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Mini-review

Mobile elements and viral integrations prompt considerations for bacterial DNA integration as a novel carcinogen

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ABSTRACT

Insertional mutagenesis has been repeatedly demonstrated in cancer genomes and has a role in oncogenesis. Mobile genetic elements can induce cancer development by random insertion into cancer related genes or by inducing translocations. L1s are typically implicated in cancers of an epithelial cell origin, while *Alu* elements have been implicated in leukemia as well as epithelial cell cancers. Likewise, viral infections have a significant role in cancer development predominantly through integration into the human genome and mutating or deregulating cancer related genes. Human papilloma virus is the best-known example of viral integrations contributing to carcinogenesis. However, hepatitis B virus, Epstein-Barr virus, and Merkel cell polyomavirus also integrate into the human genome and disrupt cancer related genes. Thus far, the role of microbes in cancer has primarily been attributed to mutations induced through chronic inflammation or toxins, as is the case with *Helicobacter pylori* and enterotoxigenic *Bacteroides fragilis*. We hypothesize that like mobile elements and viral DNA, bacterial and parasitic DNA may also integrate into the human somatic genome and be oncogenic. Until recently it was believed that bacterial DNA could not integrate into the human genome, but new evidence demonstrates that bacterial insertional mutagenesis may occur in cancer cells. Although this work does not show causation between bacterial insertions and cancer, it prompts more research in this area. Promising new sequencing technologies may reduce the risk of artifactual chimeric sequences, thus diminishing some of the challenges of identifying novel insertions in the somatic human genome.

Introduction

In 2013, 1.6 million people were estimated to develop cancer in the US, while 49% of men and 38% of women will develop cancer in their lifetime [117]. Genetic changes, environmental factors, and infectious agents can all cause increased cell proliferation leading to cancer through abnormal epigenetic alterations, point mutations, translocations, and other modifications. Infectious agents and mobile elements that integrate into the human genome, in whole or in part, are an example of events that inflict such DNA damage. Here, we explore whether bacterial integrations may also occur in tumors.

Role of mobile elements in carcinogenesis

Mobile elements basics

Mobile elements are possibly the best-studied insertional mutagens of the human genome. While currently inactive in the human genome [87], DNA-based transposons account for ~45% of the human genome [38]. RNA-based retrotransposons can be divided into classes based on the presence/absence of long terminal repeats (LTR). The LTR-retrotransposons, such as endogenous retroviruses, are not currently active in humans [75]. However, the non-LTR retrotransposons actively jump throughout the human genome acting as mutagens [38,51,75] (Fig. 1A). These non-LTR retrotransposons consist of long interspersed elements 1 (LINE-1s or L1s), *Alu* elements (a type of short interspersed element, or SINE), and SVAs (a combination of SINE-R, variable number of tandem repeats, and *Alu*-like sequences). L1s are the only non-LTR retrotransposons that encode enzymes for retrotransposition [51], and as such, they mobilize themselves as well as

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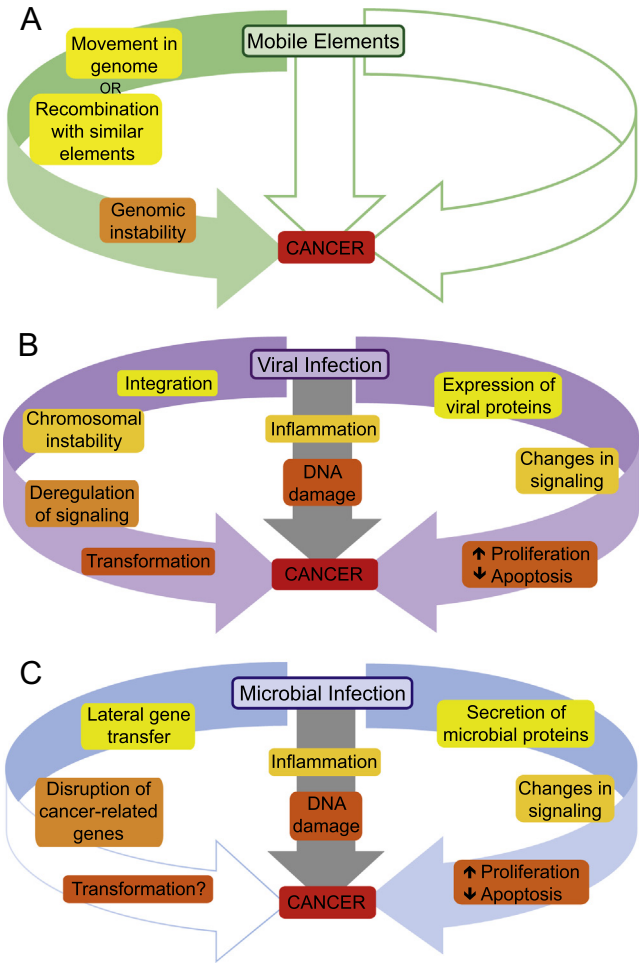

