Spontaneous Neoplasia: A Destiny of Viviparous Mammal

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Abstract

True cancers are more frequent among vertebrates, including viviparous mammals. The most evidenced risk factor for these pathologies among vertebrates seems to be retroviral infections. A part of their genome is incorporated mainly in mammalians as endogenous retroviruses (ERVs). This parasitic genome is vital for viviparous mammals, because functional ERVs are essential host system for transient immune suppression and tolerance of “foreign” embryo at the stage of trophoblast implantation. After that, the ERVs genome gets imprinted due to epigenetic mechanisms. In aging mammals, the ERVs genome could be epigenetically reactivated as an attempt to bypass the replicative cell senescence, leading also to the potential development of neoplasia. These facts may lead to the suggestion that ERVs genome is an evident risk factor per se in the development of spontaneous cancers among mammals. Generally, the development of cancer-like disorders among other phyla needs the stimulant effect of strong pollutants and the development of true cancer among other vertebrates needs the retroviral infections. In contrast to them, viviparous mammals contain the ERVs in their genome and therefore may develop the neoplasia even in absence of environmental oncogenic agents. This suggests that artificial exclusion of carcinogenic genome could be fatal for the viviparous mammalian self or at least for its natural reproduction, as long as ERVs genome is essential for transient immune suppression and tolerance of “foreign” mammalian embryo.

Neoplasia in Animal Kingdom

“To be or not to be (... active): This is the question!” Shakespeare

Neoplasia disorders result from abnormal, uncontrolled proliferation of genetically altered cells that invade and destroy adjacent tissues [1]. The genetic abnormalities (e.g., mutation, translocation, etc) of transformed or tumor cells could be caused by physical (e.g., radiation), chemical (e.g., carcinogens) or infectious (e.g., oncoviral) agents. Different studies have demonstrated that neoplasia is widespread in the whole animal kingdom from sponges to human, but only in the vertebrate subphylum there is abundant evidence of a large variety of malignancies associated with metastasis [1]. The causes for many of tumors in vertebrates are often unclear, but oncoviral infections appear to be involved in several cases. This involvement is reported in various jawed vertebrates such as bony fishes [2-12], different amphibians [13-22], reptiles [23-26], as well as endothermic vertebrates (birds and mammals) [27-30]. In mammals these pathologies are more abundant and better characterized, and in some of them are developed various models of aggressive multi-organ spontaneous metastasis [1,31,32].

Meanwhile, evidence suggests that both the frequency and the diversity of types of neoplasia in invertebrates are less than in vertebrates [1]. In both marine and fresh water invertebrates, the major factors for neoplastic disease appear to be environmental stressors (e.g., pollutants), whereas there is little to no evidence of virally-induced tumors. This includes different phyla such as freshwater and marine sponges [1], chordates [33,34], nematodes [35,36], mollusks [37-41], various classes of arthropods (insects and crustaceans) [42-47], or deuterostomes [48-51]. However, similar tumor-like mass of cells frequently occur within echinoderm tissues and can also correspond to unwanted material, mostly degenerating ceolomocytes [49]. This indicates that multiple examples of neoplastic diseases in diverse invertebrates exist, but definitive evidence in this group of spontaneous metastasis such as a clear invasion of multiple tissues by tumor cells is rare [1].

Oncogenic Retroviruses and the Mammalian Reproduction

As already mentioned, neoplasia has been reported far more frequently in vertebrates, while a potentially more fundamentally important difference in neoplastic diseases between invertebrates and vertebrates is metastasis or real malignancy [1]. In general, the malignancies in vertebrates are caused by oncoviruses, especially retroviruses. Retroviruses are viruses that have RNA as their genome but make DNA...
copies of it in the infected cell [52]. Some retroviruses are known to transduce tumor genes into the new host, which, while promoting the proliferation of the infected cell, often bring disaster to the organism [53,54].

Retroviruses that are not normally present in healthy hosts are called exogenous viruses, while DNA sequences in cellular genomes that are homologous to retroviruses are called endogenous retroviruses (ERVs). Retroviruses are allowed to insert multiple copies of proviruses into different sites of the same host genome. Integration of proviruses into the host’s germline cells will result in inherited retroviruses [55]. Notably, the genomes of all vertebrates and especially viviparous mammals harbor multiple copies of ERVs. Thus, mammalian genomes contain a heavy load (42% in humans) of retroelements, and elements of retroviral origin (ERVs) constitute about 8% of the human genome - a proportion much larger than the sum of all single-copy genes [56-61]. These elements are most probably the proviral remnants of ancestral germ-line infections by active retroviruses, which have thereafter been transmitted in a Mendelian manner [61].

