Natural selection: Fighting cancer by drawing inspiration from the genius of Darwin

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215 years ago today, on February 12, 1809, the famous English scientist Charles Darwin was born, whose genius work on the evolution of living species revolutionized modern science. This fabulous legacy left by Darwin is still relevant today and could even play a leading role in the discovery of new therapies against cancer.

Darwin's great discovery was to notice that the great diversity that exists between individuals of the same species, especially when they live in a distinct environment, was the result of biological transformations allowing them to adapt to this environment.

Individuals who are better adapted have a greater probability of surviving longer and therefore a greater chance of passing on these characteristics to their offspring.

CANCER, A DARWINIAN DISEASE

Thanks to this natural selection, the life of all organisms, from simple viruses to complex animals like humans, is a very dynamic process, in constant evolution since its appearance on Earth.

Darwin certainly did not know it when his work was published in 1859, but the evolution he described at the macroscopic scale of living species also applies at the microscopic level of cells. When cancer develops, for example, a cell manages to acquire genetic characteristics that give it a growth advantage over normal cells.

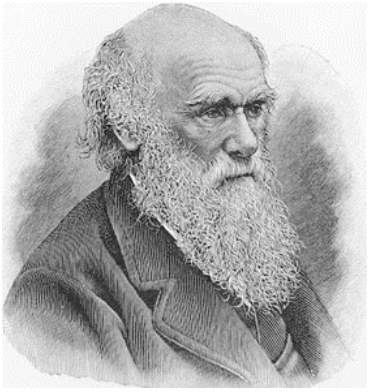
If these new properties allow it to be better adapted to the microenvironment in which it finds itself, this abnormal cell will win the competition against normal cells and over time become the dominant cell species to form a mass that invades the organ: this is clonal selection.

Darwin's principles of natural selection are also at work in the treatment of cancer. A high dose of chemotherapy, for example, often succeeds in eliminating the vast majority of cancer cells, but it is enough for a single cell (a clone) to manage to acquire resistance to the treatment for this characteristic to be transmitted to its descendants and generate a population of resistant cells which will cause the cancer to recur and make it resistant to future treatments.

ANTITUMOR THERAPY

It has recently been proposed that a Darwinian approach may also prove valuable in the treatment of certain cancers, notably prostate cancer (2).

The principle of this approach is that instead of attempting to completely eradicate cancer cells with aggressive chemotherapy, which generates resistant cells that have adapted to the drug, we instead seek to control the



growth of the tumor, without eliminating it completely, by controlling its exposure to chemotherapy agents.

In this way, cancer cells that acquire resistance are in direct competition with non-resistant cancer cells (which have not been eliminated by low doses of treatment), which limits their growth and prevents the appearance of incurable resistant tumors. This resistance to conventional chemotherapy is one of the main causes of death in clinical oncology.

This revolutionary new approach, called adaptive therapy, was tested in a pilot study in 17 patients with metastatic prostate cancer (1).

Patients were treated with abiraterone (a drug that lowers testosterone levels) until their PSA levels (the prostate cancer marker) were reduced by 50%, indicating a partial tumor response. The treatment was then stopped, which allowed the cancer cells to start growing again, but since there is no longer any selective pressure exerted by the chemotherapy agent, the cell population of the tumor that recurs is without much resistance to chemotherapy.

When PSA levels become high again, treatment is started again to reduce them again by 50% and this cycle of treatment/stopping treatment is repeated as many times as necessary with the aim of preventing progression of the cancer.

The results of the pilot study are very encouraging: compared to standard treatment using continuous chemotherapy, patients treated with the adaptive approach lived longer without progression of their cancer (33.5 vs 14.3 months) and presented a clear improvement in their overall survival (58.5 vs 31.3 months).

It should also be noted that all patients treated standardly saw their cancer progress during the study and died, while four patients subjected to adaptive therapy were still alive when the study was published.

Nearly 200 years after its discovery, evolution through natural selection remains an essential element for understanding the life around us and the diseases that afflict us. As they often say, great ideas never die.

Darwin's genius continues to influence the evolution of humanity.

(1) Gatenby RA et al. Adaptive therapy. Cancer Res. 2009; 69:4894-903.

(2) Zhang J et al. Evolution-based mathematical models significantly prolong response to abiraterone in metastatic castrate-resistant prostate cancer and identify strategies to further improve outcomes. Elife 2022; 11:e76284.

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