Fig. 1. Carcinogenesis by mobile element movement, viral integrations, and microbial infections. (A) Mobile genetic elements, such as retrotransposons, can play a role in cancer mutagenesis. They can either move to a new location in the genome or recombine with similar mobile elements and cause genomic instability. This vulnerability often contributes to cancer progression. (B) Viruses use three broad mechanisms to promote carcinogenesis. Viruses can integrate into the human genome inducing genomic instability (purple arrow on the left). The deregulation of signaling pathways induced from these chromosomal disruptions transform normal cells into cells with cancerous phenotypes. Regardless of life cycle stage, viruses can express proteins that alter normal cell cycle patterns by increasing proliferation and decreasing apoptosis (purple arrow on the right). Viruses can also alter inflammatory responses that cause DNA damage and contribute to cancer development (gray arrow), a mechanism that is not discussed in this review. (C) Microbial infections can lead to carcinogenesis through multiple different pathways. It is important to note that these pathways can occur in conjunction with each other or individually. Microbes can first cause irritation and inflammation that leads to DNA damage and thus cancer (gray arrow). Or bacteria can secrete microbial proteins that alter host-signaling pathways, leading to increased cell proliferation and decreased apoptosis, the classic characteristic of cancer (blue arrow on the right). While multiple examples of viral integrations that progress to cancer have been described, evidence for microbial integration into the human genome has only been reported recently.

Alu elements and SVAs [51]. Of the >500,000 L1s in the human genome, only a few are highly active and responsible for the majority of new insertions [13]. In every generation, L1s and *Alu* elements move to new genomic locations through germline retrotransposition [51]. Many disease-causing transpositions have been identified thus far including ones in breast cancer [72,123], Apert syndrome [86], hemophilia [45,81], and colon cancer [73,118]. While L1s and *Alu* elements tend to be inactive in somatic tissues, their reactivation could aid in tumorigenesis [51].

L1 insertions and cancer

L1s have been implicated in tumorigenesis of various epithelial cell cancers [14], including lung cancer [38,44]. A genomic comparison of 20 lung cancer samples with normal matched samples revealed 9 L1 insertions in only the tumor samples [44]. Six of these samples had 1–3 new L1 insertions/tumor and also showed an increase in hypomethylated DNA when compared to the matched normal samples [44], meaning the DNA in these samples had decreased methylation. Since host cells reduce transposition through increased methylation, hypomethylated tumor cells are more permissive to L1 transposons [44].

Colorectal cancer samples also have an increased rate of L1 insertions, some of which have disrupted genes with known cancer driver functions [118], like the *APC* gene [73]. More tests are necessary to resolve the exact effect of most L1 insertions since they may be passenger mutations or may be directly related to tumor formation [44,118]. It has recently been reported that the methylation status of L1 insertions in rectal cancer predicts the clinical outcome of the patient, with individuals with L1 hypomethylation having shorter survival times and higher incidences of tumor recurrence [8].

Alu elements and cancer

Alu elements are the most successful type of transposon with >1 million copies in the human genome [56]. *Alu* insertions have been associated with familial adenomatous polyposis, breast cancer, acute myeloid leukemia, and hereditary non-polyposis colorectal cancer syndrome [38].

Alu elements can disrupt DNA repair

Alu elements have been found to mutate tumor suppressor genes that aid in DNA repair, like *BRCA1* and *BRCA2*, which are important for homologous recombination in DNA double strand break repair. Recombination between two similar *Alu* elements led to the loss of a 3-kbp region in exon 17 of the *BRCA1* gene and subsequent inactivation of *BRCA1* causing breast cancer [78]. Other breast cancer studies have demonstrated multiple *Alu*-mediated mutations in the *BRCA1* and *BRCA2* genes [91,99,124]. Likewise, hereditary non-polyposis colorectal cancer syndrome can occur when mutations arise in genes involved in the mismatch repair system, such as *MLH1* or *MLH2* [76]. Both of these genes have increased *Alu* concentrations in their introns with about 75% of the rearrangements in the *MLH2* gene caused by *Alu*-mediated non-allelic homologous recombination [61].

Alu elements and leukemia

In acute myeloid leukemia, *Alu*-mediated partial duplications frequently occur in the coding regions of the *MLL1* gene, most commonly resulting in duplicate exons 5 through 11 or 12 to fuse upstream of the original exon 5 [107]. *MLL1* is part of the mixed lineage leukemia gene family, which have histone methylase capabilities and are involved in *HOX* gene regulation [2]. Some experiments suggest that the wild-type allele can be suppressed, allowing for expression of the *MLL1* copy containing the *Alu*-mediated partial duplication. This in turn induces a leukemic phenotype [129] through altered protein structure and inactivation of inherent *MLL1* function [106]. Overall, transposable elements could play a major role in somatic and germline mutagenesis and more focused research in this area is necessary before rates of L1 and *Alu* element involvement in cancer development and progression can be estimated.