Retroelements including ERVs are normally suppressed from expression or transposition by extensive DNA methylation, RNA interference, heterochromatin formation, etc., to maintain genomic stability of the cell [52-54]. A part of ERV genomes are considered as long terminal repeat (LTR) retrotransposons (e.g., Ty elements), in contrast to non-LTR retrotransposons, like LINE and SINE [58,59,62]. An ERV provirus consists of the typical retroviral coding regions: gag-pro-pol-env, flanked by 5' and 3' LTR [57,61]. The genomic stability is enabled due to presence of many regulatory sequences, such as promoters, enhancers, polyadenylation signals and factor-binding sites in the LTRs [57,63]. To date 31 distinct groups and over 100 different ERV families have been found integrated throughout the human chromosomes and represent different copy numbers [59,64].

Some of these genetic elements are expressed at certain stages of the host’s lifetime to the benefit of the host [65-67]. Thus, some env genes are expressed in normal tissues and associated with positive and beneficial physiological functions, such as placentogenesis [68-71]. After binding to cellular receptors they are responsible for cell-cell fusions, like fusions of human placental villous trophoblasts into a multinucleated syncytiotrophoblast responsible for gas and nutrient exchange [69,71]. To date, three ERV-env genes, Syncytin-1, ERV-FRD (Syncytin-2) and env-Pb (or Syncytin-3) have been demonstrated as promoting cell-cell fusions in vitro [60,69,70,72-75]. While this effect is demonstrated in different mammals, human ERVs (HERVs) are shown to have also immunosuppressive properties [70,76-78]. An additional role is mammalian tissue organization: many of ERV genes are expressed during genome-wide DNA demethylation in gametogenesis and embryonic development. These functions are important for reproduction, while complex interplay between retroelements and gene silencing mechanisms suggests ERVs are integral parts of the genome [54,66,79,80].

It has been suggested that all mammals express ERVs in extraembryonal tissue during trophoblast implantation in order to suppress the local initiation of recognition by the mother’s immune system and allow the growth of the embryo. Because they give birth to live young and their semiallogeneic embryos have no protective rapidly expressed eggshell such as that of birds, all members of the class Mammalia will absolutely require embryonic and placental ERVs to prevent the initiation of a maternal anti-embryo immune reaction [65,66]. These ERVs, which would be essential for all placental orders, are proposed to be the normal host system for inhibition of the induction of a mother’s embryonic immune recognition. Called syncytns, they also enable embryonal fusion during human trophoblast development [66,79-83]. However, the ERVs are not proposed to control most normal host development or immune cell differentiation but rather are thought to specifically and transiently repress the local development of maternal immune recognition of an embryo [65,84].

The different amount of repeated ERV genes may explain the general tendency of genomes of higher organisms to evolve an ever decreasing gene density with higher order. For example, E. Coli has a ERV gene density of about 2 Kb per gene, Drosophila 4 Kb per gene and mammalian about 30 Kb per gene [65,85]. They are found in most organisms prior to mammalian radiation, but the levels of these genomic agents are relatively low in non-mammals. The increased ERV level in the genome of viviparous mammals is vital for their development in trophoblast stage. The ERVs suppress mother’s immunity in order to provide tolerance for the paternal part of “foreign” embryo [86].

Taken together, on the first hand vertebrates (including mammals) are frequently-affected from
malignant neoplasia compared to other phyla and the most evidenced risk factor is retroviral infection(s). On the other hand, mammals (especially viviparous ones) have in their genome integrated ERVs, which enable the suppression of mother's immunity from the paternal part of embryo.

