

Research into epigenetic based cures for cancer



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Introduction

Cancer is one of the most prominent diseases of modern times that a consistently effective cure has not been discovered for. Those born after 1960 have a 50% chance of being diagnosed with any given type of cancer in their lifetime; inferring that almost everyone will be affected by cancer during their lives (Cancer Research UK, n. d.). However, only half of people diagnosed with cancer survive their disease for ten years or more (Cancer Survival Statistics, n. d.). This shows that the current treatments for cancer are not consistently successful; nor directly hitting the core cause of the cancer occurring. Epigenetic based cures could begin to target the root cause of cancer (precision cancer medicine) and be revolutionary in solving this modern day global epidemic that is causing the second highest amount of death each year (Who, n. d.).

The Greek word 'epigenesis' summarises the study of the progression of genetic processes from a fundamental cell through development of undifferentiated cells to a fully functional organism. 'Epi' meaning upon or in addition to and 'genesis' referring to origin or creation; in combination meaning on top of origin which we now know to be the addition of epigenetics to our base script of DNA. Conrad H. Waddington originally coined the term epigenetics in 1942 to mean the impression on development of various genetic processes (C. H., 1942). Waddington described the concept of passing on genetics similar to a ball rolling in to different valleys on a landscape; it only takes a small 'nudge' from the environment for the genetics to be changed into a different valley (representing a different route the genes could take). He first put this theory into practice on his initial

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experiment into *Drosophila (fruit flies)* where he placed the flies under stress-causing heat shock which led to changes in development like change in eye colour and wing defects. These defects were then passed onto offspring despite them not having personally suffered the heat shock – showing that environmental factors affecting a parent can change their genetics permanently and in a way that can be inherited (C. H. Waddington, 1953).

Our bodies are made up of over 30 trillion cells, inside most of these cells is a nucleus which contains our genetic material (our DNA). Deoxyribose nucleic acid (DNA) codes for every aspect of our phenotype and is a continuous script determining all of our characteristics. This script was previously thought to be expressed exactly as it is written but scientists have now come to realise this is untrue. Each cell nucleus contains two metres of DNA into an area which is 6 micrometres across; the only way this could fit is it was coiled repeatedly (How Long is Your DNA, 2018). It is coiled around proteins called histones which not only help to compact the DNA but decide whether the genes will be switched ‘on’ or ‘off’. This switching is fundamental in epigenetics. It is important to recognise that epigenetics is not a process that occurs to increase the amount of defects in an organism, it is completely necessary in order for us to function e. g. to differentiate our cells – skin cells vary greatly from our white blood cells in size, function etc. but contain the exact same DNA instructions to work off of.

Epigenetics decides which genes are expressed and which genes are not. This occurs when genes are methylated or not methylated; if a methyl group is attached to the DNA sequence the RNA polymerase cannot read it and

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therefore not use that part of the gene, if the gene is not methylated then it will be read and transcribed (expressed). Whether methylation occurs is affected by many factors including inheritance and environmental factors.

Such as exposure to pollution or availability of food.

Pollution is one of the primary causes of lung cancer causing nearly 1 in 10 lung cancers but it is difficult to create a chain of causation as we are exposed to it in varying degrees due to the change in the harmful chemicals from area to area and the effect altering between people. Miniscule particles in the air (primarily the smallest known as PM2.5 (How air pollution can cause cancer, n. d.)) affects the methyl groups attached to our DNA – research has shown inhaling exhaust fumes correlates with epigenetic changes that impact up to 400 genes (Air Pollution Could Alter Tags on DNA and Increase Risk for Neurodegenerative Disease, n. d.). These epigenetic changes include those which can cause lung diseases such as cancer or neurodegenerative illnesses.

