How single cell genetic sequence information would guide systemic cancer therapy

Summary

Recent progress in isolating the ultra-rare circulating tumor cells from blood finally lets physicians make use of the potentially best tumor cell sample available for cancer diagnosis, the common blood sample. Blood samples contain the spreading cancer cells, i.e. the harbingers of clinical cancer spread.

Cancer starts with a single cell, that then grows and divides and ultimately may spread. Cancer therapy therefore needs to be based on the properties of those single tumor cells to be truly effective. By genetic sequencing, scientists have discovered that there exist a limited number of cancer "driver" mutations, about 2 to 8, in the genome of cancer cells. Reversing the lethal effects of those mutations is the aim of curative cancer therapy. By sampling a limited number of individual single cells from a blood sample, the diagnosticians can now determine the number and type of cancer driver mutations, the extent to which they may vary in subpopulations of cancer cells and discover whether any treatment resistance mutations may have developed. Based on that information the treating physician determines if any treatment is necessary, if so, what the best treatment options are and, importantly, how to adapt the treatments as any unwanted treatment resistance may develop.

The result is a potential for new and effective single or combination cancer treatments, and new incentives for drug companies to develop new targeted anti-cancer drugs.

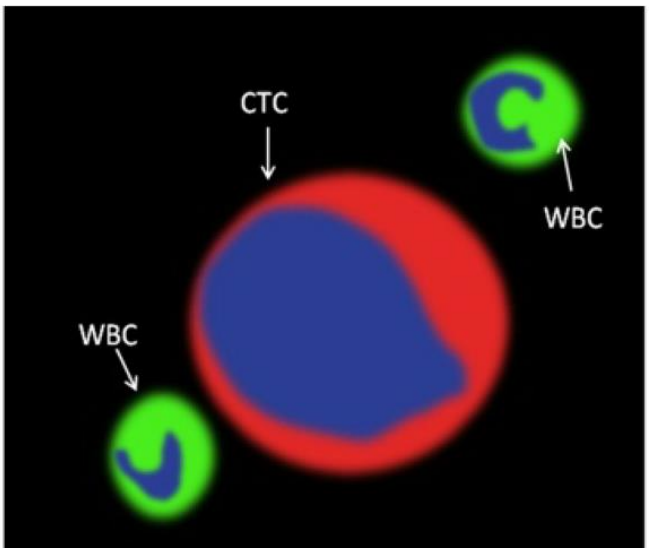
Cancer occurs at the single cell level

Cancer originates at the single cell level. We know this because tracing the life history of a cancer back to its origins shows that it, with a few interesting exceptions, started with a single cell. Cancer also spreads by way of one or more single cells, from its tissue of origin to neighboring lymph nodes or to distant organs, through the lymph or blood, to form metastases. Furthermore, cancer cells can "repopulate" existing tumors with new variants of the original cancer clone, including with new sub clones that are treatment resistant.

This is important information in the fight against cancer, since it informs us of at what level the fight needs to be fought; at the level of individual cells. If we can fight cancer at the right level, we are much more likely to be successful. In fact, not fighting cancer at the right level goes a far way towards explaining why cancer still is such a threat to our health.

Cancer cells from blood samples are easily available and appear representative of the disease

Circulating tumor cells have migrated from either the primary tumor or from metastases into the blood stream. It therefore seems reasonable *a priori* that they are representative of the tumor cells in those locations, and thus a good sample-type to base the diagnosis on. Nevertheless, there existed a possibility that the circulating tumor cells might represent a very special subpopulation of the cancer, with little or no similarity to its solid tissue origins, and thus to be a poor representation of the disease. Scientists have therefore sought long and hard to discover if there are any peculiarities with the circulating tumor cells, but none have been found. It therefore now seems like the circulating tumor cells are indeed a good sample type, since they appear to be no different from the solid tumors that are the intended objective. Clinical trials are being used to test this inference. Indeed they may be the best possible sample type since they are already suspended making them relatively easy to isolate and analyze individually. Blood samples are also relatively easily available compared to tissue biopsies, and can be taken repeatedly, so that the treatment can be continuously monitored in its cellular and genetic detail.



