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Transposable Elements in Human Diseases: Evolutionary and Therapeutic Perspectives

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Abstract

Transposable elements (TEs) ubiquitously exist in the human genome, and some have the ability to copy and paste themselves to other locations, resulting in new insertions. Organisms have evolved with mechanisms and machineries to repress such activity. TEs are also co-opted for beneficial functions by the host and are thus maintained in the genome. During the lifetime of humans, aberrant TE activity might cause or contribute towards diseases including neurological conditions such as Alzheimer's Disease (AD) and cancer. While inflammatory pathways linked to TEs may be a part of the disease pathology, on the other hand altered TE activity involving inflammatory pathways could be recognised by disease suppression mechanisms. For this reason, TEs could be targeted for therapeutic applications aiming to prevent TE activity or reduce initial inflammatory pathways as well as to activate disease suppression mechanisms. In this review, we describe the contributory and potential preventative roles of TEs in neurological conditions and cancer from a molecular and evolutionary perspective. Evolutionary paradigms both at the unicellular and organismal level aid understanding the role of TEs in disease. These observations could pave the way for the development of novel therapeutic approaches targeting TEs.

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INTRODUCTION

TEs and their lifecycle

Transposable elements (TEs) make up half of the human genome, and exist in almost all sequenced eukaryotes (Huang et al., 2012). Depending on their replication cycles, TEs are divided into two groups: i-) DNA transposons that are excised and reintegrate elsewhere in the genome ii-) RNA transposons (retrotransposons) that use an RNA intermediate followed by reverse-transcription to copy themselves and move to different locations (Klein and O'Neill, 2018) (**Figure-1**). TEs act as selfish elements and replicate to spread through the genome. While cells generally have low TE activity, during development and dysregulated conditions including cancer and neurobiological diseases, they exhibit elevated TE activity (Garcia-Perez et al., 2016; Anwar et al., 2017).

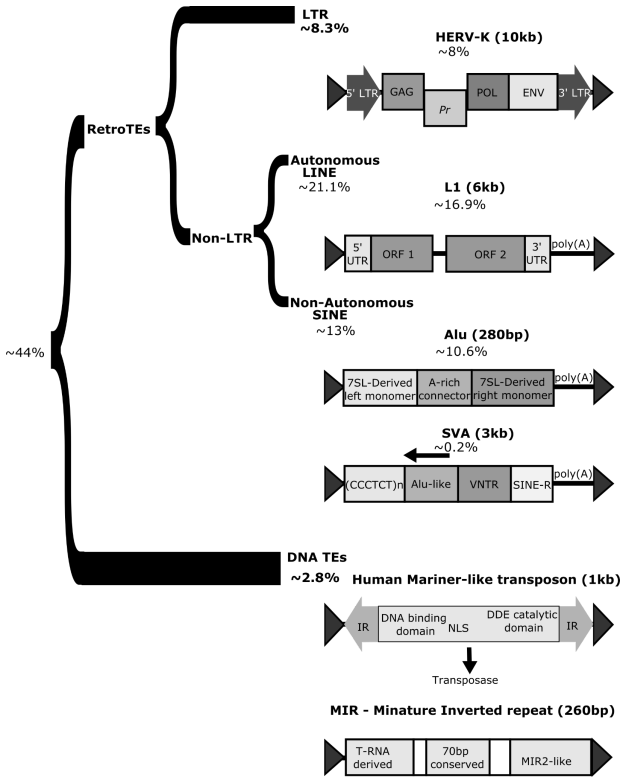

Figure-1: Transposable element classes in the human genome: The type, structure and percentage of each element in the human genome. Abbreviations: human endogenous retrovirus-K (HERV-K): LTR, long terminal repeat; Gag, group-specific antigen; Pol, polymerase; Env, envelope protein; L1, LINE-1; UTR, untranslated region; ORF, open reading frame; A-rich connector, the adenosine-rich segment separating the 7SL monomers; VNTR, variable number of tandem repeats; SINE-R, domain derived from a HERV-K.

Autonomous TEs possess the required machinery to mobilise in genomes, however, nonautonomous TEs lack this and may rely on existing machinery. Among autonomous TEs, DNA transposons, ERVs, and LINEs are mobilised through different mechanisms. DNA transposons use cut and paste

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mechanisms (Muñoz-López and García-Pérez, 2010) whereas ERVs have similarities with viruses and use reverse transcriptase and integrase (Grandi and Tramontano, 2018). The role of mobilisation of ERV and DNA transposons to new loci in human disease is less well documented when compared to RNA transposons. Long Interspersed Elements (LINEs) use a retrotransposition mechanism with an endonuclease and reverse transcriptase (**Figure 2**). Once full length untruncated LINE1 is transcribed by RNA Polymerase II, polyadenylated and capped mRNA is exported into the cytoplasm and translated into ORF1p and ORF2p (Beck et al., 2011). These proteins are then combined with the mRNA, forming an RNP complex (Beck et al., 2011; Elbarbary et al., 2016). An unknown mechanism shuttles the RNP complex into the nucleus and binds an A/T rich target nicked by the endonuclease (Jurka, 1997; Doucet et al., 2010). This target priming is the substrate for the reverse transcriptase. The reverse transcription might also take place in the cytoplasm (**Figure-2**) (Thomas et al., 2017). The non-autonomous Short Interspersed Elements (SINEs) such as Alu and SVA can *trans* mobilise using the LINE1 machinery (Raiz et al., 2012). LINEs and SINEs have been shown to mobilise readily in human diseases (Hancks and Kazazian, 2016).

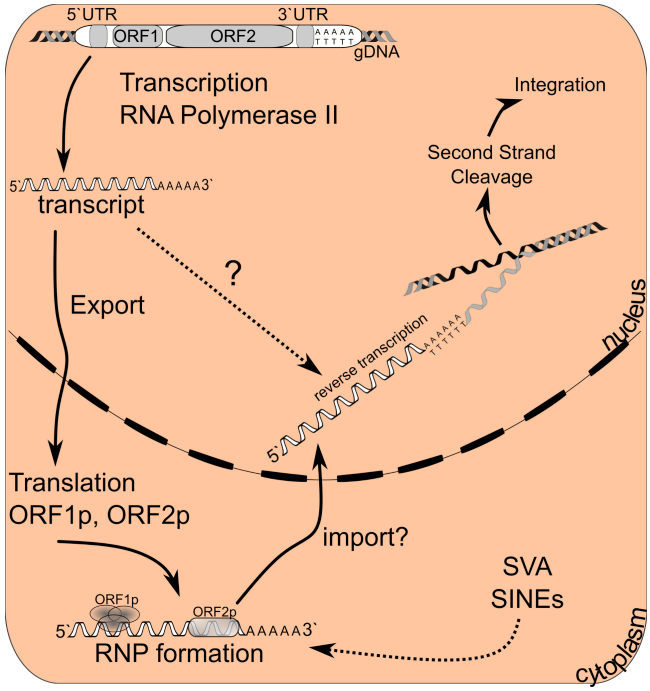

Figure-2: LINE1 retrotransposition cycle: After untruncated LINE1 is transcribed and transported to the cytoplasm, a ribonucleoprotein (RNP) complex is formed with the translated ORF1p and ORF2p. LINE1 RNP is then imported into the nucleus. Target-site primed reverse transcription (TPRT) is a mechanism that mediates L1 retrotransposition. During TPRT, genomic DNA is nicked by the L1 endonuclease. This creates a free 3' hydroxyl group (OH) that can be used as a primer for the reverse transcription. It is still unclear how second-strand cleavage, second-strand complementary DNA (cDNA) synthesis, and completion of LINE1 integration is processed mechanistically. TPRT creates a 5′-truncated L1 copy insertion at new genomic locations. In rare cases, SINEs and SVAs, and some cellular mRNAs might mobilise through L1 retrotransposition machinery. Unknown mechanisms are indicated by question marks.

