and co-workers [10]. In this study, Nicoloso and colleagues utilized this tool and explored miR-23b and Btbd7 as novel prognostic predictors of colorectal cancer metastasis both in vitro and in vivo [1]. These findings will be more accurate and more credible than studies employing other tools such as viruses in need of huge amounts of sequencing. As a result, utilization of liquid biopsy following the Sleeping Beauty genetic screen data could show good potential in medicine.

Nevertheless, in this context, other six genes were transformed due to the Sleeping Beauty insertion. So whether the miR-23b::BTBD7 interaction is essential in the process of metastasis in colorectal cancer remains uncertain. More evidences should be acquired to confirm the full potency of miR-23b and Btbd7 as well as the Sleeping Beauty transposon system as liquid biopsy in the clinical management of patients with colorectal cancer.

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Declaration of Competing Interest

None.

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References

[1] Grisard E, et al. Sleeping beauty genetic screen identifies miR-23b::BTBD7 gene interaction as crucial for colorectal cancer metastasis. EBioMedicine 2019. https://doi.org/10.1016/j.ebiom.2019.06.044.

[2] Miller KD, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin 2019. https://doi.org/10.3322/caac.21565.

[3] Heitzer E, et al. Current and future perspectives of liquid biopsies in genomics-driven oncology. Nat Rev Genet 2019;20(2):71–88.

[4] Weiser KC, Justice MJ. Cancer biology: Sleeping Beauty awakens. Nature 2005;436(7048):184–6.

[5] Ivics Z, et al. Molecular reconstruction of Sleeping Beauty, a Tc1-like transposon from fish, and its transposition in human cells. Cell 1997;91(4):501–10.

[6] Plasterk RH. Molecular mechanisms of transposition and its control. Cell 1993;74(5):781–6.

[7] Ivics Z, Izsvak Z. The expanding universe of transposon technologies for gene and cell engineering. Mob DNA 2010;1(1):25.

[8] Tschida BR, et al. Sleeping beauty insertional mutagenesis in mice identifies drivers of steatosis-associated hepatic tumors. Cancer Res 2017;77(23):6576–88.

[9] Zanesi N, et al. A sleeping beauty screen reveals NF-kB activation in CLL mouse model. Blood 2013;121(21):4355–8.

[10] Starr TK, et al. A transposon-based genetic screen in mice identifies genes altered in colorectal cancer. Science 2009;323(5922):1747–50.