**Retroviral Genome and Spontaneous Development of Neoplasia in Mammals**

The essential role for embryonal ERV genome is the suppression of maternal immunity in order to facilitate its implanting, but in a further life stage a proposed role for the ERV genome is that its reactivation may lead to the development of ERVs-induced malignancies. Thus, the embryonal full immunosuppression through an ERV involves many viral genes (such as *env* and *gag*), which are reported to be active during development of carcinoma pathologies [65]. For example, the HERV-K sequence of the human teratocarcina-derived virus type is reported to be able to make retrovirus like particle and can express *gag, pol* and *env* genes [84]. ERV-3 can express *env* gene in human embryonal placenta, while some HERVs (such as the feline RD1-14, ERV-3, and HERV K10+) are expressed in mammary tumors as well as in placental tissues [87]. Presence of *gag, env* and *tat* genes is demonstrated in HIV, inducer of Kaposi sarcoma in humans [88]. Different *env* genes had a high cDNA expression in endometrial carcinoma (e.g. envH1-3, Syncytin-1, envT, envFc2, ERV-3, Syncytin-2, and envV2) [57]. Regarding tumor parameters, Syncytin-1 and Syncytin-2 were significantly over-expressed in advanced stage pT2 compared to pT1b, suggesting for a prognostic role. In less differentiated endometrial carcinoma, glandular epithelial cells of polyps and hyperplasia Syncytin-1, Syncytin-2, ERV-3, envT or envFc2 were also significantly over-expressed [57]. Additional significantly over-expressed ERV-*env* genes in endometrial carcinoma and endometrial pre-implantation mouse embryos are non-permissive for expression of retroviral genomes [52,99,100]. Retroviruses introduced into differentiated derivatives of EC or into postimplantation mouse embryos at day 8 of gestation, however, were able to replicate efficiently. This defines a switch of early differentiating cells in their ability to support retroviral expression, which is developmentally regulated [99,100]. These findings demonstrate that activity of genomic retroviruses can depend on epigenetic mechanisms. *De novo* methylation of ERV genomes occurs only after chromosomal integration, while embryonal cells may possess an efficient *de novo* methylation activity that inactivates any DNA which is introduced into the immune response of the viviparous mammalian mother to the embryo, the genomic retrovirus seems to be a potential risk factor for the development of tumoral disorders. Thus, expression of intercysternal A-type particles (IAPs, a family of ERVs), although normally highly repressed after early embryonal stages, is often observed in various tumor tissues [87]. If these ERVs are a normal host system of immune modulation, it could be expected that tumors would select for the expression of immuno-modulatory ERV or ERV gene products (such as immunosuppressive domain p15E) in order to avoid immunosurveillance. This is observed in different cancers, which affect human breast, urinary, and reproductive systems [98]. These findings are similar to functional analyses showing that 10 different *env* genes were regulated by methylation in endometrial carcinoma using the RL95-2 cell line. [57]. Under effect of immunosuppressive ERVs, some testicular derived teratocarcinoma cells can differentiate from embryonal stem cells (ES) into several cell types (which characterize parietal trophoectoderm or the 3.5 day blastocyst) [65]. The significant reduction of IAPs levels in differentiated embryonal carcinoma cells (EC) indicates that IAPs expression is tightly linked to DNA methylation, while the switch in gene expression was correlated with efficient *de novo* methylase activity in pluripotent cells [99,100]. The results obtained in an experimental system established that both EC and pre-implantation mouse embryos are non-permissive for expression of retroviral genomes [52,99,100].
risk for neoplasia [57].

Endoviral Genome and Epigenetic Mechanisms in Neoplasia

As proposed by Villareal, the viviparous mammals express ERVs in extraembryonal tissue during trophoblast implantation in order to suppress the local initiation of recognition by the mother’s immune system, enable fusion and allow growth of the embryo [65,66,81-83]. After that, regulatory mechanisms suppress ERVs activity possibly due to genomic imprinting. This process consists in expressing of certain genes in a parent-of-origin-specific manner, which achieves monoallelic gene expression without altering the genetic sequence [101,102]. In mammals there are two major mechanisms that are involved in establishing the imprint: DNA methylation and histone modifications [101]. In general, active chromatin is associated with low DNA methylation status and histone acetylation, whereas silenced gene are typically in inactive regions of chromatin exhibiting DNA hyper-methylation and histone deacetylation [102]. The control of expression of specific genes by genomic imprinting is unique to therian mammals. It is now known that there are at least 80 imprinted genes in humans and mice, many of which are ERVs involved in embryonal and placental growth and development [101,103-106]. Experiments in preimplantation embryos and EC cells have shown that early development of mice is associated with variations in methylation and expression of active genes [53,54,100]. Additional findings have demonstrated that DNA methylation is involved in the maintenance of retroviral repression, and that retroviral expression in ES cells is repressed by methylation-dependent as well as methylation-independent mechanisms [107]. These data indicate that failure of the cell to control ERVs can lead to mutations or diseases including neoplasia [52].

In this respects, hypo-methylation and reactivation of LINEs and HERVs may be important in the pathophysiology of cancer [54,108]. However, in many common cancers such as transitional cell carcinoma, specific genes are hyper-methylated, whereas overall DNA methylation is diminished [109]. Analysis of the entire ERV-W 5’LTR (U3/R/U5) has shown a significant hypo-methylation of ERV-W 5’LTR, which is considered as potential molecular mechanism responsible for increased expression of Syncytin-1 in endometrial carcinoma [57]. Additional support for regulation of ERV-W by methylation was observed from luciferase studies using endometrial carcinoma cell lines, where a shut-down of luciferase expression occurred upon methylation of ERV-W 5’LTR containing vectors.

Evidenced data confirmed that methylation of these sequences depends on adequate expression of DNA methyltransferase 1 (Dnmt1) during DNA replication, while transcriptional repression is thought to be mediated by both cis-acting de novo methylation of the integrated proviruses and cell-type-specific trans-acting transcriptional repressors [107,109-111]. In Dnmt1 knockout mouse embryos (lacking maintenance of DNA methylation), unmethylated copies of IAPs are observed along with a significant accumulation of transcripts, suggesting that transcriptionally silent endogenous retroviral elements are reactivated upon loss of genomic methylation [107,112,113]. The genetic decrease of Dnmt1 expression to 10% of wild-type levels and consequent substantial genome-wide hypo-methylation in all tissues resulted at 4 to 8 months of age in development of aggressive T cell lymphomas that displayed a high frequency of chromosome 15 trisomy [108]. These results provide direct evidence that DNA methylation is causally involved in long-term retroviral repression, while DNA hypo-methylation plays a causal role in tumor formation, possibly by promoting chromosomal instability [107,108].