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TEs over evolutionary timescales

The mobilisation of TEs results in interactions with the host organism that resemble those seen with pathogens (Cosby et al., 2019). Hosts have evolved with mechanisms and machinery to control deleterious activities of the pathogen. Similarly, pathogens might evolve with beneficiary functions to the host in order to increase chances of survival (Cosby et al., 2019). Mechanisms to control TE activity in eukaryotes include DNA (5mC) methylation (Jansz, 2019), histone modifications (Walter et al., 2016; Igolkina et al., 2019) and small RNA pathways (Hyun, 2017) which provide an extra layer of security to maintain genome stability (Reik, 2007). While these mechanisms function widely throughout the lifetime of humans to suppress TEs, they allow flexibility for TE expression during embryogenesis and differentiation where they perform essential co-opted regulatory functions (Bourque et al., 2018).

TEs can be co-opted for diverse functions including gene regulation which positively affect organism fitness and are selected for during evolution (**Figure-3**). Long Interspersed Element (LINE) and Endogenous Retroviruses (ERV) proteins are required during mammalian development for the integrity of two-cell stage embryos, and alterations in their expression during these stages could change the fate of the embryo in mice (Rowe and Trono, 2011; Macfarlan et al., 2012; Ohnuki et al., 2014; Garcia-Perez et al., 2016; Gerdes et al., 2016; Huang et al., 2017; Percharde et al., 2018; He et al., 2021; Xiang and Liang, 2021).

TEs show co-opted functions in other animals, as well. A recent work analysing TE variation in *C. elegans* wild isolates identified TE insertions in genes crucial for interaction with the environment (Laricchia et al., 2017). One other well-known example is the Short Interspersed Element (SINE) composition of the Chinese Yangtze River fish *Coilia nasus* in olfactory cells giving rise to resident and migratory ecotypes (Liu et al., 2020).

An extraordinary example of a co-opted TE function came from transgenerational inheritance studies in the nematode *C. elegans.* These showed that virus-like particles (VLPs) formed by the GAG protein of the *Cer1* retrotransposon were required in mothers for small RNA-mediated learned pathogen avoidance, which could be inherited through four consecutive generations (Moore et al., 2020). Expectedly, wild isolates of *C. elegans* lacking *Cer1* were impaired in transgenerational inheritance of the learned pathogen avoidance behaviour (Moore et al., 2020).

TE associated factors have also been implicated in the formation and memory of vertebrate immune systems that are restricted to somatic cells and are therefore not heritable (Broecker and Moelling, 2019). In jawed vertebrates, the variation of antibodies and T Cell Receptors (TCRs) takes place through the recombination of V(D)J segments utilising a RAG transposase (Janeway et al., 2001). Consistent with this, *RAG* knockout mice show a complete defect in lymphocyte development (Mombaerts et al., 1992; Shinkai et al., 1992). Another example for the role of TEs in immune systems is highlighted in a recent preprint from Cedric Fechotte's group. This study demonstrated that an endogenous retrovirus (ERV) derived protein, Suppressyn, that has lost its C-terminus transmembrane

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domain during evolution, blocks viral infection in preimplantation embryos via binding the ASCT2 receptor, a common port of entry for the RD-114 and Type-D retroviruses (RDR) in humans (Frank et al., 2020). This presents a clear example of a defence mechanism utilising an evolutionarily old enemy to fight novel infections.

TEs can shape the three dimensional architecture of the genome via compartmentalization (Lu et al., 2021) and the dynamic nature of chromosomes by contributing to the formation and evolution of centromeres and telomeres (Morrish et al., 2007; Casacuberta, 2017; Klein and O'Neill, 2018; Anderson et al., 2019). Species specific subfamilies of SINE repeats act as binding sites for the axial element proteins during meiosis (Johnson et al., 2013) and transposons help form the centromere identity (Henikoff et al., 2001). Telomeres that are located on chromosome ends suffer from constant shortening after each successful DNA replication during the cell cycle. The enzyme responsible for the maintenance of telomeres, telomerase, uses RNA as a template (Zhang et al., 2011). It has been proposed that Telomerase evolved from retrotransposon machinery (Eickbush, 1997; Nakamura and Cech, 1998; Nosek et al., 2006). LINE elements have also been implicated in human telomere regulation (Kordyukova et al., 2018).

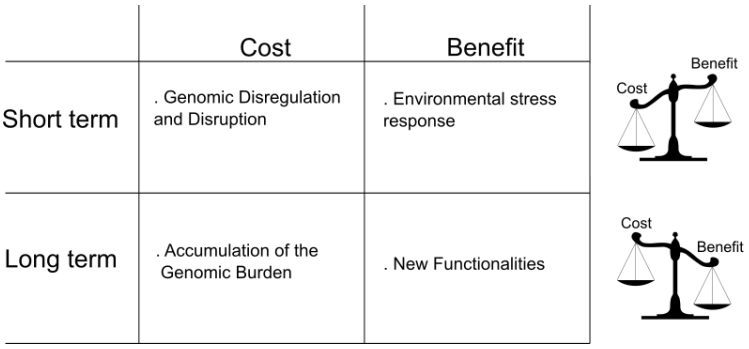

Figure-3: Costs and Benefits of TEs in timescales: Over long timescales, TEs can contribute to organismal fitness and biology by new functionalities.

The scope of the review

TE activity and insertions altering native genes could potentially cause disease in humans. Accumulating evidence in the field has already established some causative roles for TEs in various human neurological diseases and cancers (Hancks and Kazazian, 2016). This review will first introduce the evolutionary functions of TEs using their co-opted neurological roles to demonstrate the evolutionary benefits. We will then discuss how dysregulation of these functions and activation of TEs that are evolutionarily young and old, native and co-opted, functional and truncated, may contribute towards human neurological conditions and cancers, respectively. Finally, this review discusses questions that still need to be answered in this field.

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Co-opted functions of TEs in neurobiology

We are becoming increasingly aware of the role of TEs in mammalian evolution and their evolutionary acquired roles in mammalian brain development, as well as their contribution towards both neurodevelopmental and neurodegenerative diseases (Notwell et al., 2015; Platt et al., 2018; Jönsson et al., 2020). New advances in bioinformatics approaches including novel methods of precisely mapping TE transcript reads are enabling a better understanding of TEs in the brain despite the challenges of investigating repetitive elements (Guffanti et al., 2018; Tokuyama et al., 2018). Although it was initially thought that transposition events only occur in early development and in diseases late in life, when epigenetic silencing mechanisms were relaxed or dysregulated, there is now increasing evidence that this is not entirely true (Lapp and Hunter, 2019). TE sequences may be transcribed and transposition events occur at different levels in different cells and tissues of the adult organism, and this may serve important functions. From a species evolution perspective, indeed transpositions in early development, like that of ERVs which were found to have highest expression in oocyte, zygote, and four-cell stages, are most important as these are passed down to future generations in the germline (Lapp and Hunter, 2019; Fu et al., 2021). The acquired roles in their new loci and functions in development and adulthood are key to organism fitness and thus have a clear evolutionary role. However these co-opted roles are not limited to direct roles, for example as enhancers, but may include activity in adulthood to serve a function.

