DUO FINDS PATHWAY THROUGH SIGNALLING MAZE

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Their two worlds may be separated by an immense divide – yet physicist Hauke Busch and medical biologist Melanie Börries have found a common language combining theory and experimental science. Working as equal leaders of their FRIAS lab, the pair are a model for the historic scientific developments of the past ten years that have led to the emergence of modern systems biology. Their FRIAS project literally goes under the skin by asking how different cell types communicate with one another in this the largest of human organs. Cell communication is a complex, highly dynamic process involving cell division, proliferation, differentiation and cell migration. And it is one that can sometimes go wrong, leading, for example, to the development of skin cancer. “We use theoretical and cell biology methods to close the gap between the molecule and the system,” states Busch, who initiated the project in 2008 as a Junior Fellow of the School of Life Sciences – LifeNet.

The big question posed by systems biologists today is: how is the great made from the small and the small from the great? “On the one hand, cell communication takes place at the level of individual signalling molecules, which are exchanged between cells and trigger complex genetic programmes within neighbouring cells,” explains Börries. Melanie Börries, a medical doctor and cell biologist who gained experience in experimental cardiology at the Institut für Strukturbiologie at Biozentrum Basel between 2001 and 2005, has been working at FRIAS since 2009 – first as a postdoc and then as a Principal Investigator. “This causes cells to divide, differentiate themselves into specialised cell types, migrate or die.” On the other hand, these processes – as can be observed under a microscope – have an effect on the signalling molecules, as cells constantly send information to neighbouring cells about what they are currently doing, allowing these neighbours to respond.

“These complex systems organise themselves at every level – from individual molecules to large tissues,” says Busch. Using mathematical methods, a good theorist is able to construct models that simulate the biological processes in an organism. Busch first came into contact with this approach between 2001 and 2004 during his doctoral studies at TU Darmstadt, where biologists and physicists together attempted to understand how nerve cells function. It was here he learned that theoretical approaches can only advance research if they stay connected with the experimental work. “In order to be able to communicate with my colleagues I had to spend years teaching myself the basics of biology,” Busch declares. After obtaining his PhD, he joined the German Cancer Research Center in Heidelberg as a postdoc where he helped to establish a systems biology group.

In the FRIAS laboratory of Busch and Börries at the Center for Biological Systems Analysis (ZBSA), theory and experimental science have worked hand in hand since 2009. Busch is the official group leader and Börries the project manager, though these titles are merely administrative formalities. In reality the two researchers share joint leadership. Initially, some collaborative partners were sceptical of this structure but the duo’s potential soon won them over. Where one researcher struggles to find the right words the other feels more at home, and vice versa. However, the added value is most readily visible in the pair’s research.

Busch and Börries have spent the past three years investigating how keratinocytes and fibroblasts in the skin communicate with one another before, for example, the keratinocytes migrate to perform tasks such as healing wounds. Keratinocytes form the outermost layer of the skin, known as the epidermis, while fibroblasts sit beneath the dermis and synthesise the extracellular matrix – a molecular network that offers stability and protection to the cells within tissue. In their experimental set-up, the researchers separated the two cell types from one another and exchanged the media in which the different cell types were cultivated several times. This allowed the signalling molecules released by the fibroblasts to influence the keratinocytes and vice versa. With the aid of modern systems biology methods, the two FRIAS-based researchers were able to identify all the signalling molecules exchanged and to measure the gene activity of the cells, as well as the temporal dynamics.

This enabled them to uncover the sequence of steps within the cell communication process: the keratinocytes are evidently the first to send a molecular message to the fibroblasts. They in turn send messengers back, and only then do the keratinocytes migrate. The discovery of this seemingly simple model was preceded by both sophisticated lab work and complicated theoretical work. This is because systems biology experiments supply a veritable maze of data points. The researchers measure the activity of approximately 15,000 genes and hundreds of transmitters at any one time. Each of these processes runs on a different time-scale. The first molecular changes may occur within seconds, while processes such as cell division or migration usually take hours or days.

The really ingenious part to the team’s theoretical interpretation of the data is therefore Busch’s approach of only taking into account the specific time-scale relevant to the biological process under observation within each model. For example,

if the process is cell migration, the molecular changes that occur within hours are relevant. “The quicker molecular processes then become the focus of attention in a second step,” explains Börries – the small to the great and back again. As its next project, the research duo wants to listen in to communication in cancerous skin tissue, working again in a collaboration that draws on the effective exchange between experimental practice and theory. As of 2013, the two researchers will continue their work at the Institute of Molecular Medicine and Cell Research in Freiburg and the German Cancer Research Center in Heidelberg. *(mn)*