HERVs, transposons and human diseases – Part III

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Implicated Pathological Functions of TE (e.g. HERVs; LINEs, and SINEs)

(i) Cancer

It is being postulated that in somatic cells, the transposition of HERVs and other TEs may land into tumour suppressor genes and this could cause neoplastic transformation. It is a known fact that many cancers feature **global DNA hypomethylation** and **localized hypermethylation of CpG islands of tumour suppressor genes.**[1] Since DNA methylation is one of the epigenetic mechanisms that cells have evolved to check on TEs from being unleashed and doing havoc in their genome, it is being postulated that with the event of global DNA hypomethylation, the TEs transpose because the epigenetic constraints are lifted. If some TEs end up in or near the promoter region of tumour suppressor genes, the chromatin structure is heterochromatized (i.e. become condensed and compacted) and hence silenced for transcription. With the function of tumour suppressor genes switched off, neoplastic transformation sets in. Generally, tumorigenesis occurs because the silenced tumour suppressor genes result in (i) altering the cell cycle, (ii) blocking apoptosis or (iii) blocking DNA repair.[1] Later on as the global DNA hypomethylation continues, genes inhibiting cell invasion and dissemination also get involved and are silenced by their promoter undergoing CpG island hypermethylation.[2] Examples of such genes (called **metastasis suppressor genes**) that get silenced and result in dissemination, often normally code for proteins that make cells 'stick' together but not only (Table 11). Thus when they get silenced, the tumour cells do not 'stick' in the original site but start to detach, invade and disseminate.

Other retroelements that have been found to cause cancer are LINE-1 sequences, involving the **myc gene** in breast carcinoma and involving the **APC (adenomatous polyposis carcinoma) gene** in colon cancer.

The HERV-K provirus family is implicated in several cancers. This is because members of this family have **open reading frames (ORFs)** for all their viral genes. An ORF is a DNA sequence without a stop codon in the given frame. This translates that HERV-K are the most likely to be biologically active and potentially pathogenic because their sequences are most likely to be expressed.

Table 12: Putative association of HERVs in cancer

Cancer	Implicated HERV
Breast cancer	HERV-K
Ovarian cancer	HERVs
Melanoma	HERV-K
Myeloproliferative disease	HERV-K
Testicular tumours (seminomas; teratomas)	HERV-K (sub-group HML-2)

Table 11: Some examples of 'Metastasis Suppressor Genes' and the effects of their products

Genes ® Proteins	Effect
laminin genes ➔ laminins	Laminins induce and maintain cell polarity; establish barriers between tissue compartments; organize cells into tissues; protect adherent cells from detachment-induced cell death.
TIMP genes ➔ Tissue inhibitors of proteinases (TIMPs)	TIMPs antagonize matrix metallo-proteinases (thus suppress tumour growth, angiogenesis, invasion and metastasis).
semaphorin genes ➔ semaphorins	Semaphorins are axon guidance proteins that block VEGF (vascular endothelial growth factor) autocrine activity.
Thrombospondins (THBS) genes ➔ thrombospondins	Thrombospondins are proteins that regulate tissue genesis and remodelling.
Cadherin genes (e.g. E-Cadherin, H-cadherin, R-cadherin) ➔ cadherins	Cahderins are a group of cell adhesion molecules that form stable cell-cell junctions.

Table 13: Putative association of HERVs in autoimmune diseases

Autoimmune Disease	
Rheumatoid arthritis	HERV-K
Systemic lupus erythematosus	HERV-K
Insulin Dependent diabetes mellitus	HERV-K
Psoriasis	HERV-E

Table 14: Putative association of HERVs in neurological diseases

Neurological Disease	
Schizophrenia	HERV-W, HERV-K
Motor neuron disease	HERV-W
Multiple sclerosis	HERV-W, HERV-H

(ii) Autoimmune Diseases

- **Rheumatoid Arthritis (RA)**

The expression of HERV-K18 was up-regulated in patients with juvenile rheumatoid arthritis.[3] The possible mechanism offered is that of a super-antigen (SAG) stimulation in auto-reactive T cells causing the autoimmunity.

- **Systemic Lupus Erythematosus (SLE)**

Here it is being implicated that HERV-K *env* protein is the culprit causing autoimmunity through **molecular mimicry** and immuno-modulation. Molecular mimicry refers to similar structures that molecules share between them despite arising from dissimilar origins. For example the molecules might share some linear amino acid sequences or their 3-D conformational fit, even though their origins are separate (e.g. a virus and a normal host self determinant). In SLE, it is being implied that the determinant shared by the host and the HERV-K *env* protein evokes an immune response and causes the destruction of cells and tissue.[4]

- **Insulin Dependent Diabetes Mellitus (IDDM)**

The culprit here is a viral sequence appertaining to a HERV-K family.[5] Specifically, HERV-K *env* encodes a super-antigen which allegedly is being held responsible to play a part in the etiology of insulin-dependent diabetes mellitus (IDDM).

- **Psoriasis**

Moles J. P. et al.[6] found 3 HERV families in psoriatic lesions, (HERV-W, HERV-K, and HERV-E). They proposed that the expressed sequences of these HERVs have roles in the development of psoriasis and are doing further research in this regard.

