The enemy within our DNA? Endogenous viruses in skin cancer

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What do we study: mobile DNA elements

Mobile DNA elements are parts of the DNA that makes us human. Mobile DNA elements constitute 45% of human DNA. They are defined as DNA sequences which can copy themselves from one place to another, within the DNA contained in a cell (known as the cell's genome).

Human Endogenous Retroviruses (HERVs) are mobile DNA elements and they constitute about 8% of our DNA (Figure 1). HERVs are derived from retroviruses (similar to the HIV-1 retrovirus, that causes AIDS) that integrated into our DNA, becoming part of our genome, over millions of years.

Most HERVs are defective due to mutation of their DNA, but a few recently integrated HERVs are still partially functional. Just like when they originally infected our cells, proteins produced by HERVs can have significant biological effects. We are looking at whether reactivation of these HERVs in melanoma (skin cancer) can either be used as a biomarker, to help diagnosis, or have a direct role in disease progression.

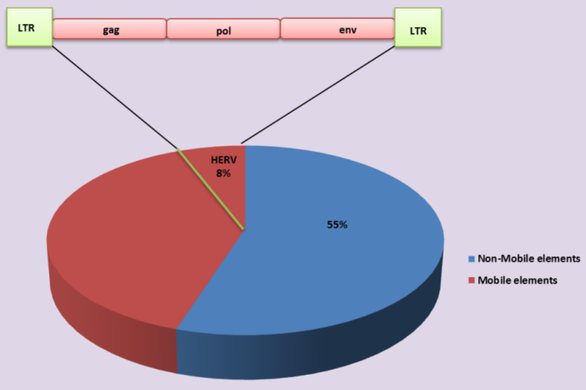

Figure (1):Mobile elements in the human genome

The HERV "life cycle"

The life cycle of a HERV starts with the infection of the host germline (the cells that produce sperm or eggs) by a retrovirus. As part of the infection cycle, the viral RNA is converted into DNA by viral proteins and the DNA integrated into the host genome as a provirus.

As these events occur in the germline, the offspring of the infected individual will carry the new HERV provirus as a part of their genome (Figure 2).

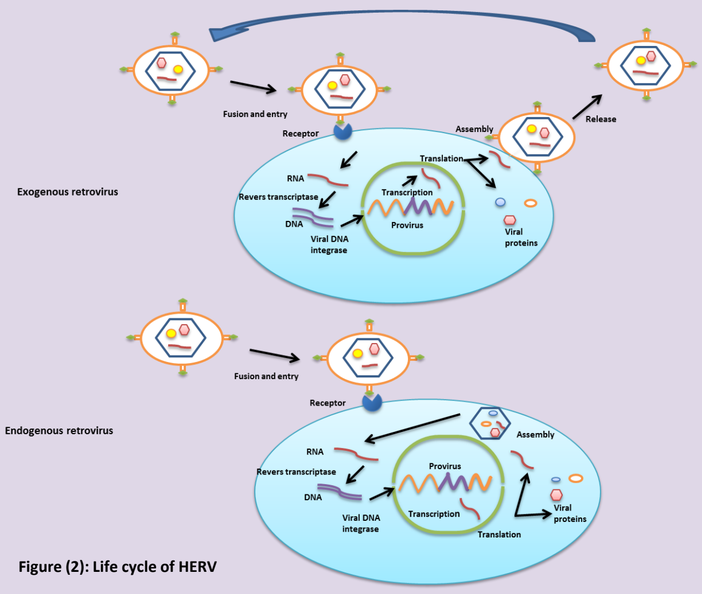

Figure (2): Life cycle of HERV

HERV and melanoma

The most malignant type of skin cancer is melanoma. Patients with aggressive malignant melanoma can die only 6-8 months after diagnosis. There is much evidence suggest that HERVs may play some role in human cancer, especially melanoma (Figure 3).

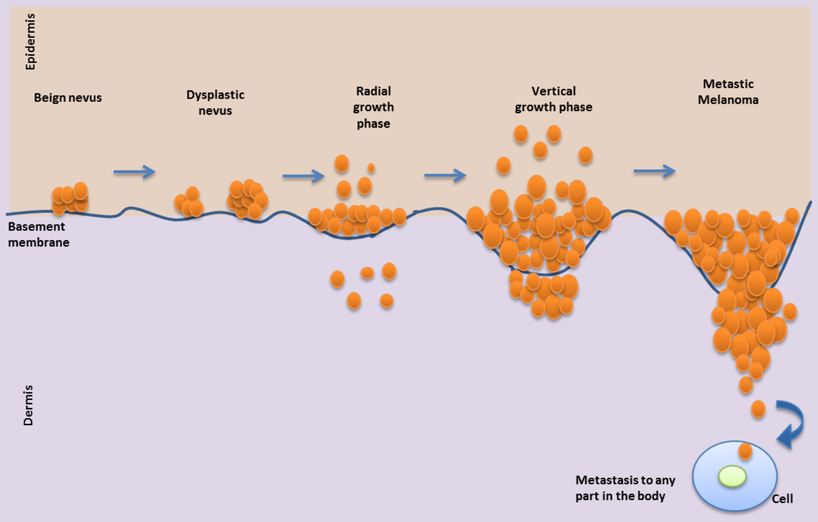

Figure (3): Stages of Melanoma

Experimental approaches

PCR amplification of newly integrated HERVs

To study which HERVs might be expressed in melanoma cell lines and other cancers we need to know which ones are present.
The Polymerase Chain Reaction (PCR) is a sensitive amplification method that can simultaneously show all the HERVs in a genome (Macfarlane *et al*., 2015).

