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REVIEW ARTICLE

L1 retrotransposons, cancer stem cells and oncogenesis

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Retrotransposons have played a central role in human genome evolution. The accumulation of heritable L1, *Alu* and SVA retrotransposon insertions continues to generate structural variation within and between populations, and can result in spontaneous genetic disease. Recent works have reported somatic L1 retrotransposition in tumours, which in some cases may contribute to oncogenesis. Intriguingly, L1 mobilization appears to occur almost exclusively in cancers of epithelial cell origin. In this review, we discuss how L1 retrotransposition could potentially trigger neoplastic transformation, based on the established correlation between L1 activity and cellular plasticity, and the proven capacity of L1-mediated insertional mutagenesis to decisively alter gene expression and functional output.

Introduction

Mobile genetic elements (MEs) are found in nearly all eukaryotic genomes. MEs can be divided into two major classes, transposons and retrotransposons. Transposons use a 'cut-and-paste' process to relocate in genomic DNA, whereas retrotransposons mobilize through an RNA intermediate in a 'copy-and-paste' mechanism termed retrotransposition. ME sequences account for at least 45% of human DNA [1], with some estimates ranging as high as 66% [2], mainly due to the activity of the long interspersed element 1 (LINE-1 or L1) retrotransposon family. L1 is present in all mammals and, in humans, it is the only retrotransposon that remains capable of autonomous mobilization [3,4]. A retrotransposition-competent L1 is ~ 6 kb in length [5,6]. The core L1 sequence comprises a bicistronic ORF that encodes two proteins, ORF1p and ORF2p, which are essential for L1 mobilization. ORF1p is a 40 kDa protein with nucleic acid binding activity [7,8] and ORF2p is a 150 kDa protein with demonstrated endonuclease and reverse transcriptase activities [9,10]. The L1 5′-UTR harbours an internal promoter [11], as well as an antisense promoter of unclear function [12]. New L1 insertions are typically flanked by target-site duplications, a hallmark of the L1 integration process [13].

L1 retrotransposition begins with the transcription of a full-length mRNA from the L1 internal promoter. This mRNA is transported to the cytoplasm and translated, giving rise to the L1-encoded proteins. ORF1p and ORF2p bind to their encoding L1 mRNA in a phenomenon termed *cis* preference, forming the L1 ribonucleoprotein particle [7,14–18]. The L1 ribonucleoprotein particle gains access to the nucleus by a mechanism that is not completely understood, but can

Abbreviations
L1, long interspersed element 1; ME, mobile genetic element.

occur independently of nuclear envelope breakdown during cell division [19]. Inside the nucleus, L1 integration occurs by a mechanism termed target-site primed reverse transcription [20]. During target-site primed reverse transcription, ORF2p endonuclease activity produces a single-stranded nick in genomic DNA, exposing a free 3′ hydroxyl residue that serves as a primer from which the ORF2p reverse transcriptase activity synthesizes a cDNA copy of its associated L1 mRNA [9,16,21]. Despite the marked *cis* preference of L1 proteins for their encoding mRNA [16], other cellular RNAs can be mobilized in *trans* by the L1 enzymatic machinery. These sequences include the non-autonomous retrotransposons *Alu* and SVA, as well as protein-coding mRNAs, the reverse transcription of which gives rise to processed pseudogenes [14,22–24]. Thus, L1 has played a pivotal role in human genome evolution.