(iii) Neurological Diseases

- **Schizophrenia**

When sera of schizophrenic patients are tested with antibodies to HERVs, a greater frequency of positives is found than control subjects. Researchers continue to look at a possible link between HERVs and schizophrenia. Karlsson et al.[7] *have provided* intriguing data that implicate the possibility of this link. The culprit that they implicate belongs to HERV-W. Indeed, they found that RNA transcripts homologous to members of this family are up-regulated to different levels in the frontal cortex obtained post-mortem from schizophrenic patients.

- **Motor Neuron Disease**

Here elevated expression of HERV-W *env* and *gag* genes have been detected and proposed in the pathogenesis.[7]

- **Multiple Sclerosis**

HERV-W RNA has been detected in the circulating viral particles (called Multiple Sclerosis associated Retroviral element, MSRV), which for many years have been associated with the evolution and prognosis of Multiple Sclerosis. Specifically, HERV-W *env* gene codes for an envelope protein called syncytin-1.[8] Here syncytin, unlike its beneficial function in the morphogenesis of the placenta, acts as a powerful immuno-pathogeneic molecule that triggers a pro-inflammatory and autoimmune cascade.

(iv) Other Medical Diseases Where TEs Are Proposed To Be Involved

Table 15 gives other examples of medical diseases were retroelements cause insertional mutagenesis and re-combinations in specific genes.

Repercussions

A very promising transposable element that is being used by researches worldwide is the ***Sleeping Beauty*** (SB) TE. This is an ancient transposon from fish which has been reconstructed. Its usefulness is three-fold. Firstly, it is being used to gain knowledge into the basic molecular machinery of DNA transposition and its regulation in vertebrate cells. Secondly it is being used as a vector for insertional mutagenesis screens in model organisms; this is because SB can transpose in cells of different vertebrate classes in tissue culture. Such screens help in the discovery of genes. Thirdly, it is intended to be applied in human therapeutics.[9]

In the field of medical therapeutics, understanding the underlying processes of how these relic HERVs and other transposons bring about human diseases could help in their prevention and treatment. Just to give an example, in multiple sclerosis a new therapeutic approach is to target the human endogenous retroviral protein MSRV-Env, which as said above has been found to be a key factor in the pathogenesis of MS.[10] A fully humanized monoclonal antibody is being proposed to target this pathogenic protein. But this is not all. Indeed, MSRV could be used as a biomarker for the prognosis of the disease since patients with higher loads of MSRV fair worse. Similar approaches could also be used for the other medical diseases mentioned in this essay.

Table 15: Cases of insertional mutagenesis and re-combinations caused by retroelements

Retroelement Involved	Gene Affected	Functional Role
LINE-1	Factor VIII	Haemophilia A
LINE-1	Dystrophin	Muscular dystrophy
SINE	Fukutrin	Muscular dystrophy
Alu	NF1	Neurofibromatosis
HERVs	AZFa (azoospermia factor a) region	Male infertility

Table 16: The four epigenetic drugs approved for clinical use in the US

DNMTs inhibitors • 5-azacytidine • decitabine	DNA methyltransferase inhibitors	act as DNA demethylating agents and so reduce the levels of DNA methylation
HDAC inhibitors • vorinostat • valproic acid	Histone deacetylase (HDAC) inhibitors	acetyl groups are not removed from histone tails

Important strides are being made in the cancer field. For example **HERVs transcriptomes** (i.e.HERVs signatures) associated with specific types of cancer are being deciphered and databased. These are intended to be used in the future as a means for assessing (i) an individual's risk status for cancer, (ii) the early detection of cancer and (iii) the monitoring of its treatment and prognosis. These signatures taken together with epigenetic signatures (e.g. DNA methylomes and histone codes) are very promising candidates as bio-indicators for the early detection of carcinogenesis. Again similar goals could also become applicable to other medical diseases where HERVs and epimutation signatures are found.

If as is being found HERVs and epimutation signatures cross talk in the pathogenesis of medical diseases, then as has been the case in some cancer types, **epigenetic-based treatment strategies** would become rational also. Already the FDA has approved the first generation of epigenetic-based drugs. Indeed, the use of such drugs is establishing that **epigenetic modulation** can be a feasible treatment option, not only for cancer, but also for the growing list of diseases where epigenetic mechanisms of gene expression underline their pathogenesis.[11] And since epigenetic changes are thought to be responsible for a wide range of diseases, the scope of epigenetic therapy is likely to expand.[12]

The four epigenetic drugs available for clinical use in the U.S. include two DNA demethylating agents, **5-azacytidine** and **decitabine**, and two histone deacetylase (HDAC) inhibitors, **vorinostat** and **valproic acid**.
At present the targets for epigenetic drugs are DNMTs and HDACs, the latter generating the most excitement. It is worth mentioning that since many other molecules are also involved in epigenetic mechanisms, there are other potential targets as well. Similar 'bullet-targeting' of other molecular players involved in HERVs-associated pathological pathways will surely be found and used in medical therapeutics.

Conclusion

For some HERV loci it has already been shown that they are implicated in certain gene expression and diseases. Large scale studies of HERV transcriptomes should be carried out to detail in the expression of more active HERV loci. This should be done in every human tissue both in health and in disease. Doing so one could then start to comprehend more the functions of HERVs in human diseases.

It is becoming clearly evident that an old relation in our genome is gaining new perspectives. But if the accumulating evidence definitely shows that this old relation is implicated in many of our medical diseases, then one could also surmise that these medical diseases that afflict us could be the prize that we have to pay for our marvellous evolution. S

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