In contrast to these results, methylation-independent mechanisms determine initial retroviral expression in ES cells. Wild-type or Dnmt1?/? ES cells infected with Moloney virus-based vectors were transcriptionally silent, and therefore this silencing was independent of the DNA methylation status of the cells [107]. Because the basal level of expression of the mouse stem cell virus LTR in ES cells is lower than in differentiated cell types and not affected by the methylation status of the ES cells, trans-acting factors must regulate the initial level of expression. These findings demonstrate that epigenetic abnormalities including the aberrant DNA hyper-methylation of the promoter CpG islands play a key role in the mechanism of gene inactivation in cell carcinogenesis [114]. In case of endometrial carcinogenesis the frequencies of aberrant hyper-methylation were 40.4% in hMLH1, 22% in APC, 14% in E-cadherin, and 2.3% in RAR-beta in endometrial cancer specimens. In atypical endometrial hyperplasias the frequencies of aberrant methylation were 14.3% in hMLH1 and 7.3% in APC, whereas
normal endometrial cells showed no aberrant hyper-methylation of any of the mentioned genes [114]. The high frequencies of the aberrant DNA hyper-methylation of hMLH1, APC and E-cadherin suggest that the methylation of the DNA mismatch repair may be associated with endometrial carcinogenesis. Methylation analysis of the ERV-K(HML-2) 5’LTR-U3 region demonstrated that CpG-hypo-methylation was linked with transcriptional activity in melanoma cell lines, while in testicular cancer methylation of the 5’-LTR-U3 region of ERV-W, ERV-FRD and ERV-H decreased compared to control tissue [91,115]. Similar to this, analysis of the entire ERV-W 5’LTR demonstrated a significant hypo-methylation of 14 of 20 CpGs in endometrial carcinoma, reducing the overall ERV-W 5’LTR methylation degree for respective patients by 19% [57]. Additional found changes during development of endometrial carcinoma were increased microsatellite instability due to defects in mismatch repair genes, gene mutations in PTEN and p53 and DNA aneuploidy [112,116-118]. These data demonstrate that ERVs contribute to genome wide instability, most likely contributing in tumor initiation and progression [114,119,120].

As above-mentioned, a significant proportion of the human genome consists of stably inherited retroviral sequences that became defective over time [121]. This is possible because among DNA alterations occurring in neoplasia (such as in case of endometrial carcinoma), it is demonstrated that some genome-integrated ERVs still have an open reading frame (ORF) and protein expression [57]. Up to date, there are described at least 19 different fully coding ERV env genes and two ERV env genes with stop codons from 11 different ERV families [68]. Although envE of ERV-E4-1 is not a full length env, due to a stop codon after 428 amino acids, antibodies detected an envE protein in control and tumor tissues [89]. Furthermore, envW2 (which shows a DNA similarity of 93.5% to the ERV-W env, called Syncytin-1) was demonstrated as transcribed, but harbored an N-terminal stop-codon after 117 bp [122]. These findings suggest that aberrant hypo-methylation of Syncytin-1 and other env genes can lead to reactivation of expression, where these env genes could possibly function together in early endometrial prestages and endometrial carcinoma [57].

Especially, the increased sensitivity to epigenetic hypo-methylation of ERV genes is associated to the presence of open reading frames (ORFs) for respective gene promoters [57]. Promoters CpG-methylation is associated with the inability of transcription factor binding, leading therefore to a loss of transcriptional activity [90]. Although the ERV-H family is one of the most common ERVs in the human genome, only three (p59, p60, p62) out of 100 env-containing proviruses have a full length ORF transcribed [77,123]. In a combined qPCR all three ERV-H env p59, p60 and p62 genes represented the highest transcript levels of all ERV env tested for control endometrium, polyps, hyperplasia and endometrial carcinoma [57]. Moreover, the several largely preserved HERV-K(HML-2) element has conserved ORFs for all its proteins in addition to a functional LTR promoter [121,124]. According George et al. this indicates that the gag gene product Pr74Gag of HERV-K(HML-2) is processed to yield p15-MA (matrix), SP1 (spacer peptide of 14 amino acids), p15, p27-CA (capsid), p10-NC (nucleocapsid) and two C-terminally encoded glutamine- and proline-rich peptides, QP1 and QP2, spanning 23 and 19 amino acids, respectively [124]. The LTR promoter activity for nearby genes enables homologous and non-homologous recombination and therefore initiates new mutations [125-128]. Because DNA methylation in general targets copies of transposable elements, it is important for the host to manage the impact of epigenetic regulation of the copies that remain near genes. In mammals, it has been suggested that DNA methylation spreads into the mouse Aprt and rat Afp genes via nearby methylated SINE copies, and this is associated to spreading of heterochromatin (histone H3 trimethylation of lysine 9 (H3K9me3) and DNA methylation) from an ERV LTR to a gene promoter in mouse ES cells [129,130]. In addition, display of differential early transposon and IAPs DNA methylation between their two LTRs suggests that the environment surrounding gene promoters can prevent methylation of the nearby LTR [112].