Of ~ 500 000 L1 copies in the human genome, the vast majority have been rendered immobile by 5′ truncation, internal deletions and other mutations [1]. As a consequence, only 80–100 retrotransposition-competent L1s, as well as an estimated 2000–3000 *Alu* and < 100 SVA copies, are found per individual [25–27]. These elements continue to drive pervasive genetic variation in human populations [28–34]. Spontaneous and inherited occurrences of insertional mutagenesis mediated by L1 have been observed in > 100 diseases, including diabetes, haemophilia and cancer [4,35–37]. Presumably to limit deleterious mobilization events, eukaryotic cells have developed several defence mechanisms that affect various stages of the retrotransposition process (Fig. 1). Foremost among these is the methylation of retrotransposon promoters to enforce transcriptional repression, as seen in numerous spatiotemporal and environmental contexts in which methylation of the canonical L1 promoter is inversely correlated with its expression [38–40]. Numerous epigenetic modifiers participate in retrotransposon silencing, including the DNA methyltransferase-like protein Dnmt3L, which is critical for Dnmt3A-mediated methylation of retroelements in primordial germ cells [41,42]. Suppression of retrotransposition is also reinforced in germ cells by small RNAs, including the Piwi-interacting RNA silencing pathway [43,44]. Interestingly, abrogated retrotransposon promoter methylation due to methyltransferase and Piwi-interacting RNA inactivation has been described in association with spermatogenic disorders, illustrating the evolutionary importance of these suppression mechanisms [41,45]. Piwi-interacting RNAs, along with other small RNAs, including repeat-associated small interfering RNAs and micro-RNAs, also act to degrade retrotransposon transcripts via RNA interference [46–51].

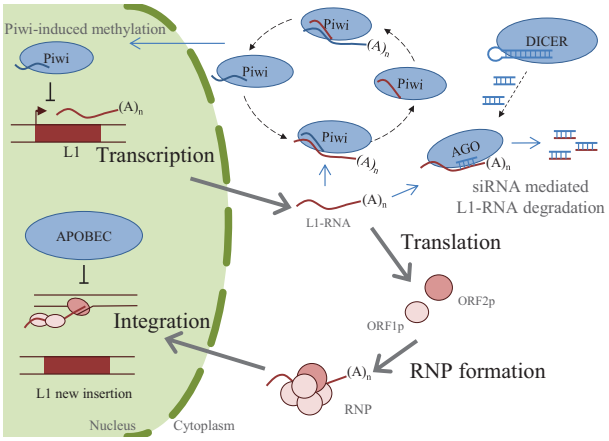

Fig. 1. L1 retrotransposition and silencing pathways. L1 mobilization requires the key steps of transcription, mRNA export to the cytoplasm, translation, ribonucleoprotein particle formation, entry into the nucleus and, finally, integration. The Piwi-induced methylation silencing pathway involves a selective amplification cycle fuelled by Piwi-mediated cleavage of L1 transcripts. The repeat-associated small interfering RNA degradation pathway is regulated by the generation of siRNAs from dsRNAs by Dicer and the fragmentation of L1 RNAs by AGO family proteins. L1 integration is also inhibited by several host factors, including members of the APOBEC3 family. Proteins and RNAs implicated in L1-silencing pathways are represented in blue. L1 RNAs and proteins are represented in pink.

Insights gained from human cancer cells [52], as well as other eukaryotes, suggest that RNA interference is a highly conserved defence against retrotransposition, particularly in germ cells [50,53–55].

Epigenetic and post-transcriptional suppression of retrotransposition are complemented by host factors that target L1 target-site primed reverse transcription intermediates during the generation of new insertions. The exonuclease Trex1, for instance, metabolizes reverse transcribed retrotransposon DNA [56]. Numerous studies have reported restriction of L1 mobilization in cultured cells by members of the APOBEC3 (A3) family of cytidine deaminases [57–63], although deaminase-dependent and -independent modes of action likely play roles in retroelement restriction by different A3 factors. Notably, two studies recently reported a pan-cancer APOBEC3 mutagenesis signature [64,65], indicating that APOBEC3 deaminases can target genomic DNA and suggesting a role for APOBEC3-mediated deamination in the accumulation of mutations during oncogenesis. Thus, paradoxically, APOBEC3 activity might protect cells from potentially oncogenic retrotransposition events, yet exact a mutagenic toll of its own if not tightly regulated. Another factor, the putative RNA helicase MOV10, has been

demonstrated to restrict L1 retrotransposition in cultured cells [66–68]. MOV10 associates with the key RNA-induced silencing complex component AGO2 and the L1 ribonucleoprotein particle, and may thereby degrade, or block the translation of, L1 mRNAs [69]. This relationship, along with the evolutionary conservation of RNA interference in germ cells, underlines how host genome suppression of retrotransposons gains efficacy through redundant organization, but also vulnerability due to interdependence. Therefore, the absence or reduction of at least some retrotransposition defence mechanisms post fertilization, such as Piwi-interacting RNAs [70], may disproportionately accentuate somatic cell retrotransposition, a view supported by fewer occurrences of L1 retrotransposition in gametes compared with soma [71–73].