There is increasing evidence that TEs have been essential to primate evolution and one key characteristic of primates is their brain and behavioural complexity (Mariño-Ramírez et al., 2005; Feschotte, 2008; Linker et al., 2017). TEs have been co-opted through evolution for a number of neurological roles including regulation of development, response to environmental stress, behaviour and cognition, and cellular senescence and ageing, which are briefly presented below.

Co-option of TEs for regulatory roles in Brain Development

TEs have shown to be co-opted for various regulatory roles in the brain of mammals, for example as serving enhancers and promoters to regulatory genes during development. One example demonstrating co-option of TEs for regulation of neural development is the recruitment of MER130 non-autonomous interspersed TEs as neocortical enhancers in mice. MER130 transposon sequences are enriched among active enhancers in the mouse dorsal cerebral wall which gives rise to the neocortex (Notwell et al., 2015). MER130 likely originated in tetrapods or earlier ancestors which is before the evolution of the neocortex, a brain region unique to mammals responsible for sensory perception and cognition. It was therefore co-opted for its current functions (Notwell et al., 2015).

A human specific example is the evolutionarily recent co-option of SVA, HERVK and HERVH subgroups for roles in embryogenesis. These TEs are involved in chromatin opening during embryonic genome activation, with more than a third of genomic sites open in pre-implantation embryos embedded in TEs, and human specific TE integrations tending to be close to genes transcribed in embryonic genome activation (Pontis et al., 2019). The TEs act as Krüppel-like factor (KLF)

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stimulated enhancers in naive human embryonic stem cells, as well as later on functioning as tissue specific enhancers (Pontis et al., 2019). Krüppel-associated box (KRAB) zinc finger proteins of corresponding evolutionary ages regulate the TEs by repressing transcriptional activity, thus incorporating the TEs into human gene regulatory networks (Pontis et al., 2019). Dysregulation of the KRAB zinc finger proteins could therefore elevate TE activity and result in downstream consequences including contributing towards disease.

TEs activity in neural cells in response to the environment in early life

There is considerable brain development in mammals in early life and TEs are increasingly thought to be involved in this development. There is more and more evidence that early experiences during neuronal development and pre-adulthood have implications for TE activity and transposition in the brain (Lapp and Hunter, 2019). In mice, analysis of hippocampal tissue DNA demonstrated that L1 copy number in the hippocampus of offspring inversely correlated with the total percent time spent by dams on maternal care in the first two weeks (Bedrosian et al., 2018). This observation was not replicated in the copy number of SINE B1, SINE B2 and intracisternal A particle (IAP) TEs. The difference in L1 copy number was also shown to be unrelated to neurogenesis rates which was not influenced by the differing maternal care. Low care offspring had less methylation, particularly at the YY1 transcription factor binding site necessary for L1 transcription, indicating decreased methylation as a potential mechanism for the increased L1 copy number (Bedrosian et al., 2018). The function of this response to the environment, the influence on observed behavioural differences, and whether it may have potential organism fitness benefits under the specific conditions is unclear. However, responses to the environment that alter TE activity and perturb normal epigenetic regulation, may have downstream implications to disease (Lapp and Hunter, 2019). One potential human example of differences in TE activity in response to the environment, is that children with higher hair cortisol, a well known biomarker of chronic stress, had lower levels of SINE methylation, and hypomethylation near an intronic DNA transposon in the PRDM14 gene encoding a protein involved in TET-mediated demethylation (Nätt et al., 2015). A zinc-finger transcription factor, ZNF263, was also identified as having binding sites overrepresented in regions with the methylation loss, indicating a potential mechanism involving its dysregulation or altered function in response to stress (Nätt et al., 2015).

Stress and plasticity of the brain in adulthood

Several studies have reported that the frequency of LINE1 retrotransposition varies by brain region and cell type (Upton et al., 2011; Evrony et al., 2012). Much research has focused on retrotransposition in the hippocampus during adulthood and has found that it is associated with environmental stimuli and genomic mosaicism linked to processes such as memory formation (Bachiller et al., 2017). The dentate gyrus, part of the hippocampus and one of the few regions in the brain with significant adult neurogenesis occurring, has been shown to be a hotspot for LINE1 activity in neural progenitor cells, and LINE1 activity could influence the fate of neuronal progenitor cells in vitro (Muotri et al., 2005). These observations may support the idea that LINE1 retrotransposition in the adult brain is adaptive. This is further supported by studies demonstrating that new LINE1 insertions are enriched in actively expressed genes (Muotri et al., 2005; Singer et al., 2010; Coufal et al., 2011; Lapp and Hunter, 2019).

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Further evidence for potential adaptive roles for TEs comes from the link between transposons and the stress response with different responses reported for different stressors (Pappalardo et al., 2021). Histone methylation, a transcriptional repressive mark, has been reported to occur at SINE elements in the hippocampus in response to acute restraint stress in rats (Hunter et al., 2012), however SINE elements upregulated in response to ischemia in the hippocampus CA1 region in Mongolian gerbils (Kalkkila et al., 2004). Although the somatic retrotransposition in neural cells is not directly evolutionarily significant and can't be passed to future generations, the propensity for retrotransposition in specific adult neural cells is a trait which may enable maintenance of increased brain plasticity in adults and may have been selected for to enable increased behavioural responses to changes in the environment (Lapp and Hunter, 2019). There may be consequences of adaptive TE activity later in life, post reproductive age, and links to neurodegenerative disease.

Roles in cell senescence and ageing

Transposable elements have also been proposed to play a role in ageing and senescence. In Drosophila for example, the transposons *R2*, a LINE-like element, and *gypsy*, an LTR element, were found to be elevated in normal ageing, and mutation of *dAgo2* (*Drosophila Argonaute 2)* resulted in elevated brain transposon expression, more rapid age-dependant memory impairment, and shortened lifespans (Li et al., 2013). In humans, transposable elements have further been implicated in senescence and immune mediated clearance of senescent cells. Transposable elements are robustly expressed in senescent human stem and progenitor cells (s-HSPCs) and the pathways of inflammation are activated leading to secretion of inflammatory cytokines (Capone et al., 2018; De Cecco et al., 2019). Hypomethylating agents result in expression of TEs activating dsRNA recognition pathways and downstream interferon-stimulated genes and may thereby result in cell death and clearance of cells (Capone et al., 2018; Colombo et al., 2018). Senescent cell clearance has been shown to be important in rejuvenating ageing hematopoietic stem cells (Chang et al., 2016), restoring tissue homeostasis in response to ageing and chemotoxicity (Baar et al., 2017), and an increase in lifespan (Zhu et al., 2016).

All the above roles of TEs may have important evolutionary benefits and therefore have been selected for, however dysregulation of these roles may contribute towards disease. In order to utilise transposable elements for the organism's benefit, it is evident that tight regulation is key. Dysregulation at low frequencies in development and adulthood may result in disease, however the benefit of TEs may outweigh their costs leading to the maintenance of TEs in their evolutionary roles together with low frequencies of resultant disease. Dysregulation of TEs post reproductive age when selection is less powerful may result in TEs contributing towards age related diseases. In the following section the role of specific TEs in disease is discussed.