In summary, silencing of retrotransposons occurs by co-suppression during early embryogenesis, but this process is imperfect and produces a mosaic pattern of retrotranspanson expression in somatic cells [131]. Transcriptional interference by active retrotransposons perturbs expression of neighboring genes in somatic cells, in a mosaic pattern corresponding to activity of each retrotransposon. The stochastic nature of retrotransposon activity, and the very large number of genes that may be affected, produce subtle phenotypic variations, which may affect disease risk and be heritable in a non-Mendelian manner [131].

In other words, the above-mentioned data may support the idea that ERVs incorporated in
mammalian genome are an evident risk factor per se in the development of cancers. This agrees with Hayakawa hypothesis which proposed that evolution of viviparity may have increased susceptibility to malignancies [132]. Indeed, true cancers are more frequent among vertebrates, and especially viviparous mammals. The most evidenced risk factor for these pathologies among vertebrates seems to be retroviral infections, which in mammals are incorporated in genome [1,65,66]. Analyses of clinical data in human and experiments in rodents show that ERVs genome activation correlates with immunosuppression and the immunosuppression strongly correlates with cancer incidence [133]. In general, the development of cancer-like disorders among other phyla needs the stimulant effect of strong pollutants and the development of true cancer among other vertebrates needs the retroviral infections. In contrast to them, viviparous mammals contain the ERVs in their genome and therefore may spontaneously develop the cancer even in absence of environmental oncogenic agents [1,65,134]. Beside this, predator mammals are exposed even to additional ERVs during consumption of their prey, and therefore, they might be more often affected by neoplasia than non-carnivora mammals. If correct, this might be reflected in human life as an epidemiological difference between neoplasia frequencies (and inversely their lifespan) among populations with different nutritional traditions. Consequently, traditionally vegetarian (or even seaside) populations should longer life and be less-affected from neoplasia than traditionally omnivore populations. These lead to the supposition that, if a functional ERV is an essential host system for the mammalian genome not only telomerase but also retrotransposon reverse transcriptases (RTs) which stabilize telomere length by adding hexameric (TTAGGG) repeats to the telomeric ends of the chromosomes, thus compensating for the continued erosion of telomeres [135,136]. In crisis cells progressively lose telomeres with each cell division, leading to a growth arrest known as replicative aging [138,139]. Normal human cells bypass replicative senescence and continue to proliferate until many telomere ends become uncapped leading to a phenomenon known as crisis [139-142]. In crisis cells have critically shortened telomeres but continue to attempt to divide leading to significant apoptosis and progressive genomic instability [142,143]. Rarely, a human cell escapes crisis and these cells almost universally express the enzyme telomerase, and maintain stable but short telomeres.

Telomerase is a cellular ribonucleoprotein reverse transcriptase (RT) which stabilizes telomere length by adding hexameric (TTAGGG) repeats to the telomeric ends of the chromosomes, thus compensating for the continued erosion of telomeres [140,143-145]. In mammalian genome not only telomerase but also other retrotransposon reverse transcriptases (RTs) synthesize the mentioned hexameric DNA repeats by using the 3’-OH at the end of the chromosome as a primer and telomerasete RNA as a template [62,144]. Apart from maintenance of chromosome ends, retrotransposon RTs can repair DNA double-strand
breaks of mammalian genome [144-149]. This is because tandem arrays of TTAGGG hexamers are present at both telomeres and intrachromosomal sites (interstitial telomeric sequences - ITTs) [143,148]. In contrast to telomeres that are typically confined to chromosome ends, the retrotranscripts of ERVs and transposons can target a plethora of sites [62]. Mutational analysis of the TTAGGG arrays in the different species suggests that they were inserted as exact telomeric hexamers, further supporting the participation of telomerase in repairing ITTs formation [148]. The functional similarity between RT telomerase and retrotransposon RTs can be demonstrated with finding that loss of telomerase activity may induce alternative lengthening of telomere (ALT) systems [150]. Ty1 elements, which are LTR-retrotransposons in *Saccharomyces cerevisiae*, are mobilized when DNA lesions are created by the loss of telomere function [144,149]. When telomerase is inactivated, Ty1 retrotransposition increases substantially in parallel with telomere erosion and then partially declines when cells recover from arrest by forming alternative telomere structures [62]. Ty1 cDNA is incorporated into the genome at frequencies high enough to extend telomeres in the absence of telomerase. While Gladyshev and Arkhipova describes retroelements that are similar to telomerases and transpose to telomeres, the work by Morrish et al. shows that artificial disruptions can drive a target-primed (TP) retrotransposon to unprotected chromosome ends [151,152]. These findings highlight similarities between the mechanism of TP retrotransposition and the action of telomerase, because both processes can use a 3’ OH for priming reverse transcription at either internal DNA lesions or chromosome ends [144]. In addition, *Drosophila* telomerases are long tandem arrays of two non-LTR retrotransposons (HeT-A and TART), suggesting that retrotransposon telomeres constitute a robust system for maintaining telomeric chromosome ends [153,154]. Successive transpositions of these telomeric elements yield arrays that are functionally equivalent to the arrays generated by telomerase in other organisms [155]. These findings suggest that in established ALT systems, subtelomeric satellite repeats may replace the telomeric minisatellite repeat whilst maintaining the recombination/replication mechanisms for telomere elongation [144,150].