Figure (4): PCR machine

Using HERV specific reactions and a PCR machine (Figure 4) , each band in (Figure 5) is an individual HERV, within the DNA of the cell lines.

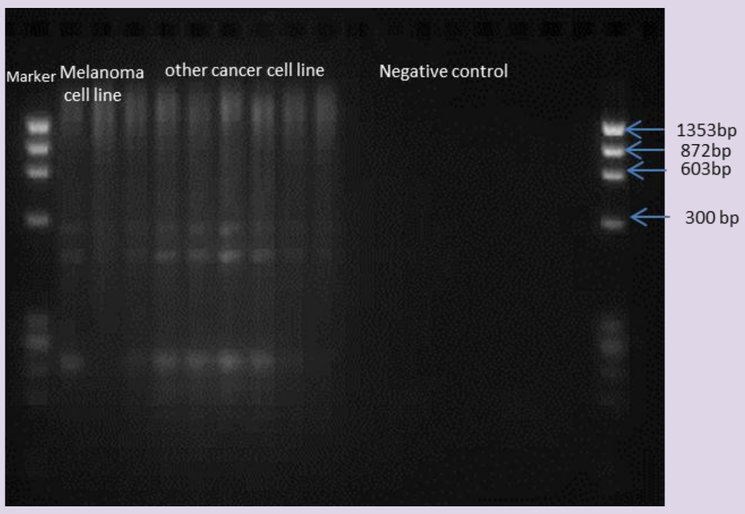

Figure (5): HERVs within the DNA of the cancer cell lines.

HERV activity in melanoma cell lines

We also used PCR to measure the expression of HERV genes (which produce the proteins detected in melanoma). This is done by converting the RNA from HERV genes into DNA and using PCR to amplify it.

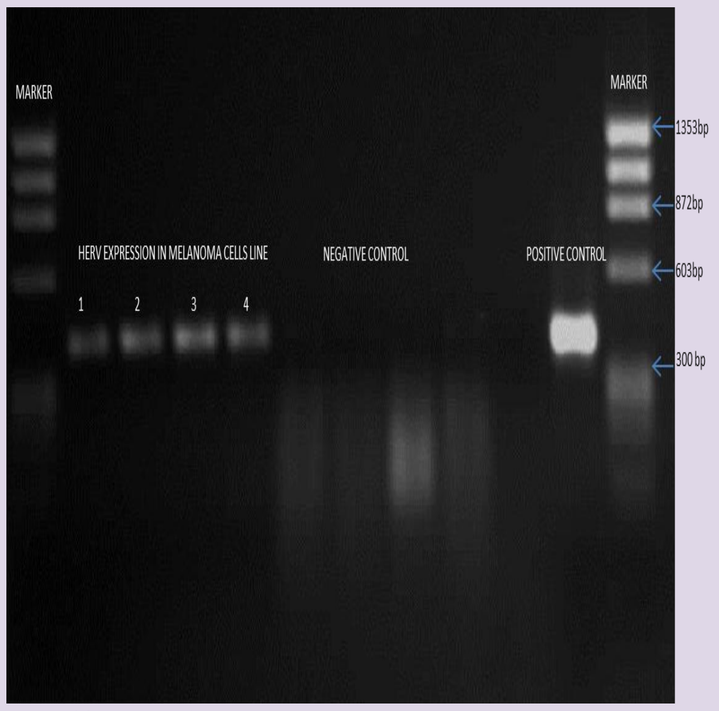

Figure (6): Expression of HERV genes in Melanoma cell lines

Quantifying HERV gene expression

To tell whether HERV gene expression is changing in cells in different conditions we need to measure it accurately. Quantitative PCR (qPCR) follows the amplification of HERV genes in real time, allowing the accurate measurement of the amount of gene expression.

Figure 7 shows the gene expression measurement of two different melanoma cell lines: A375P, and an invasive derivative, A375M. The further to the left the curves begin the more gene expression.

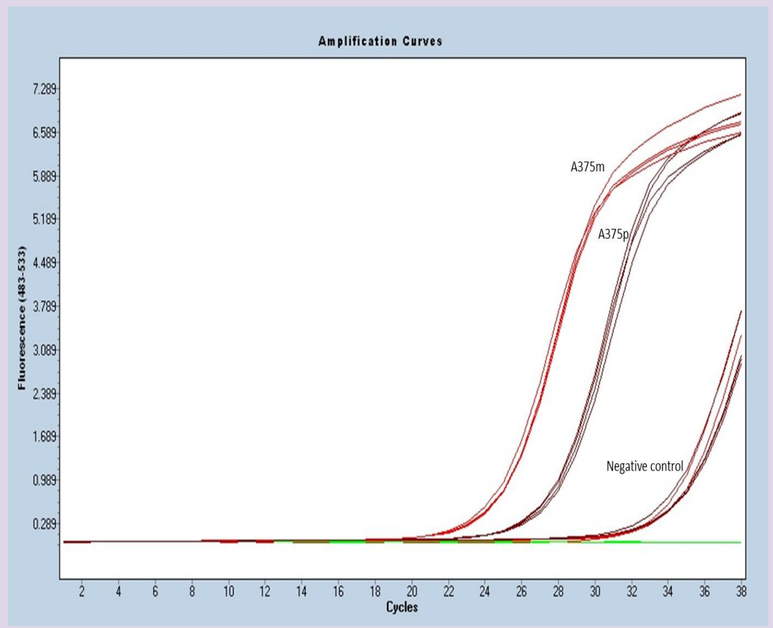

Figure (7): qPCR analysis for A377P andA375M cell lines

Future work

1. Examine variation in HERV expression in other cancer cell lines.

2. HERV insertions will be assessed for utility as markers of HERV activation in melanoma.