It follows that L1-mediated mutagenesis may contribute meaningfully to cancer, a disease driven by mutations in somatic cells; indeed, the idea that retrotransposition could often be involved in tumorigenesis is not new [74–76]. Numerous cancers exhibit pronounced L1 activation [32,38,77–85]. Nonetheless, a range of key issues remain unresolved, including the most obvious question of whether L1 mobilization causes cancer, or vice versa. Here, we summarize some of what is known of L1 activity during oncogenesis and tumour progression, and propose an explanation for why L1 retrotransposition appears to be a common feature of epithelial cancers.

Environmental triggers common to L1 activity and oncogenesis

Cancer encompasses a broad group of more than 200 diseases that involve the uncontrolled growth of cells leading to tumour formation, as well as several other common hallmarks [86,87]. At the molecular level, cancer is a complex disease attributed to the accumulation of multiple risk factors, from genetic predisposition to environmental factors such as diet, lifestyle and exposure to toxic compounds [88]. Epidemiological twin studies suggest that environment influences cancer aetiology far more decisively than genetics [89,90]. For instance, the contribution of environmental factors to sporadic cancers ranges from 58 to 82%, versus the highest genetic contribution of 27–42% for colorectal, breast and prostate cancers [89]. Interestingly, inherited risk far exceeds the frequency of mutations already reported in cancer genes, suggesting that other contributing mechanisms or types of genetic alteration, such as rare variants and retrotransposition events occurring in noncoding genomic regions, may contribute to cancer development.

Differentiating those mutations that cause oncogenesis ('drivers') versus those mutations accumulating in a deregulated genomic environment during the course of oncogenesis ('passengers') is a long-standing challenge in cancer genomics. Furthermore, L1 insertional mutagenesis is only one among a constellation of different types of genetic aberrations that frequently underpin cancer. It is nevertheless intriguing that L1 insertional mutagenesis occurs in tumours [76], cancer cell lines [91–93] and during development [71,72,94]. Somatic L1 retrotransposition can occur in both dividing and nondividing cells [19], generating mosaicism and, potentially, tumorigenic mutations. L1 mRNAs are present in differentiated tissues such as brain, kidney, liver and heart [77,78], and L1 mobilization has, to date, been identified in liver and brain tissue [80,95,96]. Given the substantial, predominantly deleterious effects of intragenic L1 insertions upon host gene expression [79,97], L1 insertions may be more likely, on a per mutation basis, to have an impact on tumorigenesis than other genetic aberrations observed in cancer.

Several carcinogenic environmental factors [98] have been demonstrated to increase ME activity in cultured cells [99]. For instance, benzopyrenes have been identified as a risk factor for lung, colorectal and breast cancer [100–102], and have been demonstrated to increase L1 mobilization in HeLa cells [103]. Nickel exposure is a risk factor for lung and breast cancer [104,105], and has likewise been shown to induce L1 mobilization [106]. Tumours often show increased levels of free radicals involved in oxidative stress [107]; again, oxidative stress has been shown to increase L1 mobilization [83]. Oxidative stress and DNA damage occurring as part of senescence can increase chromosomal instability and retrotransposon activity [108], thereby contributing to genomic mosaicism associated with cancer development [109,110]. Hence, if we take as given that retrotransposition is a stochastic process, and that most somatic cells present a basal L1 activity that has evaded silencing [77,78], it is plausible that environmental factors increase the probability of a somatic L1 insertion affecting an oncogenic locus, thereby triggering neoplastic transformation.