Although HeT-A and TART belong to different subfamilies of non-LTR retrotransposons, they encode very similar retroviral gag proteins, which suggests that gag proteins are involved in their unique transposition targeting [154,155]. They imply a symbiotic relationship between the two elements, with HeT-A gag directing the telomere-specific targeting of the elements, whereas TART provides reverse transcriptase for transposition [155]. The RNA of LTR retrotransposons is used as a template for synthesis of not only RT but also of the structural protein gag, which forms a virus-like particle wherein the RNA is reverse-transcribed [62].

Retromotile enzymes such as telomerase or TP retrotransposons (termed L1s or LINEs), get reactive in mammalian cell lines defective for both telomere capping and non-homologous end joining, suggesting that the chromosome end must be exposed and stabilized to serve as a target for L1 retrotransposition [144,156]. Their activation may be thought of as a mechanism to slow down the rate genomic instability due to dysfunctional telomeres [139]. Introduction of the telomerase catalytic protein component into normal telomerase-negative human cells results in restoration of telomerase activity and extension of cellular lifespan [140,143].

Human cells with introduced telomerase maintain a normal chromosome complement and continue to grow in a normal manner. Unfortunately, the regulation of telomerase activity in human cells plays a significant role in the development of cancer [62,142,143]. The mechanisms for telomerase have not fully defined, but the need for telomere genome repairing during elderly can be associated with reactivation of telomerase. Mechanisms for telomerase reactivation can interfere with reactivation of other RTs, and as consequence with replication of previously-imprinted oncogenic ERVs. Thus, the telomerase activation in cancers includes telomerase catalytic subunit gene (hTERT) amplification and trans-activation of the hTERT promoter by the myc oncogene product [142]. Ectopic expression of hTERT is sufficient to restore telomerase activity in cells that lack the enzyme and can immortalize many cell types. There is accumulating evidence that hTERT favors an immortal phenotype by blocking apoptosis independently of its protective function at the telomere ends [157]. The level of hTERT increases along with colorectal cancer progression, and patients with high hTERT levels showed a significantly worse survival than those with low ones [157-159]. Cancer cells (like aging ones) evade replicative senescence by re-expressing telomerase, which maintains telomere length and hence chromosomal integrity [160]. The attenuation of telomerase activity could be induced by inhibition of hTERT promoter, which would lead cancer cells to senescence and therefore prevent cancer cells from growing indefinitely [157,159]. This demonstrates that telomerase does not drive the oncogenic process;
however, its effect is permissive and required for the sustain growth of most advanced cancers [139,141]. This is strongly supported by the fact that telomerase is tightly repressed in the vast majority of normal human somatic cells but becomes epigenetically activated during cellular immortalization and in cancers [142,143,157].

Telomerase is cross-linked with different interplaying signaling pathways that regulate cell proliferation, DNA damage repair, and also cell death [157]. With the extension of life span get epigenetically increased the probability for genetic instability, oncogenic activation and/or onco-suppressor gene inactivation (i.e. p53, pRB, ras, TRF1, TPP1 and Rap1): the cancer transformation can be then induced in predisposed cells, depending on their genetic context, by the activation of telomere maintenance [118,141,143,145,161]. Induction of telomere dysfunction by deficiency in the telomerase RNA component (mTER) in a p53 mutant mouse background results in significant levels of breast adenocarcinomas and colon carcinomas [161-163]. The study of these proteins demonstrates that telomere dysfunction, even if telomeres are of a normal length, is sufficient to produce premature tissue degeneration, acquisition of chromosomal aberrations and initiation of neoplastic lesions [145].

As suggested, the telomerase activation due to epigenetic mechanisms is associated with potential reactivation of previously-imprinted ERV genes, leading to the spontaneous development of cancers in aged mammals [143,159]. While DNA methylation is thought to be a general mechanism used by cells to silence foreign ERV genome and other transposable elements, hypo-methylation and genome expression opens a “window of opportunity” for retrotransposition and recombination that contribute to inherited disease including neoplasia [54,107]. Target of the hypo-methylation are not only reduced telomeres, but also interstitial ERV genomes (especially some genome-integrated ERVs with an ORF and protein expression) [57,124]. In the control of mentioned elements, epigenetic mechanisms involve mammalian DNA methyltransferases (DNMTs) [164]. In general, chromosomal subtelomeric regions are heavily methylated, but this modification is decreased in DNMT-deficient cells. Mouse ES cells genetically deficient for dnmt1, or both dnmt3a and dnmt3b have dramatically elongated telomeres compared with wild-type controls [164]. Lack of DNMTs also resulted in increased telomeric recombination as indicated by the presence of ALT-associated promyelocytic leukaemia bodies. This increased telomeric recombination may lead to telomere-length changes, although these results do not exclude a potential involvement of telomerase and telomere-binding proteins in the aberrant telomere elongation observed in DNMT-deficient cells [164]. Together, these results demonstrate a previously unappreciated role for DNA methylation in maintaining telomere integrity.

