INTERFERing: the immune responses helping cancer cells resist treatment

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Cancer treatments like chemotherapy and radiotherapy generally work by causing damage to the DNA of cancer cells. Unfortunately, cancer cells can become resistant to this DNA damage and therefore resistant to the treatments. Recent collaborative research in the WIMM between labs in the Department of Oncology and the MRC Human Immunology Unit sheds light on this process, revealing new markers of treatment resistance in patients and potential future drug targets. Layal Liverpool explains more.

DNA is quite literally the stuff of life and so it is unsurprising that our cells invest a lot of resources into looking after it. Our DNA can be damaged by various environmental factors such as UV light, ionising radiation or chemicals. Fortunately, our cells have evolved an extensive network of proteins that can sense DNA damage and activate repair processes.

Another threat faced by our cells is infection. A similar network of proteins can sense DNA from invading microbes and activate potent immune responses. These proteins are called innate immune DNA sensors, and the responses they activate form our cells' first-line of defence against invaders like viruses and bacteria.

These innate immune responses are like a fire alarm. They alert the cell to unwanted intruders, so that it can prepare to fight back. However, whereas a false alarm is merely annoying in the case of a fire, a false alarm in our cells can actually be harmful. When activated in the absence of an infection, these immune responses can cause damage to our healthy cells.

In fact, this is exactly what happens in people with certain auto-immune or auto-inflammatory diseases, for example lupus. Understanding how our cells tell the difference between our own DNA and DNA coming from foreign invaders could give insights relevant not only to infectious diseases, but also to auto-inflammatory diseases where this system has clearly gone wrong.

One way that our cells can tell the difference is based on where in the cell the DNA actually is. Our own DNA is usually stored away safely in the nucleus – the control centre of the cell – whereas DNA from invading microbes tends to be present outside of the nucleus, in the cell cytoplasm. By keeping the innate immune DNA sensors away from the nucleus, our cells keep our own DNA safe from detection, while still allowing these sensors to trigger alarms when they spot DNA from intruders.

One scenario where DNA becomes damaged is in cancer cells, as a result of chemo- or radiotherapy. In this case, the DNA damage is a good thing because, left unrepaired, it kills the cancer cells. A big problem is that cancer cells can become resistant to these treatments by activating DNA damage repair proteins, which fix the damaged DNA, allowing the cancer cells to survive.

Researchers have recently found that there is an overlap between the DNA damage sensing and innate immune DNA sensing systems in our cells. This turns out to be critical in understanding patient responsiveness to cancer treatment. In the study, which

was a collaboration in the WIMM between the labs of Peter McHugh and Adrian Harris, in the Department of Oncology, and Jan Rehwinkel, in the MRC Human Immunology Unit, the overlap between DNA damage repair and innate immune DNA sensing was explored in cancer.

The team discovered important new roles for two proteins involved in this DNA repair process – one of which unravels DNA (BLM) and another that trims it (EXO1). This unravelling and trimming that occurs during DNA repair, leads to the production of small pieces of DNA.

It turns out that these small pieces of DNA occasionally leak out of the nucleus and into the cytoplasm, where they can activate innate immune DNA sensors. This is not good news, because the resulting immune responses activated, including the production of an anti-viral molecule called interferon, is associated with higher levels of treatment resistance in breast cancer.

They also identified the involvement of another protein, whose job it is to keep the cell cytoplasm free of this escaped DNA from the nucleus. Similarly to their other findings, higher levels of this protein, called TREX1, were associated with reduced resistance to radiation in cancer cells. This is because TREX1 usually sweeps away any escaped nuclear DNA before it can activate innate immune responses, which are associated with treatment resistance.

The study not only highlights key markers for predicting treatment resistance in cancer, but also identifies BLM and EXO1 as potential targets for new anti-cancer therapeutics. In future, it will be interesting to understand precisely how innate immune responses, and interferon in particular, contribute to DNA damage resistance in cancer cells. Their findings also reaffirm the link between the DNA damage repair pathways and innate immune DNA sensing pathways in cells, which is relevant to our understanding of infectious and auto-inflammatory diseases as well as cancer.

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