Picture 1. A circulating tumor cell (CTC) between two white blood cells.

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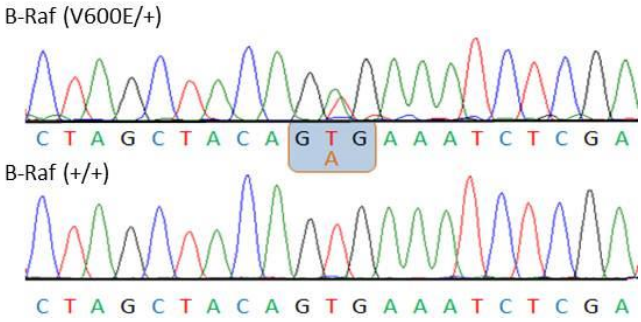
The required number of successive "driver" gene mutations in a cancer cell is known

We now know how many gene mutations are needed for cancer to develop, and that they need to develop incrementally in one and the same prospective cancer cell. In fact, that information has been around since 1953, when Watson and Crick discovered the structure of DNA. With brilliant insight, and with no DNA sequence information available to him, C.O. Nordling postulated, based on his observations of the relationship between age and the incidence of cancer, that about 7 successive mutations in the same cell causes cancer. This conclusion has recently received stunning confirmation from large-scale cancer DNA sequencing projects. We can now conclude, with only a slight modification of C.O. Nordling's original conclusion, that about two to eight mutations, occurring together in a single cell cause cancer. We also know that these mutations can either occur more-or-less all at once[1] or be acquired incrementally over many years, to accumulate in the progeny of the founder cancer cell; the cancer clone. This explains why cancer is mainly a disease of middle and old age.



Picture 2. A muted gene.

The identity of the cancer "driver" genes operating in a cell

We need to know which specific genes are mutated in each individual cancer if we are to treat it effectively, "magic bullet" style. Close examination of individual genes, followed by experimental verification, has identified a relatively small number of genes responsible for cancer, in the hundreds (out of a total of about 20,000 genes in the whole human genome). The census is still ongoing but it now seems clear from extrapolation that there will ultimately turn out to be only several hundred genes that can mutate to contribute to cancer, a manageable number. An individual cancer is therefore made up of various combinations of 2 to 8 out of the total of several hundred cancer genes. Single cell genetic sequencing can determine which 2 to 8 mutations exist in the various subclones that make up an individual patient's cancer. We can therefore tally what gene mutations that need to be targeted for treatment in each individual patient. There may, or may not, exist treatments for all the various mutation. As we complete the census of potential cancer genes and mutations and as the drug companies develop new drugs targeting them, we can increasingly treat the root causes of cancer, based on individual cell information.

How single cell genetic sequence information would guide cancer therapy

Genetic sequencing of mutations in cancer is already successfully guiding a small number of novel, targeted, cancer therapies. Targeted therapies are based on the recognition that tumors contain either activating mutations in oncogenes, or inactivating mutations in tumor suppressor genes, and that gene-specific inhibitors or activators can in effect normalize the mutated genes. In so doing the targeted drugs will also inhibit the growth, survival, invasion and other harmful effects of the tumor. Examples include the use of epidermal growth factor (EGFR) kinase inhibitors to treat cancers with EGFR gene mutations, anaplastic lymphoma kinase (ALK) inhibitors to treat cancers with ALK gene translocations, and specific inhibitors of mutant BRAF. There is reasonable hope that this short list of treatment targets can be extended to include at least many, and perhaps ultimately all, of the several hundred driver genes in cancer.

Counteracting the treatment of cancers with targeted drugs is the development of drug resistance. Also drug resistance occurs at the single cell level and is caused by genetic mutations. Drug resistant subclones will gradually overgrow, under selective pressure by the treatment. Thus also drug resistance can be monitored by single cell genetic sequencing. The treatment can then be shifted to alternative therapies for which the tumor is not resistant, resulting in continued successful treatment.

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[1] As in childhood cancer.

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