Mapping retrotransposition in cancer genomes

Despite the large effect size of many intragenic L1 insertions, their relative importance to oncogenesis versus the cornucopia of other mutations usually observed in a tumour is unclear. Cancer genome sequencing typically reveals a host of somatic cell mutations, including tens or hundreds of thousands of

single nucleotide variants, as well as insertions, deletions, translocations, rearrangements and other more exotic mutations, all found within a given tumour [111]. Are a few additional L1 insertions important in this context? One route to address this question is to map the locations of L1 insertions in cancer genomes and ascertain which protein-coding genes are affected by mutations, following the same logic developed for transposon mutagenesis screens in mouse models of cancer [112]. The first success in mapping a *bona fide* somatic L1 insertion in a tumour occurred > 20 years ago, with the discovery by Miki *et al.* of an exonic L1, flanked by target-site duplications and integrated in the *APC* gene of a colorectal cancer patient [76]. Because *APC* is the pre-eminent tumour suppressor gene in colorectal cancer caused by familial adenomatous polyposis [113,114], it is reasonable to conclude that, in this case, a single L1 insertion was sufficient to drive oncogenesis.

Spurred by this paradigm, and aided by the advent of high-throughput sequencing, several exemplar strategies have been developed in recent years to map endogenous somatic retrotransposition events in tumours (for detailed reviews see [115,116]). The first of these methods, presented by Iskow *et al.*, digested genomic DNA using restriction enzymes that recognize the 3′-end of L1 and *Alu* and linked adapters to the resultant fragments to obtain retrotransposon libraries by PCR. Sequencing of these libraries revealed nine *de novo* L1 insertions in lung tumours [32]. More recently, Lee *et al.* used a computational method to analyse paired-end whole-genome sequence data, from tumour and matching blood, searching for paired-end-reads mapping to unique genome locations and a distal ME. Using this strategy, they identified 194 *de novo* ME insertions in colorectal, ovarian and prostate tumours [79]. Newly detected somatic insertions were located preferentially in tumour suppressor genes, where integration of an intronic L1 typically inhibited transcription, as expected [79,97]. Similarly, Solyom *et al.* analysed colorectal tumours and matching tissues by hemi-nested PCR coupled to sequencing (L1-seq) [29] and detected 69 *de novo* L1 insertions, including in the introns of genes previously reported to be involved in cancer [81].

More recently, we identified 12 *de novo* L1 insertions in a cohort of hepatocellular carcinoma patients using retrotransposon capture sequencing, a hybridization-based approach to enrich DNA for recent L1, *Alu* and SVA insertions, followed by deep sequencing [80,95]. Interestingly, one somatic L1 insertion was shown to activate a putative oncogene through ablation of a negative feedback loop [80]. This model might explain why expression increases for at least some genes harbouring tumour-specific L1 insertions [79]. Retrotransposon capture sequencing also revealed a validated somatic L1 insertion in nontumour liver, as well as germline L1 and *Alu* insertions in the tumour suppressor gene MCC that would, by definition, precede tumorigenesis [80,117].

As these works demonstrate, cancer is arguably the most promising immediate context in which to assess the phenotypic effects of somatic retrotransposition *in vivo*. In other tissues, such as the brain, the majority of mosaicism due to L1 mobilization is thought to occur late in differentiation [94], meaning that each individual insertion is present in a handful of cells and necessitating single cell or deep targeted sequencing to detect somatic L1 insertions [95,96]. By contrast, some tumour cells containing new L1 insertions are likely to undergo clonal expansion, meaning that the mutations they contain can reach sufficient abundance to be detected even via standard whole-genome sequencing [79]. Extensive cancer gene catalogues [118] somewhat simplify the process of linking mutations to tumorigenesis, and these predictions can be validated *in vitro* and *in vivo* using cancer cell lines and animal models, respectively. Nonetheless, tumours do present challenges in retrotransposon mapping. Cellular heterogeneity can obscure subclonal mutations that may have been important in oncogenesis, but not tumour growth. Another issue is that wholesale genetic aberration is commonplace in cancer genomes, leading to difficulties in distinguishing retrotransposition from other structural variation involving retrotransposons, such as rearrangements. As we have observed, this latter problem is surmountable through stringent parameters in calling *de novo* insertions, and yet can still require extensive validation via PCR and capillary sequencing [80]. Despite these challenges, and the numerous unanswered questions remaining in the area, the recent studies discussed above have nevertheless demonstrated that: (a) ME activation can reduce the tumour suppressor capacity of somatic cells, and (b) oncogenesis can be driven by individual ME insertions.