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IMPLICATION IN HUMAN DISEASES

The first evidence for the causative role of a retroelement in human diseases came from the analysis of a coagulation factor (F8 gene) in haemophilia A patients. A LINE disrupted exon 14 of the Factor VIII gene involved in blood clotting, thereby resulting in a defective protein being produced (Kazazian et al., 1988). With the advancements in methods and sequencing technologies to study the repetitive nature of genomes, many other individual cases of TE insertions have now been documented in human diseases. Among these, insertional mutagenesis of TEs in essential genes are the most widely reported examples. These influence host gene function by creating impaired transcription and splicing, alternative or premature polyA signals, and frameshift mutations (Hancks and Kazazian, 2016). We will review the causative effects of TEs in neurological conditions (neurodevelopmental and neurodegenerative diseases) and cancer (tumour initiation and progression), respectively (**Figure-4**). Overall, three important questions shape previous and current research in this field: i-) How do TEs initiate disease in healthy human tissues? ii-) How do TEs contribute to disease maintenance and prevention? iii-) What are the potential therapeutic approaches using TEs to treat human diseases?

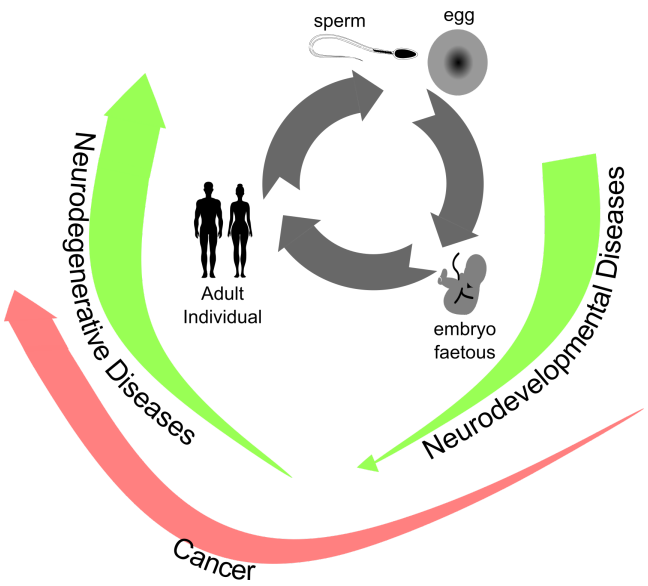

Figure-4: Human diseases linked to TEs during early life and adulthood: TE activity contributes towards neurobiological conditions (green) and cancer (red) at different stages of development and adulthood. Thickness of the green and red arrows indicates disease risk.

Neurodevelopmental Diseases

Neurodevelopmental disorders are a group of disorders where the normal neural developmental programme to form the adult brain is disrupted (Mullin et al., 2013). Neurodevelopmental diseases are characterised by impaired function which may affect cognition and learning, communication,

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behaviour and motor skills as well as resulting in other physical symptoms like seizures (Bozzi et al., 2012; Mullin et al., 2013). The development of the brain and CNS is tightly spatiotemporally regulated and influenced by both genetic and environmental factors (Lenroot and Giedd, 2008; Zhu et al., 2018; Jönsson et al., 2020).

Several developmental psychiatric disorders which may have both environmental and or genetic links have been shown to have dysregulated TEs affecting their pathology (Guffanti et al., 2014). Rett syndrome, caused by mutations in the methyl-CpG binding protein 2 (*MeCP2*) gene, results in developmental delay, seizures and intellectual disability, and has been associated with increased LINE1 transposition in neural progenitor cells (Amir et al., 1999; Yu et al., 2001; Muotri et al., 2010; Lapp and Hunter, 2019). LINE1 elements were also implicated in ataxia telangiectasia (Louis-Bar syndrome), a similar genetic disorder with resultant neurological impairment caused by mutations in the *ATM* gene (Coufal et al., 2011). Post-mortem hippocampal neurons of individuals with the disease had increased LINE1 copy number (Coufal et al., 2011). Comparison of the brain and blood samples through whole genome sequencing from individuals with Rett syndrome, tuberous sclerosis, ataxia-telangiectasia and autism demonstrated that the LINE 1 elevation is brain tissue specific, with LINE1 elevated in brain compared to blood samples, and higher in pathologic brains compared to healthy ones (Jacob-Hirsch et al., 2018; Lapp and Hunter, 2019). Moreover, >65% of LINE1 insertions per sample were found to be truncated at the 3′ and 5′ ends with more truncation at both the 3’ and 5’ end in brains of individuals with neurodevelopmental disorders, indicating a potential non-classical endonuclease-independent transposition mechanism (Jacob-Hirsch et al., 2018).

TEs including HERV (Balestrieri et al., 2012), LINE1 (Shpyleva et al., 2018) and Alu elements (Saeliw et al., 2018) have also been linked to Autism Spectrum Disorders (ASD) and there have been links with this and histone methylation and DNA methylation (Balestrieri et al., 2012; Shpyleva et al., 2018). Autism spectrum disorders can be attributed to genetic causes including polymorphisms of several genes and copy number variants, however much of the risk of getting the disease is still unaccounted for (Marshall et al., 2008; Luo et al., 2012; Jiang et al., 2013; Gaugler et al., 2014; Estes and McAllister, 2015; Gottfried et al., 2015). Furthermore, there is large heterogeneity in symptoms and severity. Transposable element dysregulation may be one of the factors that result in heterogeneous symptoms and severity as well as unaccounted risk. There are two potential mechanisms through which TEs may cause neurodevelopmental disorders: i-) Perturbation of their potential roles in normal development. ii-) Altered TE activity leading to neuroinflammation.

Neurodegenerative Diseases

Neurodegenerative diseases can be differentiated from neurodevelopmental diseases in that they affect those with normal neural development and function and occur later in life. Neurodegenerative diseases are caused by degradation and loss of function of adult neurons, and can result in similar symptoms to neurodevelopmental diseases (Dugger and Dickson, 2017; Hussain et al., 2018). These include cognitive impairment in learning and memory, loss of self-control and emotional effects (Gitler et al., 2017). Neurodegenerative diseases can also be split into early onset which result in premature

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degradation of adult neurons, and the late onset neurodegenerative diseases that usually occur in later life (Spina et al., 2021). They include Alzheimers, Parkinson's disease and ALS (Jönsson et al., 2020). Transposons may be linked to the pathology of neurodegenerative diseases through their involvement in neuroinflammatory pathways and cellular damage during ageing as well as through disease specific mechanisms and roles (Jönsson et al., 2020).

Alzheimer's Disease is the most common neurodegenerative disease which leads to dementia and is estimated to affect more than 13 million people in the US by 2050 (Querfurth and LaFerla, 2010). It is characterised by the build up of extracellular plaques of misfolded amyloid-β peptide and neurofibrillary tangles of Tau protein (Murphy and LeVine, 2010; Rahman et al., 2021). Alzhiemers pathology includes death of neurons and the loss of synapses which results in progressive cognitive decline (Kocahan and Doğan, 2017). Analysis of both Drosophila models as well as human post-mortem brains have indicated a role of Transposable elements in Alzheimer's pathology (Guo et al., 2018). The human post-mortem brains showed a correlation between neurofibrillary tangle burden and TE activation of the ERV1, 2, 3, and L1 families, and the activation of ERVs was also correlated to cognitive performance in the year before death. Chromatin relaxation signature, histone acetylation (H3K9Ac), was also detected at multiple *HERV-Fc1* genomic loci. In the drosophila model, Tau expression was sufficient to induce TE activity (Guo et al., 2018). Different Tau isoforms have even been indicated to have different effects on transposable element activation (Grundman et al., 2020).