One source of pollution which affects epigenetic changes is one's exposure to miniscule particles contained in diesel exhaust fumes. Recent research shows that when cells were exposed to traffic-related air pollution from a street in Shanghai the cells began to malfunction and failed to act as normal cells contributing to the development of a neurodegenerative disease. Although the UK has lower levels of pollution internationally compared, it still is not within all of the EU limits. This suggests the importance of Sadiq Khans' ultra-low emission zone in London especially due to the level of

school children who are being exposed to this disease-causing air and have stunted lung development because of this.

Disruption of this epigenetic expression can easily cause cancer as it is an interruption in the transcription and as a result cell replication and division. Cancer cells have unregulated division and continue to replicate beyond the usual number of divisions even if their DNA is disrupted. This overproduction of cells is a tumour. This has been shown by a recent study by Baylor College of Medicine whereby mice had a methyl ‘ magnet’ that silenced the gene methylation of the gene ‘ p16’ (the regulator of cell division). This interruption led to 27% developing cancer; showing the significant impact of epigenetics on the development of cancerous cells (The Scientist, n. d.). If this process can be manipulated effectively it could have a significant impact on eliminating cancer cells even in the earliest stages by reversing the faulty changes in the epigenome back to the normal positioning.

One of the largest companies occupied on these cures and the concept of ‘ precision cancer medicine’ is Dana-Farber/Brigham who have generated a research project – ‘ Profile’ – which creates a ‘ tumour profile’ from the area from which each individual’s cancer develops and the epigenetic mutations that have occurred to cause the specific type of cancer (Precision Cancer Medicine , n. d.). It registers 447 genetic mutations as well as other alterations in the DNA sequence and uses this to create a personalised treatment. This is used to assist doctors in knowing which drugs or therapies the cancer will react to and even predict how it will act as it develops without treatment present. An example of this is a trial into the treatment of 347 non-small cell lung cancer patients with a specific gene mutation (ALK gene) <https://assignbuster.com/research-into-epigenetic-based-cures-for-cancer/>

(Targeted therapy boosts lung cancer outcomes, n. d.). The sufferers received an oral drug (crizotinib) which directly targets the ALK gene by inhibiting the cancers growth and were found to continue treatment for a median of 7.7 months before the disease worsened; in contrast to 3 months for those who undergo traditional chemotherapy (Targeted therapy boosts lung cancer outcomes, n. d.). In 2014 the US Food and Drug Administration approved crizotinib for the treatment of advanced lung cancer – suggesting its potential to be an impactful treatment (Targeted Drugs Get First Test in Early Stage Lung Cancer, 2014). However, crizotinib was not without its flaws as only five percent of non-small cell lung cancer sufferers (the most prominent form of lung cancer) suffer from a mutation in the ALK gene and many of the small percentage treated experienced side effects such as gastrointestinal issues as well as visual disorders and leg swelling (Targeted therapy boosts lung cancer outcomes, n. d.). It also has since been found to possibly cause a hole in the bowel or stomach as well as possible liver failure – these side effects are possibly deadly and occur in up to 1% of those treated. In a separate study, crizotinib was found to have even more promising results as the length of time during which the patients (with the ALK+ mutation) cancer did not worsen in contrast to those treated with chemotherapy was a significant percentage longer; when taking crizotinib capsules the cancer did not get worse for 10.9 months in contrast to 7 months for those receiving chemotherapy infusions. 127 of the 172 patients in the crizotinib group had tumours shrink, the spread of cancer lessen or even had all signs of cancer disappear as opposed to 75 of the 171 patients receiving chemotherapy having a partial response to treatment (ALK+ Study Results, 2017). However, for the majority of those treated with crizotinib

