Oncolytic Virotherapy

Viruses are fascinating infectious agents; they have biochemical structures and employ metabolic processes solely for the purposes of entering and replicating within host cells. Their genomes are diverse and subject to variability within species, but they are relatively short in length. For example in the small rhinoviruses, the genome is single stranded positive sense RNA and 7,500 -8,500 base pairs long. In the rather larger poxviruses, the genetic material is ds DNA and 130-375, 000 base pairs in length. Even in the recently discovered giant viruses of amoebae the ds DNA genome is only ~ 370,000 base pairs in length. By comparison, the genome of the well-studied bacterium *Escherichia coli* is 4.6 million base pairs. Therefore many viral genomes have been sequenced, allowing the gene products to be analysed, in order to identify which are important for pathogenicity and which are essential for replication. Interactions between viral glycoproteins and host cell surface proteins are very specific, meaning that attachment and entry is usually restricted to certain cell types. For example, the haemagglutinin and neuraminidase of influenza virus are designed to bind to respiratory epithelial cells. This knowledge about viral genes and host cell specificity makes them attractive candidates for vectors. Pathogenic factors can be replaced by genes whose products are of research interest or clinical benefit and the altered virus can be grown in a particular cell type.

An area of research exploiting these properties is 'oncolytic virotherapy', as a treatment for certain cancers, as highlighted by a recent paper [1] which was reported in the news. Unlike 'phage therapy', which uses viruses to destroy the antigenically 'foreign', pathogenic bacterial cells, virotherapy is used to target host cells – albeit those operating abnormally. The use of viruses to treat cancers does at first seem counterintuitive, since one study has estimated that over 16% of newly diagnosed cancers around the worlds are linked to infectious agents [2] . Actively replicating viruses alter the host cell's metabolic state and eventually cause cell death. This can trigger an immune response which can facilitate tissue damage and associated pathological changes, which can lead to cancer; this is seen in chronic infection with Hepatitis B and Hepatitis C viruses [3]. Some viruses are known to modify the immune response to their advantage; for example Epstein Barr virus (EBV) 'hides' in host B lymphocytes while inducing B cell proliferation [3] . Where integration of the virus genome into that of the host cell occurs, this can lead to mutations associated with malignancy and this is also a potential consequence of EBV infection [3]. Viruses are also associated with contributing to with the abnormal proliferation of host cells which leads to a tumour, although this is not always malignant. While some Human Papilloma virus (HPV) types, particularly 16 and 18 are implicated in cervical cancer, other HPVs cause benign growth of warts on hands or verrucae on feet [3]. However, during the 20th century , it was noticed that natural infections with some viruses appeared to result in reduction of tumour growth [4, 5]. Research *in vitro* suggested that this is due to their affinity for cancer cells, coupled with alterations in the metabolic mechanisms by which viral replication is usually supressed [5,6] . Some success has been shown in animal models and early clinical trials with attenuated versions of species which have this tendency to bind to tumour cells, including Mumps Virus,

Measles Virus, as well as the animal pathogens Newcastle Disease Virus and Vesicular Stomatitis Virus [5,6] . However, progress has been hampered by variable results and the fact that candidates identified to date are RNA viruses which are prone to mutation *in vivo*, which raises safety concerns [5,6]. More success has been achieved with the targeted approach of specifically modifying the virus genome to remove pathogenic factors, make them able to replicate only in growing and dividing cells and also to have a tropism for a particular type of tumour marker [5 , 6.] Along with the more controlled targeted effect, virus activity should stimulate a localised immune response in the tumour region, thus contributing to its destruction and removal [6,7] Examples of selected key oncolytic virotherapy agents are discussed in detail by Davis and Fang [5] . A number of advantages and disadvantages of using these modified viruses are ant-cancer therapy are given in Text box 1.