Neuroinflammation

Dysregulation of the aforementioned roles of TEs as well as itself resulting in disease, may result in neuroinflammation as a byproduct which may affect the pathology and progression of disease (Hunter et al., 2013). TE transposition and expression have also been directly linked to inflammation and inflammatory pathways and therefore may directly contribute towards pathology in this way (Saleh et al., 2019; Rostami and Bradic, 2021). Many correlative studies have now shown the links between neurodevelopmental and neurodegenerative diseases, transposons and inflammation (Lapp and Hunter, 2019; Saleh et al., 2019). Mechanistic studies have begun to elucidate the pathways by which this occurs (Saleh et al., 2019). As our understanding of the pathways involved increases, this may enable targeted therapeutics.

Pathological agents such as viruses and bacteria can induce inflammation, activating the innate immune response. These pathological agents are recognised by Pattern Recognition Receptors (PRRs) recognising pathogenic proteins and nucleic acids. PPRs are categorised in 4 classes: i-) Toll-like Receptors (TLRs). ii-) Leucine-rich Repeat Receptors (LRRs). iii-) Retinoic-acid Inducible Receptors (RIG-1). iv-) C-type Lectin Receptors (CLRs) (Walsh et al., 2013; Amarante-Mendes et al., 2018). Among the PPRs, TLRs have been shown to be expressed in human neuronal cells (Rolls et al., 2007).

In previous sections, we have introduced and discussed how TEs are co-opted during mammalian evolution. Even though TEs are mostly domesticated, they still possess viral particles through which

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inflammation could be induced upon dysregulation (Jönsson et al., 2020). This could take place via several mechanisms. Firstly, TE transcripts such as LINE and HERV are exported into the cytoplasm after reactivation. For LINE1, RNA-DNA hybrids, single stranded DNA (ssDNA) and double stranded DNA (dsDNA) produced during reverse transcription are recognised by PRRs and could induce inflammation via the cGAS-STING pathway (Simon et al., 2019). Additionally, pathological levels of ERV envelope proteins could induce inflammation by inducing cytokines and chemokines that activate an innate immune response (Göttle et al., 2019) (**Figure-5)**.

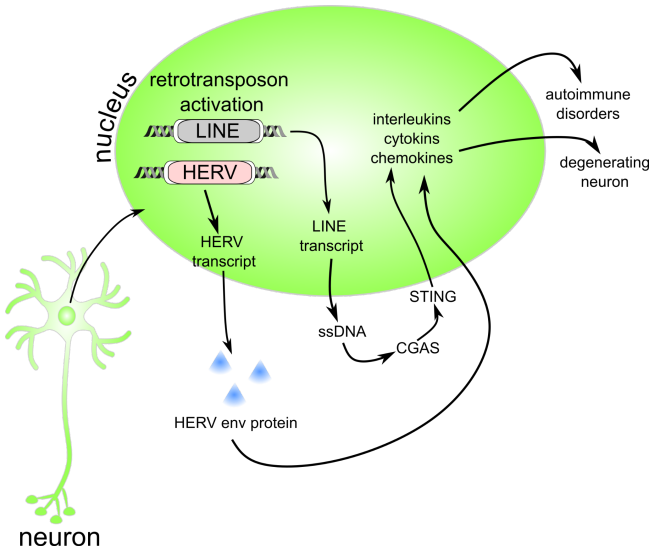

Figure-5: Inflammation in neurobiological conditions: Overexpressed TE nucleic acids and proteins can activate cytokines and chemokines. These signals initiate inflammation that is later recognised by the immune system. This results in degenerating neurons. The figure is adapted from (Thomas et al., 2017).

The role of TEs in human cancers

Since the first solid evidence for a *de novo* LINE insertion in the adenomatous polyposis coli (APC) gene of a colon cancer patient (Miki et al., 1992), there has been extensive research and published work on the causative role of TEs in human cancers.

Cancers are a group of diseases characterised by uncontrolled cell growth (O'Connor et al., 2010). This is due to a loss of extracellular and intracellular controls limiting cell division, and activation of factors promoting growth. Cancer cells, having escaped the control mechanisms that ensure all the cells in a multicellular organism behave in a cooperative way and commit to quiescence, senescence, and apoptosis, instead behave in a selfish way analogous to unicellular organisms and colonies of unicellular organisms within the environment of the body (Niculescu, 2019).

These ideas point to an important observation: Cancer initiation and progression manifest the basic properties of micro and macroevolution (Casás-Selves and Degregori, 2011), with competition

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between cancer cells (akin to intraspecific competition), and competition between cancer cells and non-cancer cells (akin to interspecific competition) (**Figure-6**). Cancer can also be explained as a host-pathogen relationship within the human body (Pelham et al., 2020). Individual cells with greatest survival fitness and reproductive fitness have a selective advantage and divide to produce progeny which increase in frequency. What differentiates cancers from other pathogens, is the rate of evolution and change due to the great selective pressure enforced by multiple control mechanisms. These serve to detect divergence from the non-pathogenic state of somatic cells. The majority of cells which accumulate mutations and begin to diverge from healthy somatic cells are rapidly targeted to senescence or apoptosis and therefore do not result in successful cancers (Fernald and Kurokawa, 2013; Maynard et al., 2015). Cancer also differs from other pathogens in that the cells start off with all the same genes as their host, and therefore cancer cells must adapt rapidly and form mechanisms to evade the human immune system (Bordonaro, 2018; Pelham et al., 2020).

The role of TEs in the evolution of cancers has been widely discussed with differing views ranging from their being a direct driver of cancer evolution, to their activation being a consequence of other changes rather than an important driver of tumour evolution (Hauptmann and Schmitt, 2006; Babaian and Mager, 2016; Anwar et al., 2017; Lynch-Sutherland et al., 2020).

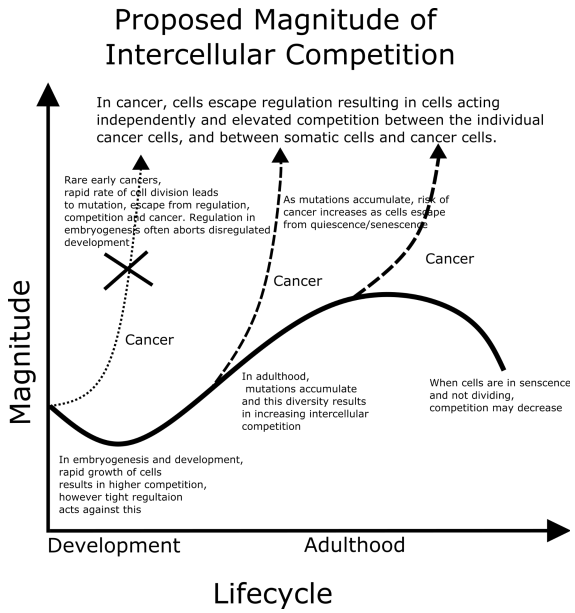

Figure-6: Proposed magnitude of intercellular competition: When cells are dividing rapidly in development, intercellular competition would be elevated resulting in cells with a selective advantage increasing in frequency in the population, however tight regulation of cell division and growth prevents cells from acting independently. During adulthood cells accumulate mutations which results in increasing competition as the reduced response to regulation acquired gives certain cells a selective advantage. Senescence serves to prevent cells from dividing and escaping regulatory control thus reducing competition. Cancer can occur at any stage in the life cycle, but increases in risk as age increases and mutations accumulate (dashed arrows). Cells escape regulation resulting in cells acting independently and greatly elevated competition between the individual cancer cells, and between somatic cells and cancer cells. Cancer cells with a fitness advantage survive and divide more rapidly and therefore increase in frequency in the population.