Do cancer stem cells promote L1 mobilization in epithelial tumours?

In-depth analysis of multiple cancer types has, to date, revealed somatic L1 retrotransposition only in cancers of epithelial origin [32,76,79–81]. One explanation for this observation is that epithelial cells are demonstrably more ‘plastic’ than other differentiated potential tumour progenitors. Epithelial cells can be transformed to yield cancer stem cells [119] and can also be

reprogrammed into induced pluripotent stem cells via deliberate activation of a mesenchymal to epithelial transition [120,121]. Interestingly, metastasis is more prevalent in epithelial cancers than in other tumour aetiologies and is thought to involve cells that have lost epithelial features and acquired a migratory phenotype [122] via an epithelial to mesenchymal transition, the reverse process of mesenchymal to epithelial transition [123]. Thus, to speculate, the basal plasticity of some epithelial cells may endow tumours with greater aggressiveness and evolutionary flexibility (Fig. 2), based on the provision of cellular plasticity by cancer stem cells resident in epithelial tumours [124].

The question of how a cell turns into a cancer stem cell *in vivo* remains unresolved. Two likely possibilities are that cancer stem cells are naturally reprogrammed from either resident tissue stem cells or from differentiated cells (Fig. 3). In the first case, a stem cell might suffer an oncogenic mutation or 'lesion' that yields a tumour cell rather than a normal differentiated cell [125]. In the second case, an oncogenic mutation might cause a differentiated cell to reprogramme towards a tumour cell-like state [126]. Given that differentiated epithelial cells are sufficiently plastic to be reprogrammable and that, to date, only epithelial tumours have been demonstrated to accommodate L1 mobilization, it is tempting to conclude that these cancers are primarily caused by reprogrammed differentiated cells, rather than resident tissue stem cell populations. Although, to our knowledge, L1 activity has not been assessed in cancer stem cells, it is established that numerous other stem cell types, from embryonic stem cells to neural progenitor cells, are permissive for L1 mobilization [71,94]. Indeed, directed reprogramming of epithelial cells *in vitro* to obtain induced pluripotent stem cells activates L1 mobilization [127]. Thus, although the relationships between cancer stem cells, epithelial cells and L1 mobilization are somewhat circumstantial, it is reasonable to propose that the plasticity of epithelial tumours explains their specific support of L1 mobilization, increasing the probability that cancer stem cells contain oncogenic L1 driver mutations or are, at the very least, permissive of L1 activity.

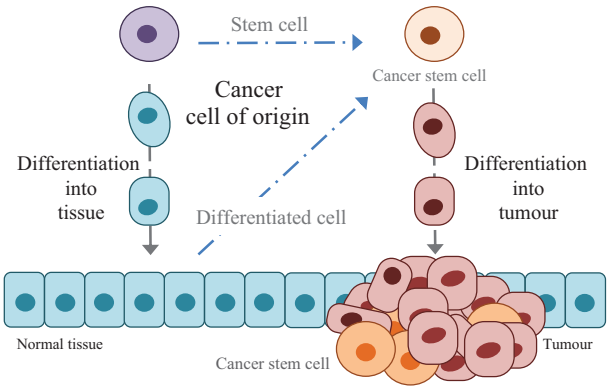

Fig. 3. Schematic representation of tumorigenesis in epithelial cancers. A stem cell undergoes differentiation, giving rise to normal tissue. If mutation of an oncogenic region occurs, a normal stem cell can turn into a cancer stem cell. This cancer stem cell can also be generated from a differentiated cell via a mesenchymal to epithelial transition. Once established, cancer stem cells can differentiate into the various cell types that form a tumour.

