New possibilities for the treatment of breast cancer arise, with the help of mathematics

March 16 2015

A means of reprogramming a flawed immune response into an efficient anti-tumoral one was brought to light by the results of a translational trial relating to breast cancer. Thanks to the innovative combination of mathematical modelisation and experimentation, only 20 tests were necessary, whereas traditional experimentation would have required 596 tests to obtain the same results.

The study was jointly conducted by Doctor Marie-Agnès Doucey (Experimental oncology, Centre Ludwig de l'UNIL pour la recherche sur le cancer), Professor Ioannis Xenarios (UNIL, SIB, Vital-IT) and Professor Jean-François Delaloye (Breast care center-CHUV, UNIL). Beyond demonstrating the continued collaboration between three of Switzerland's leading scientific institutions, the trial is noteworthy for its combination of experimental oncology and modelisation. Indeed, it is the first such trial to exploit modelisation to identify efficient therapeutic approaches to be used on cells of breast cancer patients. The funding awarded by the Fond National Suisse pour la Recherche Scientifique and the publication of its results in the scientific review Plos Comp Biologie further give weight to both the validity and to the potential of its findings.

The dialogue between monocyte and tumor

Monocytes are immune cells present in the blood. They are consequently also found in tumors. In this setting, monocytes are known to promote

the development of the tumoral blood vessels (referred to as their angiogenic action) and to suppress the immune response directed at the tumor (referred to as their immunosuppressive action). As crucial as these are to the development of the tumor, the underlying mechanisms which give rise to these actions are as yet relatively unknown in the field of human cancers.

Taking an interdisciplinary view to find the weakness

The novel approach undertaken, made possible by the interdisciplinarity of a CHUV, UNIL and SIB consortium, consists in combining clinical and experimental oncology with modelisation. The result is an ability to identify these mechanisms and to block the angiogenic and immunosuppressive actions of monocytes in breast cancer.

The trial revealed that, in patients suffering from breast cancer, once blood monocytes are present in the tumor, they considerably increase their angiogenic and immunosuppressive activity. This observation indicates that the tumor has the ability to shape monocyte activities to its advantage.

The key objective of the trial was consequently to block the tumoral monocytes' angiogenic and immunosuppressive capacities. This implied identifying the molecular mechanisms behind this activity. Bearing in mind the scarcity of monocytes within a tumor and the generally small size of tumor samples, the challenge was considerable. It is against such a backdrop that the innovative combination of mathematical modelisation and experimentation demonstrated its strengths.

Blocking the signals

A Boolean model of monocyte behavior was built, based on

experimental data. This model was then drawn on to predict which type of treatments would be able to interfere with these monocyte activities. The predictions were tested via experimentation on tumoral monocytes from patients and one double-treatment was earmarked as being extremely efficient. The treatment inhibits the signaling pathways linked to the kinase receptors TIE-2 and VEGFR which act in synergy to control the angiogenic and immunosuppressive actions of tumoral monocytes.

Advantages and discoveries

The advantages of this approach are two-fold: the modelisation is able to frame the experimentation, and new treatments can be discovered through optimum use of resources and patient samples. By way of comparison, traditional experimentation would have required 596 tests to obtain the same results, whereas only 20 tests were necessary with this new approach.

The trial led to a further trail of discovery. The tumoral monocytes are highly adaptable; as a result of the double treatment they transform themselves into cells capable of giving rise to an immune response directed against the tumor. The results underline that tumoral monocytes represent a new treatment target and suggest that this double treatment could contribute to an immunotherapy approach in the treatment of breast cancer.

Provided by Swiss Institute of Bioinformatics