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What is clear and generally agreed upon is that transposable elements provide a large “reservoir of autonomous gene regulatory elements" (Babaian and Mager 2016). These have the potential to drive aberrant gene expression that is not present in the pre-cancerous differentiated cells. Many previous studies have used exaptation to refer to abnormal use of TEs as regulators in cancer cells compared to the differentiated somatic cells. Multiple potential models exist for the exaptation of TEs in cancer including derepression and epigenetic evolution models (Lamprecht et al., 2010a; Babaian and Mager, 2016). Transposable element exaptation is rare and their potential for exaptation seems to be influenced by their evolutionary age and constrained by pleiotropic effects (Simonti, Pavličev, and Capra 2017). Many proposed cancer exaptation events present regulatory roles also presented to some extent in stem cells (Jang et al., 2019; Lynch-Sutherland et al., 2020). Studies have not often differentiated between this regulation which can occur in another cell type or state i.e. undifferentiated stem cells and a completely novel use of the TE. This distinction may be useful when assessing the mechanisms of TE action in cancer.

Transposable elements could play an important role in all aspects of cancers, with specific roles in initiation and progression. This can be through their ability to act as regulatory elements or their impact on general genome stability, and therefore ability to cause mutations with alternate phenotypes and adaptations. TEs may also have other roles such as helping cancer cells evade the immune system (Zhu et al., 2021).

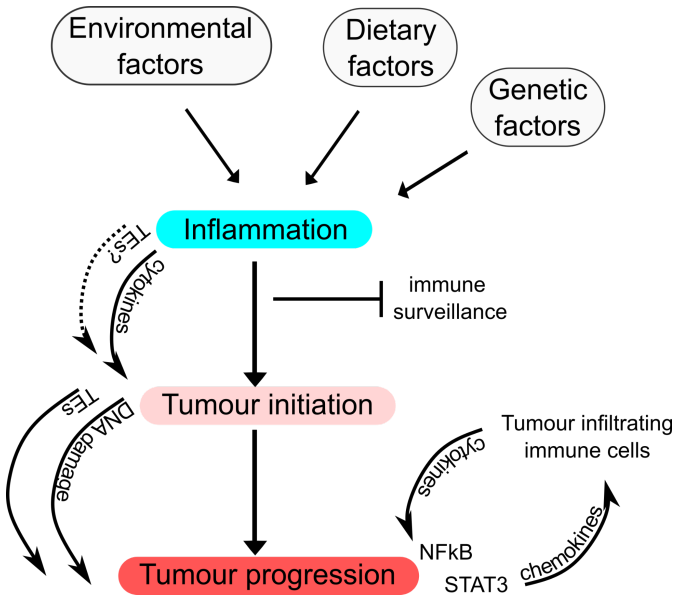

Figure-7: Inflammation in human cancers: Environmental, dietary and genetic factors contribute to tumour initiation and progression.

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a. The role of TEs in tumour initiation:

Tumour initiation is associated with functional changes or mutations in genes important for the cell cycle, cell growth, survival and differentiation (Tysnes and Bjerkvig, 2007; Williams and Stoeber, 2012). These genetic alterations emerge as spontaneous mutations or as a result of external factors such as carcinogenic agents (Siddiqui et al., 2015). In this section, we first focus on the role of TEs driving such changes in tumour initiation.

Transposable elements have long been associated with cancer, with LINE element elevation used as a diagnostic feature (Hancks and Kazazian, 2016). Interestingly, two independent articles from 2012 and 2014 identified unique somatic LINE retrotransposition events in colorectal, breast, ovarian and lung cancers compared to matching healthy tissues (Lee et al., 2012; Helman et al., 2014). Among these LINE insertions, the majority were observed in tumour suppressor genes. Thus, functional disruption of tumour suppressor genes by LINE insertion could create a selective advantage during tumorigenesis. However, somatic LINE retrotranspositions were not observed in blood or brain cancers (Lee et al., 2012; Helman et al., 2014), which raises an important question regarding epigenetic mechanisms repressing TEs in different tissues.

As well as inactivation of tumour suppressor genes via LINE insertions, oncogene activation serves as another causative role for TEs in tumour initiation. In bladder and colorectal cancer cells, hypomethylation of a LINE1 promoter can alter the expression of the adjacent MET oncogene and can result in production of an alternate transcript (Wolff et al., 2010; Hur et al., 2014). What is more, hypomethylation of the LINE promoter adjacent to the MET oncogene was associated with structural changes in the chromatin such as dinucleosome structures, histone H2A.Z deposition, and nucleosome free regions upstream of the transcription start site (Wolff et al., 2010). A similar transcriptional alteration of MET oncogene has also been documented in human chronic myeloid leukaemia (CML) cells. The hypomethylated LINE1 promoter was shown to activate sense and antisense transcription producing ORF1 and c-MET oncogene transcripts respectively, thus inducing tumorigenesis (Roman-Gomez et al., 2005). Unlike LINEs and SINEs/SVA elements that use LINE machinery, no evidence for ERV somatic retrotransposition in humans has been documented so far (Bannert and Kurth, 2006; Jern and Coffin, 2008; Magiorkinis et al., 2015). It has been questioned whether ERVs promote initiation of tumorigenesis independent of their retrotransposition machinery (Kassiotis, 2014). It is a well established phenomenon in the field that ERV LTRs are a significant source of canonical promoters in humans among which some are dormant or cryptic, consequently resulting in reconfiguration of cellular transcription upon reactivation (Rebollo et al., 2012; Grassilli et al., 2016; Maeso and Tena, 2016; Deniz et al., 2020). Oncogenes including tyrosine kinase receptors CSF1R, ALK and ERRB4 and transcription factor IRF5 become transcribed or upregulated as a result of a nearby activated LTR element leading tumorigenesis in Hodgkin Lymphoma (HL) (Lamprecht et al., 2010b; Babaian et al., 2016), skin cutaneous melanomas (Wiesner et al., 2015) and anaplastic large cell lymphoma (ALCL) (Scarfò et al., 2016). Indeed, activation of LTR (ERV) and non-LTR-based (LINE) promoters create favourable conditions driving tumorigenesis. There is evidence that TEs can

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act as enhancers in Acute Myeloid Leukaemia (AML) (Deniz et al., 2020). However it is unclear whether they play an active adaptive evolutionary role during the progression of the cancer, or are a consequence of the cell state of cancers which present a stem-like de-differentiated state. It does seem however, that in either case, their activation may result in an increased ability of cancer cells to proliferate (Deniz et al., 2020).

