What Ever Happened to Gene Therapy?

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Many people have probably heard of gene therapy; the therapeutic transfer of genes into a living human. Gene therapy is a topic that has made numerous news reports, sparked debates over ethical concerns, and made promises for numerous genetic diseases. Yet what is really going on in this field today? Yes, there is a lot of talk about gene therapy especially for those diseases for which there is no cure like xeroderma pigmentosa and severe combined immunodeficiency (SCID), but there doesn't seem to have been a lot of progress done on this topic lately. At least none that has made the news. The reason for this delay is delivery. Delivery meaning the way in which the patients' affected cells and tissue types receive the correct gene to replace their mutated gene. There is no molecular FedEx that makes sure each and every affected cell receives its fair share of the new treatment, which creates complications. Currently, the answer to this problem seems to be disabled viruses.

Disabled viruses are basically viruses which have been gutted, or had all their disease causing properties, like the ability to replicate, taken away. These disabled viruses are allowed to retain the ability to infect cells and enter the nucleus. This ability is important because in order for gene therapy to work, the gene must survive the trip throughout the body to the desired cell, somehow get inside the cell, and enter the nucleus where the gene could be transcribed and translated into protein. These steps are important because it is the expression of this protein that actually corrects the disease state. Disabled viruses seem to be able to do all of the above except that these viruses are not allowed to passively infect cells without consequences. Our bodies have active immune systems that act against this kind of an invasion. This is why gene therapy was first attempted on those whose mutation caused an immunodeficiency.

However, scientists, despite the problems previously associated with gene therapy, have taken these lessons to heart and learned from some of the early failures. This is why gene therapy is not dead. Since those early days, scientists have found new types of viruses that have shown to stimulate lower immune responses and enhance gene expression. Also, gene therapy was once considered only really relevant to those patients that had single gene mutations, however, this is no longer the case. Gene therapy can apply not only to these single gene mutations found in a limited subset of people, but also to disorders affecting millions of people, like Parkinson's disease and cancer.

The question, then, still remains whether the delivery problem was solved. The complete answer to this question is still being debated, but so far, research has focused on new viruses with better efficiency and less immunogenicity. One type of virus that has generated a lot of interest is the lentiviruses. Lentiviruses are retroviruses, meaning they have the ability to copy their RNA to DNA and then insert this DNA into the chromosomes of their host. Retroviruses have been particularly relevant for gene therapy because they promise a permanent solution. Many of the other viruses used previously did not have the ability to be permanent, and thus the expression of the desired gene tended to be only transient. The real limitation with using retroviruses is that though they can infect dividing cells, lentiviruses are a special class that can infect both dividing and non-dividing cells. This provides a new application for viral vectors because lentiviruses can infect neurons. Lentiviruses also seem not to provoke the same immunogenicity that other viral vectors do. This new delivery system is still being evaluated for safety in terms of humans yet lentiviruses are already being used effectively in mammals.

To continue, research has led to the discovery of new applications for gene therapy. One new application, which has gained the attention of many scientists, is that gene therapy strategies may be used against cancer. There is substantial evidence that tumors secrete factors that interfere with the normal immune response. Also it is not easy for the immune system to 'see' cancer. These two factors combined means that the immune system grows tolerant of tumor cells. As a result, scientists have focused on ways of sending a red flag to the immune system so that it will be able to recognize the tumor and work to halt its progression. Many scientists have come to believe that this red flag could be a vaccine given as treatment. This would be a therapeutic vaccine that is not used for prevention. Preventative vaccines, like Gardasil, the cervical cancer vaccine recently approved by the FDA, target the viruses that cause cancer. One way that this type of targeting is done is by specifically activating the scavenger cells of the immune system, the dendritic cells, with a lentivirus. These activated dendritic cells then travel to the lymph nodes where they signal to the T-cells, the soldiers of the immune system, which cells to kill. Therapeutic vaccination is just one example of what doctors are calling immunotherapy, where the immune system is used to fight cancer and other disorders. Furthermore, this is a type of immunotherapy done using gene therapy techniques, which makes it a cutting edge treatment. To date there have been encouraging results with this type of immunization strategy though more work is still needed to fully evaluate ways to increase its effectiveness.

Parkinson's disease was mentioned above because Parkinson's disease could be treated with gene therapy although by a slightly different method. Many of those affected with Parkinson's disease have no known genetic mutation to explain their disorder. Most patients, however, share a pathology associated with a protein called α-synuclein. This protein clumps in their neurons and is highly associated with the death of these neurons. Animal models have shown that the absence of this protein is not harmful, and thus depleting this protein from neurons could provide a cure or at least a cessation of worsening symptoms. This depletion also goes back to the use of lentiviruses because, as mentioned previously, lentiviruses can infect neurons and Parkinson's disease is a neurological disorder. This argument involves depleting the α-synuclein protein clumps from cells, which has already been done in mammalian models. The depletion is accomplished via a method called RNA interference or RNAi. RNAi silences the expression of specific proteins at the post-transcriptional, pre-translational level.

To conclude, gene therapy as a form of treatment is quickly becoming a reality. However, whereas gene therapy was once considered a treatment for single gene mutation disorders, it can now be used in novel ways. Not only can gene therapy be used to replace defective genes, but also to silence genes with abnormal activity, or to express genes for more efficient targeting of the immune system. RNA interference (RNAi) has potential for the treatment of more than Parkinson's disease. Especially for medical conditions wherein a protein is functioning abnormally or should not normally be present, RNAi could be very effective. There is a lot of potential for these new types of treatments to be developed in many more disorders.

References:

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