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(also known as Xalkori) they were not cured of the disease as it simply delayed the worsening of the disease for only a few months. As well as this, no significant difference in survival between those treated with Xalkori or those treated with chemotherapy (ALK+ Study Results, 2017). These trials have only confirmed that by no means is crizotinib a perfect cure. Despite its ability to consistently affect the cancer, in comparison to more traditional drugs such as chemotherapy the damage done to the cancerous cells was significantly less. This suggests that in some cases more traditional drugs (despite their increased negative side effects) can be a more effective option in the cases of some patients. In addition to these issues, crizotinib is impractical to advertise as a treatment for all those suffering from this specific form of lung cancer in countries where there is not a national health service – this is due to the cost of one course of treatment for one patient being £51, 000 (NICE, n. d.). For an average income in most countries this would make the drug completely unobtainable and therefore not significant in the global attempt to medicate lung cancer. However, it could be argued that this cost would be cancelled out as those taking it would not have to pay for chemotherapy done in a hospital (which not only incurs the primary cost of the chemotherapy medication but many secondary costs such as staff, a hospital bed, food during their hospital stay etc).

Another major innovator in the epigenetic cure industry is Johns Hopkins Medicine. They are using their scientific research to reprogram the behaviour of cells to act normally as opposed to usual lung cancer treatments which aim to destroy cells (John Hopkins Medicine, 2019). This decreases the level of damage to cells which aren't being targeted (e. g. non-cancerous cells).

This in turn reduces the negative side effects such as nausea and fatigue. Research by Stephen Baylin into this medication showed that it was highly effective for certain patients in creating a more permanent fix for the illness by preventing its growth or destroying the tumours altogether (John Hopkins Medicine, 2019). However, for most patients it didn't appear to show any effect on the tumours which created a larger debate – what differentiated between those who it did work on and those it was ineffective in treating. Further research into the longer term effects on those it was ineffective in helping showed astounding results; their cancers had miraculously become sensitised to other treatments that were previously unsuccessful. This suggests that the effect of this medication is positive on all patients even if not immediately or in the way that it was predicted to. Whether this drug will be released is still unclear due to the years of rigorous testing it must go through in order to be available for clinical use.

It could be argued that the perspective from which these cures are currently being developed from is too narrow and that scientists should first create a wider database from which to develop more specific conclusions. There is currently no database of what a healthy epigenome is; which makes it far more difficult to identify exactly which epigenetic alteration has caused the disease and therefore what treatment could be used to reverse the cancers growth.

Precision cancer medicine using epigenetic-based medicine is still in its infancy and despite its proven effect on tumours it is hard to suggest how large an impact it may have on the community of cancer treatment due to its huge cost as well as the long term effects of it on health. It also may be hard

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to distribute to a wide population due to the specificity of each medication as it is not only specific to each cancer it is specific to the gene alteration which caused the disease. There are hundreds of thousands of possible variations and to determine which alteration each person has could increase the price by a significant margin.

Research in other new areas for treatment of cancer are expanding; one of which is the rise of cannabinoid therapy usage. Cannabinoid use is rising in popularity - partially due to the widening legalising of cannabis for both medicinal and recreational use. The political and medical view of cannabis is modernising to a more liberal perspective. Research into the medicinal uses of cannabis originating products such as cannabidiol (CBD) has shown that the chemical has abilities many of which that may be useful in the treatment of cancer. Examples of this include its capability to kill cells and stop cells from dividing; this is of indispensable importance in reducing tumour size and preventing further tumour growth (Cannabis and Cancer, n. d.).

However, it is yet to show an ability to distinguish between cancerous and normal cells when acting; this issue has meant cannabinoids have been shown to harm necessary blood vessels. Another flaw of the use of cannabidiol is it has also occasionally seen to even boost cancer cell growth (Cannabis and Cancer, n. d.). One aspect of cannabinoid use that has been proven throughout many studies is its effectiveness in relieving some patients side effects of their illness. Many patients experience nausea, pain and fatigue as a result of either the illness or the harsh treatments needed to cure it. Cannabis has been shown in many diseases including cancer to act as a sort of 'painkiller' by reducing many of the most obvious side effects of

like nausea and pain. However, one of the largest positives of using this method of treatment is the affordable cost – at 1.94 dollars a day the increase in availability in contrast to the expense of crizotinib.

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