In addition to strong evidence that has accumulated in the field for TE insertions altering tumour suppressor or oncogene functions, there have also been reports presenting the role of the reverse transcription machinery of TEs during tumorigenesis (Sciamanna et al., 2016). Firstly, LINE elements are highly expressed, and their proteins ORF1p and ORF2p required for retrotransposition are abundant in tumour cells (Gualtieri et al., 2013). Interestingly, inhibition of the reverse transcriptase (RT) encoded by the ORF2p reduces cell proliferation and increases differentiation in acute myeloid leukaemia (AML) and breast cancer cells (Mangiacasale et al., 2003; Gualtieri et al., 2013). A growing pool of evidence in the field actually indicates a regulatory role for the retrotransposition machinery in cellular transcription in cancer cells, including that of coding and non-coding genes (Sciamanna et al., 2013). RNA:DNA hybrids were more abundant in cancer cells compared to matching healthy cells, indicating RTs could capture transcripts of coding and non coding genes as templates to create cDNAs (Sciamanna et al., 2013). Further evidence demonstrated RNA:DNA hybrid formation during tumorigenesis could be reversed with RT inhibitors. This proves the RNA:DNA hybrid formation is a direct consequence of reverse transcription of the LINE retrotransposition machinery (Sciamanna et al., 2014). In the light of these valuable observations, it has been proposed that RNA:DNA hybrid formation of non-coding RNA genes such as miRNA precursors during tumour initiation could deplete dsRNA templates for DICER. As a consequence, gene regulatory function of miRNAs becomes compromised, favouring cancer-prone conditions (Sciamanna et al., 2016). Because many miRNAs are linked with apoptosis including in cancer (Jovanovic and Hengartner, 2006), activation of the LINE retrotransposition machinery, while possibly a self-toxic process for the host, could also potentially be an escape mechanism from programmed cell death.

b. The role of TEs in tumour progression:

In initiation, the cancer evades cell cycle checkpoints to enable uncontrolled growth. In the progression phase of the cancer, cells continue to divide and interact with the host resulting in increased tumour size, by evading the immune system (Grizzi et al., 2006; Compton, 2020). In this stage, cancer cells must gain autonomy from the host signals to ensure and maintain survival. TEs might contribute to the progression of cancer by two main mechanisms: i-) DNA damage. ii-) Inflammation.

DNA damage

An important and perhaps one of the most well established aspects of tumour growth is elevated mutagenesis that can include large genomic structural variations (Jackson and Bartek, 2009). This variation enables the cancer to progress through providing diversity upon which selection can act (Li et

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al., 2020; Wang et al., 2020). It has been previously demonstrated in breast cancer cells that increased expression of LINE1 TEs resulted in accumulated DNA damage (Belgnaoui et al., 2006).

Increased DNA damage in cancer could result in large structural variations (SVs) in the human genome compared to healthy matching tissues. These major structural rearrangements in the genome include generation of neochromosomes formed of circular and very large linear chromosomes (Garsed et al., 2014; Klein and O'Neill, 2018). The molecular events leading to the formation of neochromosomes in cancers include chromothripsis and chromoanagenesis, which are also reviewed by others (Zhang et al., 2013; Pellestor, 2019; Pellestor and Gatinois, 2020). While 3% of all cancers exhibit massive genomic rearrangements, chromothripsis has been detected in 25% of patients with osteosarcoma and chordoma bone cancers (Stephens et al., 2011). In osteosarcoma cells, overexpression of HERV LTRs and satellite DNA was detected compared to healthy tissue derived from patients (Ho et al., 2017). Following the repetitive element overexpression, Pieter Pretorius' group identified abundant satellite, simple repeat, LINE and SINE DNA (cell free DNA, cfDNA) in the extracellular environment of osteosarcoma cells, indicating that the genomic shattering possibly occurs in specific chromosomal locations where transposable and repetitive elements are enriched, thereby raising a potential role for such elements in chromothripsis (Bronkhorst et al., 2018). There is clear evidence for the role of transposable elements accumulating and stabilising neo-centromeres of novel chromosomes during evolutionary timescales (Burrack and Berman, 2012; Klein and O'Neill, 2018), however the role of TEs in neo-centromere stabilisation during the short timescales of human disease progression is unclear and thus remain to be further investigated. Even though these molecular mechanisms are not very well characterised in cancer cells, similar events taking place in the germline by LINEs and SINEs might provide a conceptual understanding for future research (Bertelsen et al., 2016; Nazaryan-Petersen et al., 2016).

Inflammation in cancer

The connection between inflammation and cancer was first indicated by the presence of leukocytes in tumours in the 19th century by Rudolf Virchow (Virchow, 1989). Cancer has also been described as a wounded tissue without healing and regeneration ability (Dvorak, 1986). Following this, recent evidence has demonstrated that inflammation can cause cancer and contribute to its growth and metastasis, for which a more detailed explanation could be also found in other review articles (Coussens and Werb, 2002; Greten and Grivennikov, 2019).

Inflammation, as a biological concept, can be explained from two main perspectives: i-) Physiological Inflammation: This is crucial to maintain tissue homeostasis to heal the wounds, regenerate the tissue and prevent the loss of its function that is aided by local tissue macrophages, bone marrow and lymphoid tissues as well as the tissue microenvironment (Medzhitov, 2008). ii-) Chronic Inflammation: Where there is a persistent inflammatory feed-forward loop even if there is no signal (Greten and Grivennikov, 2019). Given the physiological and chronic aspects, inflammation in human cancers has been described as a "double-edged sword" (Hagemann et al., 2007). On one hand, the inflammation could cause cancer and contribute to the tumour progression, growth and metastasis.

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On the other hand, this state of cancer cells could be exploited to increase their antigenicity and hence enable recognition by the immune system that might serve for therapeutic strategies (Kong et al., 2019).

Solid examples for inflammation causing or initiating cancer are colon and gastric carcinogenesis arising from inflammatory bowel diseases such as chronic ulcerative colitis and Crohn's disease (Freeman, 2008), and infections by *Helicobacter pylori (Butt and Epplein, 2019),* respectively. Interestingly, long term use of aspirin and nonsteroidal antiinflammatory medicines significantly reduces the risk of colon cancer, consistent with a direct role for inflammation in cancer (Baron and Sandler, 2000; García-Rodríguez and Huerta-Alvarez, 2001; Chan et al., 2005).

TEs DNA damage and inflammation

In the previous section, we highlighted the role of TEs in DNA damage during tumorigenesis. Increased DNA damage by TEs could initiate or contribute towards inflammation in cancers (Kong et al., 2019). Given the inflammatory role of cytosolic DNA resulting from DNA damage in antimicrobial defence (Härtlova et al., 2015), it is likely that DNA damage such as chromosomal shattering resulting from TE activity could also initiate or induce inflammation in cancers by similar mechanisms.

TEs as Cryptic promoters and enhancers and inflammation

Some TEs such as ERVs and LINEs act as cryptic promoters and enhancers. Upon activation in cancers, they can alter the expression of tumour suppressor genes or oncogenes (Rebollo et al., 2012; Grassilli et al., 2016; Maeso and Tena, 2016; Deniz et al., 2020). Cryptic promoters and enhancers formed by TEs could positively influence the function of the inflammatory pathway genes in cancers. Considering the role of TEs as enhancers and promoters in immune cells (Ivancevic and Chuong, 2020; Ye et al., 2020), this avenue remains to be investigated in human cancers.

Cytosolic TE transcripts and inflammation

Cytosolic nucleic acid sensing is a common immune mechanism for the hosts to defend against pathogens through inflammation (Kawasaki et al., 2011; Bordignon et al., 2019). The accumulation of deregulated LINE transcripts and cDNAs in the cytosol is sensed in a similar way and results in type I interferon response via cGAS in ageing mice (Simon et al., 2019). An open question is whether this inflammation caused by TEs, independent of DNA damage as a result of retrotransposition, is sufficient to cause cancer and to what extent it may contribute towards cancer progression. An experiment to investigate this could be to induce expression of only inflammatory parts of a TE and not those that can result in transposition in a tissue. Inflammation as a result and any increase in cancer rates/progression could then be observed. In this way it may be possible to distinguish between TE integration/DNA damage dependent, and integration/damage independent inflammation and how they contribute towards disease. This could further have implications for the way transposons may be utilised as therapeutics to target cancer.

