Essay

Why is cancer so hard to cure?

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Abstract

Humanity has made significant breakthroughs in the last century, from the polio vaccine to the sequencing of the human genome, to even the creation of the internet. However, a cure for cancer, a disease that 1 in 2 people will at some point in their lifetime develop, still has not been synthesised. So why is cancer so difficult to cure? To answer that, it must first be established that cancer is not just one disease, but over 200 different diseases, each with its own quirks and variabilities that make a cancer panacea an incredibly difficult conceptual medicine to develop. This essay seeks to explore multiple key behaviours of cancer that give it these variabilities. These variabilities of cancerous cells stem from their heterogeneity – both individual and in the wider scope – and cell type. Cancers also evade the immune system's detection and invade tissue across the body through metastasis; all of which makes developing a cure even more difficult.

Keywords: Cancer, heterogeneity, immune system, immunosuppression, metastasis

Heterogeneity of Cancer Cells

Heterogeneity occurs in the nucleus of cancer cells and between individuals of a species and is one of the reasons why the same treatment would not have an equal effect across all cancer patients (Aktipis and Nesse, 2013; Ma *et al.*, 2010). Deoxyribonucleic acid (DNA) is unique to an individual, and this is what makes the concept of a cure so difficult. Some individuals may have beneficial or detrimental mutations in their DNA that affect the placement and presence of nitrogenous bases, altering the codons and leading to variability in the proteins produced (Studer *et al.*, 2013). This can impact the individual's cell's vulnerability to cancer development (Levy-Lahad and Friedman, 2007) and their response to treatments, be it drug sensitivity or therapeutic resistance (Jin *et al.*,

2019). Individuals may also have allele matchups that can impact the cell's susceptibility to cancer depending on the phenotype expressed (Pomerantz and Freedman, 2011). Cancer DNA is always acquiring new mutations due to the instability resulting from the high rate of mitosis, which is characteristic of cancer (Loeb *et al.*, 2008; Breast cancer, 2015). For example, in HeLa cells, a culture of cancerous cells taken from Henrietta Lacks over 6 decades ago that are still alive and dividing today, the nucleus contains 70-90 chromosomes as opposed to the normal 46 due to the high rate of mutation (Macville *et al.*, 1999; Heng, 2013). These mutations make each cancer cell completely different from one another and impact their vulnerability to different treatment types due to the different proteins produced from their DNA. Therefore, heterogeneity between cancer cells of the same tumour and of different individuals causes highly unique cancer cells that do not all respond to the same treatment exactly, making a cancer cure a difficult concept to develop.

Clonal Heterogeneity

The tendency for tumours to produce large populations of cancer cells with a large amount of variability leads to another reason why cancer is so hard to cure, clonal heterogeneity. This is the term for when tumours make sub-clones which have different characteristics from the original tumour (Nowell, 1976). These differing characteristics result from mutations and mean that if a form of treatment worked effectively on the original tumour, it may not work as effectively or at all on the sub-clone tumour due to differences in gene expression (Greaves and Maley, 2012), meaning the sub-clone tumour will continue to grow. This process is akin to antibiotic resistance in bacteria, where if all the non-antibiotic-resistant bacteria are killed off, the resistant bacteria will eventually become the major strain. This can also be juxtaposed with the Darwinian theory of natural selection as the treatments act as a selective pressure, causing the cancer cell population to undergo directional stabilisation in the direction of treatment resistance (Gerlinger and Swanton, 2010). Different cancers produce varying numbers of sub-clones, for example, glioblastoma can produce around 4 sub-clones each with its own unique characteristics brought on by its constantly mutating DNA (Soeda *et al*, 2015). This makes the concept of a single cancer cure even more difficult to work on.

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The Suppression of the Immune Response

While cancer responds to attacks from outside the body, such as different treatments by directional adaptation, it's also being attacked from inside the body by the immune system. Because cancer cells undergo rapid mutations, the proteins produced from the cancer DNA are deformed because of changes to the amino acid sequence in the primary structure of the protein and are therefore distinct compared to normal cells (Torkamani *et al.*, 2009; Muñoz-Maldonado *et al.*, 2019). The cancer cell's membranal proteins that end up being embedded into the outer layer of the phospholipid bilayer, such as glycoproteins, are distinct and therefore identified by the immune system as being foreign due to their abnormal structure. The immune system then tags the cancer cell to be digested by phagocytes through phagocytosis (Nagarajan and Selvaraj, 2002). However, cancer cells stemming from, or metastasising to, bone marrow can weaken the immune system by stalling the production of white blood cells there and depleting their numbers in the blood, resulting in immunosuppression and cancer being left unchecked (Freifeld and Kaul, 2019; Cancer Research UK, 2020). Certain treatments can also cause this immunosuppressive effect, such as chemotherapy, radiotherapy, and high doses of steroids (Youssef *et al.*, 2016; Cancer Research UK, 2020), which makes the use of these quite dangerous if cancer shows no vulnerability to them, as the result is artificially induced immunosuppression. This increases the difficulty of finding a single cure.

Metastasis of Cancer

Cancer can evade detection by the immune system by depleting the level of white blood cells, also known as leukocytes, in the blood, a condition known as leukopenia (Nicholson *et al.*, 1995). Cancer accomplishes this by invading the bone marrow and taking up space and resources necessary to produce neutrophils, a key type of leukocyte (Freifeld and Kaul, 2019). The depletion of neutrophils in the blood is also attributable to chemotherapy drugs, which slow their production in the bone marrow (Moore, 2016). Cancer can also invade neighbouring tissue and far off tissue by having cells detach from the original tumour and escape into the circulatory and lymphatic systems to be deposited elsewhere. This seeds the growth of a new tumour through a process called metastasis (Seyfried and Huysentruyt, 2013). This makes treatment significantly more difficult as there are

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now multiple targets with varying characteristics and immunities to certain treatments. This makes a cancer cure even more difficult to work on.

Conclusion

In conclusion, developing a single cancer cure would be extremely difficult as it would have to target over 200 different diseases, stemming from many different cell types, all with unique and constantly mutating DNA that allows it to adapt to resist treatments, that also suppresses the immune system and can invade other parts of the body to seed the growth of more tumours.

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