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Abstract

LiveMIEL: Genetically Encoded Epigenetic Probes for Enhancers Dynamics Visualization in Live-Cell Fluorescence Microscopy †

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Histone post-translational modifications (namely acetylation, methylation, phosphorylation, and some others, less abundant) play a significant role in chromatin structure and functioning [1]. In live cells specific histone modifications reader domains (HMRD) existing as parts of regulatory proteins and multiprotein complexes, are usually responsible for the recognition and interaction with such modifications [2]. However, it is still not entirely understood how these chromatin modifications affect the overall genome organization and their response to various cellular events.

In 2019 Prof. Terskikh and co-authors have developed a novel method for high-throughput analysis of epigenetic changes at the single-cell level, called Microscopic Imaging of Epigenetic Landscapes (MIEL) [3]. The pipeline of this approach includes staining of fixed cells with antibodies specific to certain histone modifications, which is followed by image analysis applying machine learning to classify and compare epigenetic patterns (landscapes). High applicability of the method to detect changes of epigenetics during drug treatment and cell differentiation was shown.

Here, based on the forementioned method, we present specific genetically encoded epigenetic probes (GEEPs), developed for adaptation of MIEL for live-cell fluorescence microscopy. GEEPs rely on the natural specificity of the HMRD to certain modifications instead of antibodies, allowing for the visualization of epigenetic landscape dynamics followed by computational analysis. These probes can be used for different cell types due to their versatility and low toxicity. They are widely applicable to a number of research tasks, namely drug development, cancer and aging research, along with fundamental studies.

Our particular interest is focused on enhancer regions dynamics. Enhancers, regulatory elements controlling gene expression, actively interact with the gene promoters. However, unlike promoters, they can perform their regulatory functions regardless of their orientation or certain spatial segregations from their target genes. Large clusters of active enhancers comprise super-enhancers which are responsible for transcriptional regulation of cell identity genes. Primed enhancers prior to activation are generally marked with H3K4me1 modification while active enhancers and super-enhancers are enriched in both H3K4me1 and H3K27ac. Poised enhancers, on the other hand, show high levels of the H3K27me3 repression mark, which is to be removed to make the enhancer activation possible [4]. We utilize these features to develop GEEPs for enhancer and super-enhancer dynamics visualization.

Keywords: fluorescent probes; epigenetics; readers; histone modifications; chromatin; enhancers; super-enhancers; visualization; fluorescent microscopy

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