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OPEN QUESTIONS and FUTURE ASPECTS

TE biology in human diseases:

One open question is whether TEs have evolved counter-defense mechanisms against silencing pathways which are activated during disease initiation and progression in humans. These could be similar to those that have already been observed in plants and animals. Examples of such counter-defense (anti-silencing) mechanisms from plant species *Oryza sativa* and *Arabidopsis thaliana* include: i-) DNA transposons carrying a mir820 site that downregulates de novo methyltransferases (Nosaka et al., 2012). ii-) Trans acting siRNAs (tasiRNA) using TEs as a template for their biogenesis which in turn downregulates translational repressor protein (McCue et al., 2013). iii-) Proteins encoded by VANDAL DNA transposons that promote demethylation of its own loci without altering other TEs (Fu et al., 2013). Analogous to counter-defense mechanisms of TEs observed in plants, a recent report using the fruit fly *D. melanogaster* non-LTR transposon TART-A demonstrated that these elements comprise of a small portion of the piRNA pathway export protein Nxf2 resulting in production of anti-sense piRNAs, hence achieving anti silencing and consistent expression by blocking the export of piRNA precursors (Ellison et al., 2020). In the field of cancer research, it remains to be elucidated whether activated TEs have acquired such counter-defense mechanisms to promote and maintain tumorigenesis. Since cells exhibiting genomic instability and elevated homologous recombination (HR) events are also associated with developing cancer (Bishop and Schiestl, 2002), it is not unusual to hypothesise that such recombination might result in TEs acquiring pieces of DNA sequences transcribing small RNAs to avoid particular epigenetic pathways such as the DNA methylation pathway. This could also be explained within the context of co-evolutionary models between the TEs and cancer cells acting as a selective advantage during tumorigenesis.

Therapeutic aspects of TEs in human diseases:

The emergence of TE regulatory networks during tumor initiation and progression compared to healthy tissue imply they could be used as targets for therapeutic strategies (Lynch-Sutherland et al., 2020). Targeting TEs through chemicals inhibiting TE machinery has been proposed as a potential therapeutic approach to treat both cancer and neurobiological conditions (Ravel-Godreuil et al., 2021). In previous sections, we have introduced the application of inhibitors targeting TE related RTs in cancer cells resulting in reduced cell proliferation and increased differentiation (Mangiacasale et al., 2003; Gualtieri et al., 2013; Sciamanna et al., 2016). In addition to RTs, other parts of TE machinery such as transcription, export, translation and nuclear shuttling might be valuable targets for the discovery of small molecule inhibitors.

Another strategy exploiting TE activity to prevent and cure cancer might be via stimulating an antitumor immune response, since increased TE activity could induce inflammatory response in some cancers (Chiappinelli et al., 2015; Roulois et al., 2015). A recent study combining ADAR1 depletion with deregulated SINE elements as a result of 5-aza-cytidine treatment inhibiting DNA (5mC) methylation showed reduced tumour size and growth in mice (Mehdipour et al., 2020).

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Synthetic lethality phenotypes are also commonly used in cancer therapy (Huang et al., 2020). A well known example is PARP inhibitors in BRCA1 deficient cancer cells, resulting in excessive double strand breaks accompanied by apoptosis (Farmer et al., 2005). Overexpressing TEs or exploiting those already overexpressed may be a potent method to induce synthetic lethality to treat cancer. These therapies, while applicable to cancer, may not be relevant to neurological conditions where it is important to maintain the integrity of neurons, and thus reducing TE activity and inflammation may be the main focus.

In the majority of human diseases where TEs are overexpressed, TE loci are demethylated (Anwar et al., 2017) however in some specific cases, TE transcript expression is controlled independent of the DNA methylation (Zamudio et al., 2015). This indicates other mechanisms of TE control including histone modifications and small/long non-coding RNAs. RNA modifications have emerged as important in human diseases (Jonkhout et al., 2017). RNA modifications of TE transcripts have also been shown to be a potential mechanism whereby surveillance mechanisms can be avoided. M6A modification of transposon RNA has been reported as one such modification (Hwang et al., 2021). Targeting these modalities where transposons are implicated in disease may be a potential further avenue of investigation for therapeutics. In addition to RNA modifications, uncharacterised DNA modifications of TEs emerging in the field may be another interesting target of further research. These include m6dA, which is present at low levels at specific locations in the human genome, is associated with increased transcript levels and has been implicated in cancer (Koziol et al., 2016; Pacini et al., 2019). It would be interesting to investigate the correlation between these markers and TE loci which are upregulated in disease.

As well as the previously proposed areas of interest, more foundational experiments and analysis including investigation of the activity of TEs over age in different tissues may enable further links between TEs and disease to be formed down the line (**Figure-8)**. As our understanding of TEs and their relation to disease improves, it will further open doors to novel potential therapeutic avenues.

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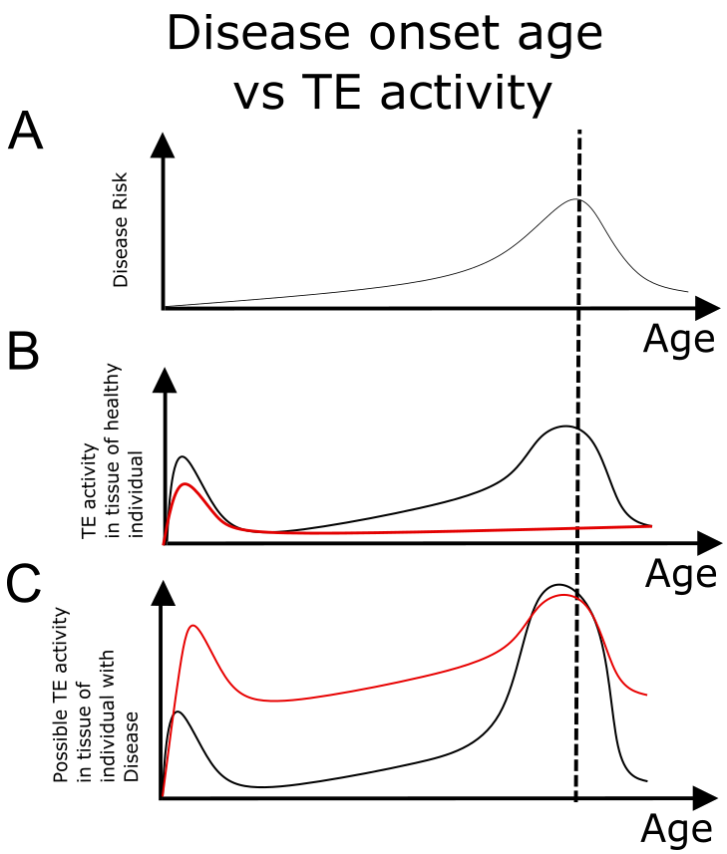

Figure-8: Proposed correlation between disease onset age versus TE activity in a lifespan of individuals: For a hypothetical disease with a risk distribution as in the top graph, it would be interesting to compare the distribution of TE activity over time in the affected tissue in healthy individuals (graph B) and individuals with the disease (Graph C). This could be done using an animal model for the disease. It would be then interesting to see if there is a clear difference between the healthy group and that with the disease, and the link between TE activity and age of onset of the disease. For example, there may be the same distribution but an elevated peak in those with the disease (Black lines graphs B and C), or new peaks around the age of onset in those with the disease (red lines graph B and C). The TE activity peaks may have a relationship with the age of onset of the disease (Graph A), both on an individual and population level.

Author contributions

K.H.S. and A.C.B. conceptualised the ideas and wrote the manuscript.

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