According to Prindull, foreign, silenced, potentially oncogenic DNA sequences, i.e. regular components of the mammalian genome such as ERVs, could conceivably be activated for expression in neoplastic transformation by epigenomic lineage leukemia deregulations [165]. This supports the concept that evolutionary interplay between retroviruses and host defenses among mammalian placentas may have contributed to the local genomic imprinting [66,80-84]. It is not excluded that every affected tissue by such processes develops embryonal-like growth abilities. This speculation can be supported by the fact that only placental tissue from normal early pregnancies possesses consistent telomerase activity [166]. During the pregnancy progression, this activity attenuates due to hyper-methylation of retroviral genome [57]. In a later life stage telomerase and other RTs get hypo-methylated in order to escape senescence, leading not only to genome repair but also to ERVs replication. Consequently, the occurrence of telomere dysfunction (like the reoccurred ERV genome replication) may be an early and potentially highly frequent genetic aberration event in the development of neoplasia [161].

Recent findings demonstrate that telomerase-induced carcinogenesis is associated with telomere end-to-end associations (telomere fusions) [161]. Human breast lesions, but not normal breast tissues from healthy volunteers, contained telomere fusions. These fusions were detected at similar frequencies during early ductal carcinoma in situ and in the later invasive ductal carcinoma stage [161]. Defects in telomere maintenance have been suggested to play significant roles in the initiation of genomic instability via breakage–fusion–bridge cycles and aneuploidy, which are associated with the development of human cancers [167-170]. Thus in a human mammary epithelial cell culture model, late-passage human mammary epithelial cell escape a stress-associated senescence-like barrier and acquire genomic deregulations, including telomere fusions [171]. In this respect, there are found small regions of LTR and non-LTR retrotransposon elements from interstitial chromosomal regions within fusion junctions in human breast invasive tissue [161]. Similar retrotransposon elements are present at Drosophila chromosome ends.
and have been reported to integrate at dysfunctional mammalian telomes in a Chinese hamster ovary cell line [152,172]. These results provide direct evidence that telomere fusions and aneuploidy are present in mammalian tumor tissue and suggest that telomere dysfunction may be an important component of the genomic instability observed in neoplasia [168, 169-171].

The telomere fusion at genomic level seems to be analogue to the embryonal one at the cellular level, as both telomerase and certain ERVs called syncytins are retroelements and show fusogenic functions [57,161]. For example, syncytin, the Env protein of HERV-W human endogenous retroviruses and putative mediator of trophoblast fusion, was also found to mediate fusion between breast cancer cells and endothelial cells [173,174]. If de-methylation occurred during tumorigenesis, this could lead to chromatin opening and availability of transcription factor binding sites (in the ERV-W 5'LTR), thus inducing Syncytin-1 expression via the cAMP response element [57]. The env gene of ERV-R (ERV-3) has been shown to be expressed in most tissues, like testis, skin, thymus and placenta and in various carcinomas, like glioma, breast, or Wilm's tumor [68]. In contrast to the three known fusogenic ERV-env proteins (Syncytin-1, Syncytin-2 and Syncytin-3), ERV-3 is considered a cytoplasmic protein due to the lack of a leader sequence, a membrane spanning domain and a fusion peptide [175]. As cell fusion plays an essential role in fertilization, formation of placenta, immune response, tissue repair, and regeneration, increasing recognition of cell fusion in somatic cell dynamics has revitalized the century-old hypothesis that cell fusion may contribute to the initiation and progression of cancer [57]. Experimental and clinical studies suggest for a potentially multifaceted involvement of cell fusion in different stages of tumor progression, including aneuploidy and tumor initiation, origin of cancer stem cells, multidrug resistance, and the acquisition and diversification of metastatic abilities. Spontaneous cell fusion in tissue culture or in animal models has been reported for a large variety of tumor cells [176,177].

While fusion efficiency can be proportional to the malignant level of tumor cells, colonization preference (organotropism) can also be determinate by cell fusion [122,178]. For example, fusion of myeloma cells with B lymphocytes resulted in a hybrid cell metastasizing to the spleen and liver, yet fusion with macrophages led to metastasis to lung [179]. Importantly, fusion of tumor cells with resident cells in a secondary organ may allow disseminated tumor cells to survive in a hostile microenvironment as minimal residual diseases and emerge as overt metastasis after accumulation of additional oncogenic alternations [57]. In a recent study, untransformed mammary cells were found to persist in the lungs as small clusters until inducible activation of oncogenes stimulated the formation of pulmonary metastases [69]. Overall, accumulating evidence has suggested a plausible involvement of cell fusion in several aspects of cancer progression.

