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Research Advance

Rewiring the transcriptional circuitries in cancer by endogenous retroviruses

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With sequence similarities to exogenous retroviruses, the proviral DNA elements named endogenous retroviruses (ERVs) make up ~8% of human genome, threatening genomic stability meanwhile nurturing regulatory innovations. Diverse host epigenetic mechanisms are enlisted to limit the ERVs' activity. However, in certain physiological and pathophysiological processes, distinct ERVs become abnormally activated, rewiring and perplexing the host regulons at different levels (Cosby et al., 2019). ERVs not only contribute to the nuclear architecture; once activated, they can also act as enhancers, promoters, or even be exonized to shape the transcriptional circuitries. Moreover, some ERVs are able to synthesize regulatory noncoding RNA species or functional polypeptides to impact the transcriptome as well as the proteome. As one of the most abundant ERV groups, the transcriptional activation of human endogenous retrovirus H (HERVH) is crucial for the acquisition and maintenance of the pluripotent state of human embryonic stem cells (ESCs) as well as the induced pluripotent stem cells (Rodriguez-Terrones and Torres-Padilla, 2018). HERVH is also active in several types of cancer including colorectal cancer (CRC), yet how it is activated and influences carcinogenic signaling pathways remains largely unclear.

ARID1A and ARID1B are two mutually exclusive subunits serving as the rigid structural core in the BAF complex, a SWI/SNF family chromatin remodeler that regulates chromatin packing and transcription by controlling the dynamics of nucleosomes. Mutational landscape analyses have revealed that ARID1A is among the most frequently mutated epigenetic factors across many cancer types, with ~12% ARID1A mutation in CRC (Luo et al., 2020). Many synthetic lethality targets of ARID1A have been identified, including ARID1B, EZH2, HDAC6, Aurora A, and GCLC. Particularly, ARID1A-mutated cancer cells manifest enhanced BRD4 activity, rendering the cells hypersensitive to bromodomain and extra-terminal domain inhibitors (Nagarajan et al., 2020). BRD4 is a binding partner of the Mediator complex and well known for its role in the organization and function of super-enhancers, which are large clusters of enhancers with exceptionally high densities of transcription factor (TF) binding. Both BRD4 and components in the Mediator complex can undergo liquid–liquid phase separation, forming transcriptional coactivator condensates to bridge TFs with RNA polymerase II (Sabari et al., 2018). How ARID1A-mutated cancer cells harness this transcriptional coactivator module was an enigma.

Yu et al. (2022) recently reported that mutation of ARID1A in CRC results in an abnormal activation of a group of HERVH loci, which involves ARID1B-dependent chromatin remodeling activity and the TF SP1. The HERVH transcripts partition into nuclear BRD4 condensates and likely co-opt its coactivator activity to drive downstream oncogenic gene network (Figure 1). Downregulation of HERVH transcript level effectively inhibits the proliferation of colorectal cells as well as patient-derived CRC organoids, suggesting the existence of molecular addictions of these cells to the activated HERVH elements. This study has revealed an unexpected function of ARID1A–BAF chromatin remodeler in restraining the activity of HERVH. More importantly, it suggests that HERVH transcripts steer the BRD4 coactivator module to promote oncogenicity. Whether HERVH RNAs directly bind to BRD4 and the Mediator complex to alter their target selection requires future biochemical interrogations. Of note, a recent study in mouse ESCs reports that RNAs of murine ERVs, such as intracisternal A-type particles, facilitate partitioning of the Mediator coactivator as well as RNA polymerase II into phase-separated droplets, thereby hijacking the transcriptional condensates away from pluripotency (Asimi et al., 2022). It is compelling to speculate that the RNA species originated from ERVs are able to rewire the transcriptional circuitries via the coactivator module in evolution.

Cancer development in many aspects parallels the process of early embryogenesis. The work from Yu et al. (2022) uncovers that mutation of a tumor suppressor ARID1A reactivates a group of pluripotency-related HERVH,

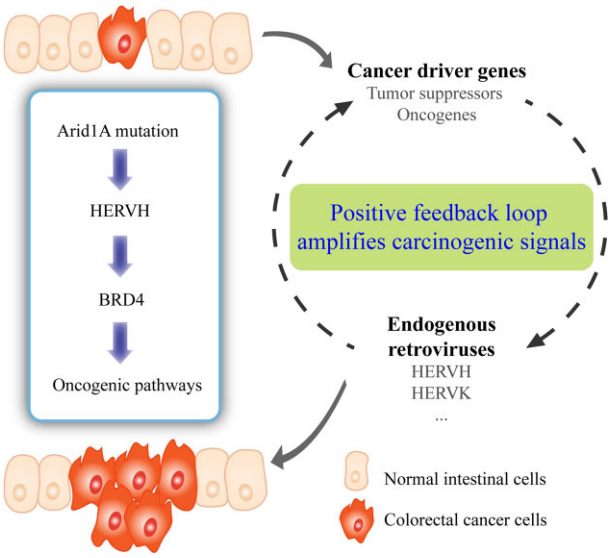

Figure 1 Positive feedback loops between ERVs and cancer driver genes amplify carcinogenic signals to promote malignancy.

enabling cancer cells to exploit and repurpose developmental programs to promote malignancy. Notably, another human endogenous retroviral element HERVK also becomes activated in many cancer types, promoting tumor growth and metastasis in multiple ways (Curty et al., 2020). Interestingly, the activated ERVs in cancer can be recruited as promoters to further drive the expression of many oncogenes in a process called onco-exaptation (Babaian and Mager, 2016; Jang et al., 2019), suggesting that ERVs in the human genome have the potential to function as signal amplifiers to boost and reinforce the initial oncogenic signal during carcinogenesis (Figure 1). Future studies shall elaborate these positive feedback loops between the protein-coding and the repetitive sections of the human genome, which might translate into new therapeutic strategies.

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