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FIRST PERSON

First person – Ateequllah Hayat

First Person is a series of interviews with the first authors of a selection of papers published in Disease Models & Mechanisms, helping researchers promote themselves alongside their papers. Ateequllah Hayat is first author on 'Low HER2 expression in normal breast epithelium enables dedifferentiation and malignant transformation via chromatin opening', published in DMM. Ateequllah conducted the research described in this article while a PhD student in Gabriella Ficz's lab at Queen Mary University of London, London, UK, and is now a lecturer in drug development at St George's, University of London, London, UK, investigating transcriptomic/epigenomic changes in cancer resistance.

Ateequllah Hayat

How would you explain the main findings of your paper to non-scientific family and friends?

HER2 is a protein that is abnormally expressed in about 25% of breast cancers, which makes the cancer more aggressive. We developed a biological system to understand the very early abnormal changes just hours and days after HER2 protein is turned on. We thought that a model that allows us to investigate changes that occur at the very onset of cancer is extremely useful as we can identify and target cancer at the earliest stage before it can spread to other parts of the body. Our research shows that the chromatin, which houses our DNA and proteins, becomes open and loose immediately (just 30 min!) after HER2 protein is turned on. We think this may be one of the mechanisms by which this cancer gains its transformative drive. These cells on their journey to becoming cancerous also gain stemness. Stem cells are the body's raw material – cells from which all other cells are specialized. The stem cells upon HER2 protein expression in breast cancer may be the main target cells for becoming cancerous and thereby contributing to the more aggressive nature of cancer.

"Our research shows that the chromatin, which houses our DNA and proteins, becomes open and loose immediately (just 30 min!) after HER2 protein is turned on."

What are the potential implications of these results for your field of research?

Generally, the higher the HER2 protein expression, the more aggressive the disease is, with concomitant high tumour grade. However, in some patients, even low HER2 protein levels can induce highly aggressive disease that is associated with worse disease outcome. We paradoxically found that indeed our model confirms this, as the cells with low HER2 protein levels induced more changes that were cancer-like compared to those cells with high HER2 protein expression. We also outlined several mechanisms as stated above that may be responsible for this aggressive behaviour. This provides a novel platform for drug discovery to target this subtype of breast cancer, with potential implications for how this disease is clinically diagnosed based on HER2 protein expression.

What are the main advantages and drawbacks of the experimental system you have used as it relates to the disease you are investigating?

The advantages of this experimental system were that we were able to capture abnormal changes just minutes after HER2 protein was turned on and at strikingly high resolution. The system is simple and cost effective, yet provides a robust setting that can be replicated in more physiologically relevant models to humans to understand the changes at a system/organism level rather than a specific type of cell, which we employed in our research.

What has surprised you the most while conducting your research?

It was surprising that some of our findings were counterintuitive to what we would have expected in our original hypothesis. For example, we found the low HER2 protein induced the most cancer-like changes; this is unlike what most other research has shown.

What do you think is the most significant challenge impacting your research at this time and how will this be addressed over the next 10 years?

The most significant challenge of this specific research is to be able to perform this research in *in vivo* models (such as mice and/or other

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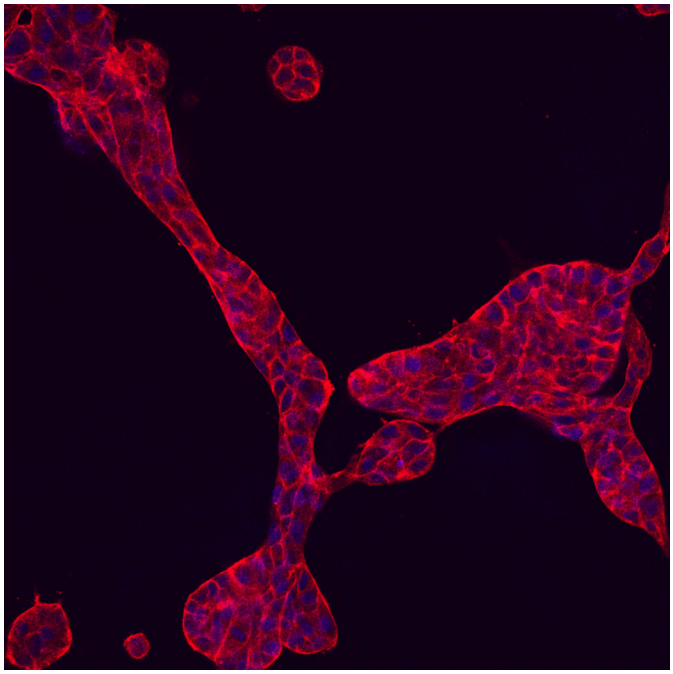

Cancer cells with HER2 protein expression budding into the surrounding matrix.

animals). The model could then be used to screen for various pharmacological inhibitors to identify improved treatments. Broadly speaking, we currently have developed relatively effective therapies against breast cancer. However, most patients develop resistance to even the most impactful therapies. I think that the rise in personalised medicine and our ability to view our genome and epigenome at incredible resolution – each DNA letter at a time – will allow us to develop more effective therapies to target cancer resistance.

What changes do you think could improve the professional lives of scientists?

I think that, as a scientist, it is critical to have a great supervisor. I have been very lucky to have some great mentors including my PhD supervisor (Dr Gabriella Ficz), under whom I performed this research. Scientists should choose a mentor who will be deeply committed to their career, someone who could continue to advise and support them well after their time working together. I think scientists should also be taught the art of making grant applications, reviewing manuscripts, and getting some time off their lab work to learn high-level data analytical skills.

What's next for you?

This project has further triggered my interest in transcriptomics/epigenomics and how cells acquire resistance. What happens to the chromatin dynamics as cells become resistant to certain therapies? What are the chromatin-related changes responsible for cancer resistance? Are there multiple pathways or do they all take a particular route to resistance? Could we identify cells that are undergoing treatment but are pre-resistant and stop them from becoming resistant? These are just some of the questions I have. I hope to be performing experiments and providing answers to these questions.

Reference

Hayat, A., Carter, E. P., King, H. W., Ors, A., Doe, A., Teijeiro, S. A., Charrot, S., Godinho, S., Cutillas, P., Mohammed, H. et al. (2023). Low HER2 expression in normal breast epithelium enables dedifferentiation and malignant transformation via chromatin opening. *Dis. Model. Mech.* **16**, dmm049894. doi:10.1242/dmm.049894