Rigorous genetic studies in animal tumor models will be needed to definitely demonstrate the extent of cell fusion to tumor initiation, drug resistance and metastasis [173]. Further investigations should discover the specific role of telomerase in placenta and its interaction with embryonal ERV genome and compare them with investigations in neoplasia development. As long as with the extension of life span the probability to get in contact with (endogenous) carcinogens increases, chemo-preventive therapies for the up-regulation of telomerase activity, able to prolong the life of cell cultures in a phenotypically youthful state, could have important applications in research and medicine [141]. On the contrary the therapeutic down-regulation of telomerase activity may be used in cancer therapy. The desperate natural or pharmacological intervention for the modulation of the living rate could lead to cancerous development of the target cells and therefore to the decreasing of their living rate [141]. Because of the unknown state of the enormous cell number of the human organism, is it safe to extend the human lifespan by therapeutic agents? Virus DNA gave rise to those of eukaryotes, and ERVs incorporation in their genome was essential for the mammals’ evolution/existence [65,180]. Consequently (and based on the actual opportunities), either mammals should remain mammalian organisms with a relative life span expectation, or they, (beside providing of healthy environment and lifestyle), should eradicate the ERVs from their genome giving up viviparous reproduction form once and for all in order to live quite much longer. Would have Shakespeare said: “To live longer with the fear of cancer or not” if he knew about ERVs?

Conclusions

In this work we propose that ERV genome in mammals is a potential risk factor for the spontaneous development of neoplasia, especially in the late adulthood. This genome could be reactivated due to epigenetic mechanisms, maybe as an attempt of longevity for aging organism. Because of the unknown state of the enormous cell number of the mammalian organism, the attempt to extend the lifespan could be not safe, and therefore, a potential hearth of neoplasia.
According to actual knowledge, neoplasia is caused by environmental factors (including retroviral infections) or oncogenic mutations. Our hypothesis suggests that integrated ERVs (which are essential for reproduction of mammals) can be at the same time risk factor per se in the development of spontaneous neoplasia. Epigenetic mechanisms serve to escape cellular senescence and aging due to telomerase activation, but these processes can be associated with re-expression of ERV genome and tumor growth. This is possible because both telomerase and ERVs are of reverse-transcription origin, under control of the same epigenetic mechanisms, and exercise similar functions in genome ends and interstitial genome. With respect to human medicine, our suggestion stresses out the role of detection of neoplastic alterations at the early stages. However, the eradication of this risk may affect our natural reproduction and mammalian being.

Acknowledgements and Authors Contribution

This work is dedicated to my lovely parents, both affected by tumor disorders (E.Mingomataj).

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Illustrations

Illustration 1

Table

<table>
<thead>
<tr>
<th>PHYLUM</th>
<th>LIFE OR TUMORIGENIC EVENT</th>
<th>NEOPLASIA/PRONEOPLASIA EVENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>INVERTEBRATES</td>
<td>EXPOSURE TO POLLUTANTS</td>
<td>NONMETASTATIC NEOPLASIA</td>
</tr>
<tr>
<td>VERTEBRATES</td>
<td>EXPOSURE TO ONCOGENIC RETROVIRUSES</td>
<td>TRUE NEOPLASIA</td>
</tr>
<tr>
<td>GENESIS OF VIVIPAROUS MAMMALS</td>
<td>INCORPORATION OF RETROVIRAL GENOME</td>
<td>INCORPORATION OF TUMORIGENIC FACTOR FOR SPONTANEOUS NEOPLASIA</td>
</tr>
<tr>
<td>MAMMALIAN TROPHOBLAST</td>
<td>ACTIVATION OF ENDOVIRAL GENOME AND</td>
<td>PHYSIOLOGICAL ACTIVATION OF TUMORIGENIC FACTORS, IMMUNOTOLERANCE</td>
</tr>
<tr>
<td>IMPPLANTATION</td>
<td>TELOMERASE, MATERNAL IMUNOSUPRESSION</td>
<td>OF &quot;FOREIGN&quot; EMBRYO</td>
</tr>
<tr>
<td>MAMMALIAN LIFE</td>
<td>IMPRINTING OF ENDOVIRAL GENOME</td>
<td>INACTIVATION OF TUMORIGENIC FACTORS</td>
</tr>
<tr>
<td>MAMALIAN AGING</td>
<td>REACTIVATION OF RETROVIRAL GENOME AND</td>
<td>REACTIVATION OF TUMORIGENIC FACTORS, SPONTANEOUS</td>
</tr>
<tr>
<td></td>
<td>TELOMERASE, ESCAPE OF CELLULAR SENESCENCE</td>
<td>DEVELOPMENT OF NEOPLASIA</td>
</tr>
</tbody>
</table>
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