Text box 1: Advantages and Disadvantages of Oncolytic Virotherapy agents

Advantages	Disadvantages
Therapeutic viral strains designed to specifically target abnormally operating tumour cells which express altered surface antigens	Specific targeting requires modification of virus – attenuated strains may revert to wild type; deliberate deletion of genes may lead to loss of vital functions
Deliberate alteration of virus genome allows inclusion of factors which enhance local immune response to tumour	Lack of clear understanding of host cell – virus interaction may lead to unexpected affects on activity of products of inserted genes
Oncolyotic virotherapy agents can be used in conjunction with more conventional cancer treatments including radio- and chemo-therapy	Safety concerns when using modified forms of viruses which naturally persist in the host, such as HSV

To date, the best candidate therapies have been based on dsDNA viruses, most notably variants of Adenovirus type 5 and Herpes Simplex Virus type 1 [5]. For example, ONYX-015 is an adenovirus strain in which the gene coding for E1B protein has been deleted [4,5]. This protein suppresses the activity of p53, which induces apoptosis in the host cell and stops the cell cycle when there is damage. Lack of a functioning p53 gene product is a feature of many tumours, including breast, bladder, ovarian and head and neck cancers, which means that the ONYX-015 adenovirus does not need to counteract it to replicate inside these cells. Thus the idea is that it can replicate and lyse the cancerous cells while being inhibited in normal healthy cells [5] . This mutant virus was developed in the late 1980s and in clinical trials it was

used in conjunction with more conventional cancer treatments such as radiotherapy and chemotherapy, with some reported success. However, the issue of exactly how the selective toxicity works and doubts as to whether the lack of p53 in the tumour cells was in fact the key to the mechanism of action led to further development of the preparation being discontinued in the 2000s [5]. Better progress was made with trials in China of another modified adenovirus, H101, used against head and neck cancers, along with anticancer drugs. This is now a licensed treatment in that country [4]. There are a number of other potential oncolytic virus treatments in development and the latest candidate is a modified version of Herpes Simplex Type 1 called Talimogene laherparepvec (T-VEC) [1,7]. The gene for the viral neurovirulence factor ICP34.5 has been deleted, along with the ICP47 gene, whose product works to suppress antigen presentation of herpes infected cells [1] . In addition, the gene for human granulocyte macrophage colony-stimulating factor (GM-CSF) has been inserted into the genome, which is intended to promote antigen presentation and activate T cell responses to cancerous cells [1] .

The paper by Andtbacka *et al* [1] which was published recently, reports a phase III clinical trial of T-VEC which was conducted between May 2009 and July 2011. Patients with melanoma at stages IIIB to IV which had been confirmed by histology and which was deemed not suitable for surgical resection were eligible for the study. Patients were recruited at 64 study centres across four countries (UK, USA, Canada and South Africa) and in the end 418 entered into the project. Around 2/3 of the patients (291) were assigned the T-VEC treatment, which was injected directly into the melanoma lesions, while the remaining 127 received a preparation containing only recombinant GM-CSF and this was given subcutaneously. The timings of the doses were slightly different for the two treatment regimens, but they were each conducted for a minimum of 24 weeks (at which point the lesion was assessed) and then continued for up to 12 months, as deemed necessary and in accordance with the patient's wishes. The results showed that 78 of the patients given T-VEC had a clinically verified response within 12 months and which lasted for 6 months or longer. The median duration of treatment needed to achieve this response was 4.1 months. This compared to 8 patients showing a similar outcome from the GM-CSF treatment, although the median time to the response was 2.8 months [1]. . The cancers were very advanced in these patients and other treatments had not been successful, so it is perhaps not surprising that for most of the patients, this therapy did not work. The median time to deciding that the regimen had failed was shorter for patients on GM-CSF than those on T-VEC (2.9 months and 8.2 months respectively). Similarly although the majority (290) of participants died, this figure comprised 65% of those on T-VEC and a median survival time of 23.3 months, in contrast to 80% of those on GM-CSF, who survived for 18.9 months on average. This study showed that the oncolytic viral immunotherapy agent, T-VEC, could remove melanomas and slow the rate of the development of the disease. However at present it is clearly not a cure and perhaps trials involving patients at earlier stages of the cancer would be beneficial.

References

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