

THE CELL DOOR

Lluís Mir – A tumour cell has only one goal in life... to divide. Otherwise, it isn't a tumour! Electro-chemotherapy is a way of targeting a drug - it opens the door of the cell to the drug. It isn't a form of tissue removal, bearing in mind that all the other physical approaches, be they X-rays, radiotherapy, cold, heat or ultrasound are physical effects that kill. And as they do, they cannot discriminate between tumour cells and normal ones.

Someone sent me an article where electric shocks were used that left the cell-wall permeable for a certain time so that things could pass through it. That made me try to do better and with a first student, practically all the cells survived the electric impulse and were made permeable. With another student, we did a pile of tests and there remained one last molecule to test, bleomycin, which is an anti-cancer drug that isn't brilliant because it isn't very efficient. He did his thing and all the cells subjected to electric shocks were killed by this agent! OK, we tried again, we checked and indeed there is ten thousand times more activity if the cell is made permeable than if left alone.

So there you have it, a story that has developed over time, my last ten years were spent trying to understand what these electric shocks really do in the membrane of cells because they affect practically nothing but the membrane. The inside of the cell is a conductor, the outside is a conductor but the membrane is an insulator. So with the electric shock, we charge the membrane and beyond a certain value, water begins to penetrate the membrane because the dipoles of water line up with one another, the fats of the membrane begin to oxidise and the membrane becomes permeable, and all this with ultrashort pulses! In clinic it is 8 pulses of 100 microseconds so the treatment lasts less than 1 millisecond, yet the cells stay open for more than 5 minutes...

Basically, this bleomycin is injected into the body by systemic routes. It goes everywhere but since it isn't effective due to the feebleness of the dose, there are no side effects. Where we apply electric shocks, the normal and tumorous cells will be made permeable, the bleomycin will certainly enter both types of cell but afterwards, this bleomycin makes a few cuts of the cell DNA in a random and not too extensive manner and it is because of that that the normal cell can keep on living since none of its genes are going to be altered. At least, none of its essential genes. And only the cells that want to divide will die because their chromosomes are broken. So they cannot separate easily and hence the cell initiates its own death because it is not managing to make two daughter cells: we call this mitotic death. So at that point we see that, well, it's extraordinary, if we render things permeable then this agent becomes lethal.

Next stop is an anticancer centre like Gustave Roussy that has mouse models with tumours and from the first attempt, mice cured by the combination of bleomycin with electric shocks. I therefore called this treatment electro-chemotherapy and not long after we passed through the in-house ethics committee etc. Trials in humans: with the first patient we were allowed to treat only one nodule even though he had five around his neck. The treated nodule disappeared after a week and he was the one who asked us to treat the others!

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