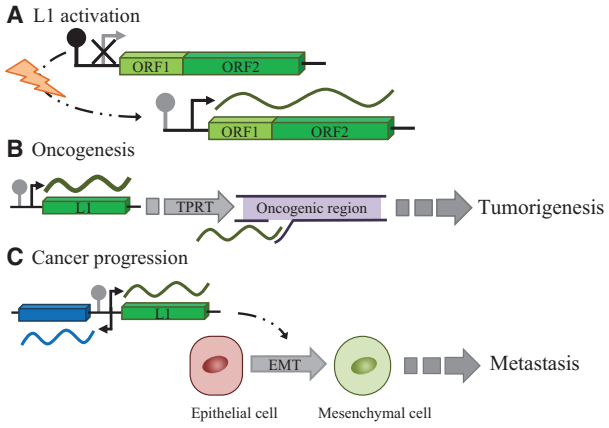

Fig. 2. Hypotheses for L1 involvement in tumorigenesis and cancer progression. (A) Environmental factors initially cause cells to change the methylation status of the L1 promoter, activating full-length L1 transcription. (B) This is followed by *de novo* L1 retrotransposition into an oncogenic region, resulting in tumorigenesis. (C) Once the tumour is established, the canonical L1 promoter is increasingly hypomethylated, potentially activating the antisense promoter and nearby genes. Moreover, L1 promoter hypomethylation appears to be correlated with an epithelial to mesenchymal transition that could eventually lead to metastasis.

Conclusions

A clear correlation has been established between L1 mobilization and cancer. However, determining how frequently L1 activity is a cause rather than a consequence of oncogenesis presents a difficult challenge that will require extensive study. L1 mobilization and cancer are both heavily influenced by environment, and it is clear that tumours often contain *de novo* L1 insertions, some of which map to cancer genes. Yet, most of the pathways leading to L1 activation in cancer remain unknown. For instance, are the key transcription factors known to regulate L1 expression, such as SOX2, RUNX3 and YY1 [128–130] perturbed by other mutations, enabling L1 activation? Or, from

another perspective, are retrotransposons simply derepressed by abrogation of genome-wide surveillance mechanisms, such as DNA methylation, in tumour cells? Although critical information is lacking, particularly experimental evidence of L1 activity in cancer progenitor cells, insights gained from pluripotent and other highly plastic cells suggest that retrotransposons opportunistically exploit any weakness or alteration in the cellular systems required for their suppression [94,127]. This, combined with the recognition that epithelial cancers specifically support L1 mobilization, leads to a plausible model in which L1 activation is due to epigenetic or other perturbations of retrotransposon suppression by cancer stem cells.

Even if found to rarely drive oncogenesis, L1 activity may be useful as a diagnostic tool for malignancy and metastasis. Various studies suggest that detectable levels of L1 mRNA and proteins are associated with poor cancer prognosis [84,131–134], whereas L1 promoter hypomethylation can indicate problematic genome-wide epigenetic deregulation [135–137]. From a clinical perspective, it would also be useful to establish whether all tumour cells from a given neoplasm, or just a subset of cells, present high L1 activity, and whether this heterogeneity assists tumour cell evolution in response to chemotherapy or radiotherapy. Finally, it is unknown whether blocking L1 mobilization, for example, using reverse transcriptase inhibitors [19,138], would in any way affect cancer progression or prognosis. In this regard, and despite perhaps being coincidental, it is interesting that cancer is not thought to occur in the naked mole rat, one of the few mammals that does not maintain active MEs within its genome [139,140]. A key experiment might, therefore, be to inhibit L1 retrotransposition, potentially in an established animal model of cancer, to assess the contribution of L1 to oncogenesis, tumour growth and metastasis. Such *in vivo* approaches would complement future, larger scale surveys of retrotransposition in human tumours based on high-throughput sequencing and, potentially, go further in elucidating the origins and importance of L1 activity in cancer.

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