Scientists Develop A New Approach For Cancer Treatment

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A new paradigm in the way we look at cancer with important implications on how we treat it is about to be published in the British Journal of Cancer by Portuguese, Belgian and American researchers. The group use a mathematical approach to reveal how by changing the dynamics of interaction between the cancer cells and those of the affected tissue it is possible to control and even potentially cure the disease. Even more interesting is the fact that this new approach can be used in any number of pathologies where different cells interact. The work has the potential to revolutionise the way we look into the treatment of disease and demonstrates the relevance of mathematical models, not only to improve our understanding of biological systems, but also to find more effective ways for dealing with problems in them.

In cancer, the apparently same disease and/or treatment can have radically distinct outcomes in different patients, and while it is easy to understand that the interactions between the cancer cells and the individual specificities have a major role determining the final outcome, how this happens and, consequently, how to control it is a major issue in medicine and one very far from being clear.

Trying to address the problem D Dingli from the Mayo Clinic, Rochester, USA, JM Pacheco from the University of Lisbon in Portugal and colleagues use evolutionary game theory a mathematical approach that studies biological entities and predicts their behaviour based on the costs and gains of the different participants to look at the specific case of Multiple Myeloma (MM), an incurable cancer of the antibody-producing cells. The idea was to develop a mathematical model that could describe and help to understand the system/disease behaviour, and consequently learn how to control it when necessary.

In MM the cancerous cells of the immune system multiply abnormally in the bone marrow occupying all the available space and stopping other (immune) cells of growing what eventually leads to immunocompromised patients. But the most visible aspect of the disease is in the bones where tumours grow leading to fractures, widespread bone thinning (osteoporosis) and generalised pain. MM affects about 750,000 people worldwide and, although quite a few treatments are available, it remains incurable with an average rate of survival of only three years.

In the work now published Dingli, Pacheco and colleagues focus on the interactions between MM cells and those from the affected tissue in this case osteoblasts or OB (the cells that form the bone) and osteoclasts or OC (the cells that destroy the bone). In fact, during normal bone homeostasis a constant balance between bone formation and destruction allows the renewal and maintenance of the healthy bone, which the MM cells disrupt. The hypothesis was that the key to control cancer cells' growth could be in the manipulation of the dynamics between the three populations.

The research starts with the construction of a matrix/table describing the biochemical interactions between the three populations. In fact, MM cells are known to negatively affect OB growth while stimulating OC, while OC stimulate both MM cells and OB, and OB stimulate OC but have no effect on MM cells. All populations are considered to have no effect on itself and this appears in the table as zero. The remaining interactions are unknown variables and, as such, are represented by a letter (from "a" to "e" since there are 5 different types of interactions MM cells affecting OB, MM cells affecting OC, etc when we take out the "no effect"/zeros).

From this table, and using the tools of game theory, a series of equations are deduced and a simplified formula to describe the system is obtained, which and here is the beauty of the whole thing has only two unknown variables: Beta and delta. Beta is described as the net effect of MM cells on
OC, while Delta is the net effect of MM cells on OB cells. Again, the effect of a population on itself is zero, but this time the effect of OB on OC or vice versa is 1.

With this much simpler formula it is now possible to (almost intuitively) understand (and predict) the behaviour of the system/disease, which depends on the values of delta and beta determining the final equilibrium between the three populations.

Their first observations reveal that only when beta is smaller than 1 so when the effect of MM cells on OC is smaller than that of OB on OC (which in the simplified formula is 1) are MM cells totally eradicated and OB:OC balance restored. Unfortunately various experiments suggest that beta smaller than 1 is extremely rare in nature. But the model also shows that the bigger the beta, the faster should be tumour progression and bone destruction. In the same way, the second variable, delta which is the negative net effect of MM cells on OB is demonstrated to be particularly important for disease severity, with the model predicting that, for a fixed beta, higher deltas lead to considerable bone loss, even when there is only a small number of MM cells.

This means that therapies that decrease beta should reduce lesions and disease speed, while those reducing delta reduce the toxicity of the myeloma, slow the progression of the disease and improve bone mass. Ultimately, both improve the patients' quality of life, but it is the reduction of beta that can effectively stop disease progression (in starkly contrast with current therapies where relapses are inevitable). And in fact, experiments that blocked some of the proteins produced by MM to stimulate OC (so experiments were beta is reduced) were shown to stop bone destruction in a mouse model of myeloma and slow disease progression in humans. The work now published explains why and how.

In the same way the model can also analyse something the team does in the article - how changes in different parameters modify the efficiency of current MM treatments, as well as how to improve them.

In conclusion, Dingli and colleagues' new work predicts that by altering the relative fitness of one cell type with respect to the others, one may effectively change disease evolution. In this way, instead of trying to kill cancer cells, therapies should aim at changing delta and beta allowing the normal cells of the body to out-compete and eliminate the malignant cancer cells.

The applications are many, but most importantly, the research gives us a new paradigm to look into disease (including cancer) and its treatment. Current approaches to disease imply, most of the time, a generalised "attack" on what is, by large, a black box of unknown mechanisms. This new approach provides a mathematical anatomy of disease that converts complex biochemical interactions into cell fitness, which ultimately affects the populations' frequency. In this way the model not only helps to explain how things works but by giving us beta and delta provides us with an effective way of controlling disease evolution.

In practical terms, Dingli and Pacheco's work tells us where we should invest resources in order to control, not only MM, but also cancer in general; the answer is in drugs capable of diminishing the fitness of the malignant cells. These have the additional advantage of working by allowing the body to restore its own balance, a much more natural and less toxic approach to treat illness. This is especially important in cases like cancer, where current treatments can be life-threatening. The fact that the model applies to any number of diseases where different populations of cells interact is an added bonus.

The work here described for now remains on the scope of trying to change delta and beta directions but, once science is capable of determine their real values, Dingli and colleagues’ research is, ultimately, the first step for what Pacheco calls "the holy grail of medicine" - personalised therapy.

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