MESI-STRAT

Systems Medicine of Metabolic-Signaling networks -
A New Concept for Breast Cancer Patient Stratification

Newsletter No 4 – December 2020

At the end of this extraordinary year, we would like to look back not only on the challenges, but especially on our successes: Numerous results of our project have been published in renowned journals. We would like to present one of these publications, which opens up the possibility of improving cancer immunotherapies.
This year, all of us had to get used to an increasing number of video conferences and to communication taking place without direct personal contact. We successfully held three meetings of our consortium online and participated in the Austrian Digital Long Night of Research.
Of course, we would also like to continue the presentation of our PhD students and PostDocs, this time it is the turn of Dr. Alexander Martin Heberle from the University of Innsbruck.

A metabolic enzyme as a new starting point for immunotherapies in cancer

Scientists of the MESI-STRAT consortium around Christiane Opitz from the German Cancer Research Center (DKFZ), together with partners, for instance, from the Berlin Institute of Health have identified an enzyme that opens up new possibilities for cancer therapies. The results were published in the scientific journal Cell.

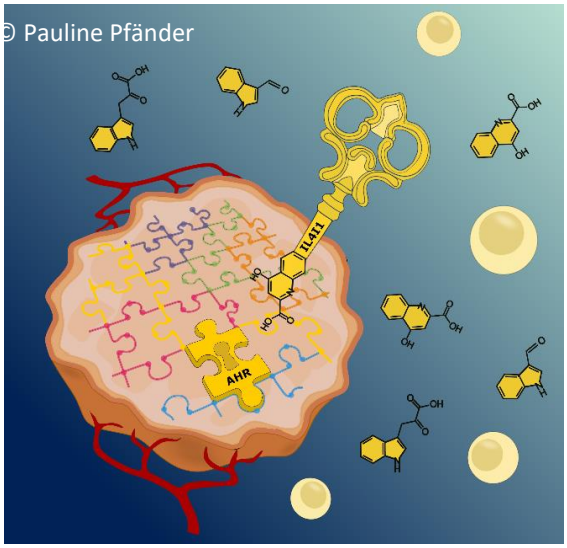
Immunotherapies activate the body's immune response against tumours and are currently revolutionising cancer therapy. Despite groundbreaking successes only a few patients benefit from the drugs currently available and tumours escape the immune system too often. The mechanisms behind this are still unclear. Understanding them may provide important clues for the development of new immunotherapy concepts.

The aryl hydrocarbon receptor (AHR) is also known as the dioxin receptor because it mediates the toxic effect of dioxins. However, not only toxins but also the body's own metabolic products can activate the receptor. One example are the degradation products of the amino acid tryptophan, which is a building block of proteins that we take in with food. In tumours, these metabolic products promote the mobility of tumour cells and weaken the immune response.

The metabolic pathways from which the degradation products arise have not been sufficiently investigated. Therefore, the scientists analysed which tryptophan-degrading enzymes are associated with an activation of the dioxin receptor in 32 different tumour types.

One molecule in particular caught their attention: the enzyme IL4I1. No other enzyme of the tryptophan metabolism was so strongly linked to the activation of the dioxin receptor. The degradation products (metabolites) formed by IL4I1 activate the dioxin receptor, which subsequently leads to a suppression of immune cells.

It was shown that in mice, which do not produce IL4I1 in the tumour environment due to genetic changes, the immune system is significantly more successful in preventing cancer progression.



"IL4I1 has great potential as a drug target. So far, substances that inhibit enzymes of the tryptophan metabolism have failed in clinical trials because the tumours did not respond to them. This could be because the role of IL4I1 has been disregarded and it has not yet been tested as a target molecule," explains Christiane Opitz.

The publication is available open access: Link to the publication

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Dr. Alexander Martin Heberle, PhD

Postdoctoral Researcher, University of Innsbruck, Austria

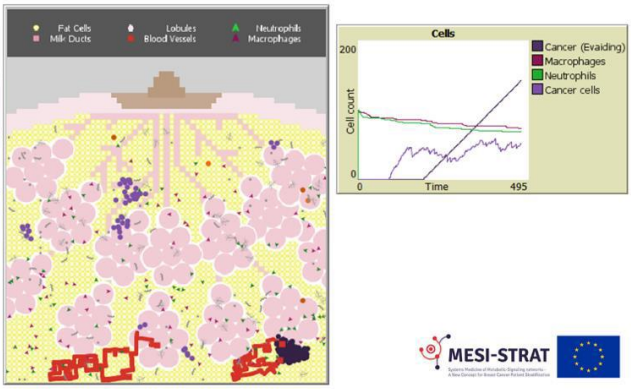
Already as a child, I had a keen curiosity for living organisms. While my parents were less happy to remove living earthworms or blindworms from my pockets, I was convinced that being a scientist in zoology was my future dream job.

In 2007, still guided by this dream, I started my Biology studies in Freiburg where I ambitiously learned how to identify and classify plants and animals. I quickly realized that biology was about more than only about Schmeil-Fitschen and Kükenthal, and my interests shifted towards the molecular mechanisms of life. Thus, I changed my focus to developmental biology and worked with various organisms including *Danio rerio* (zebrafish), *Caenorhabditis elegans* (a nematode), and chicken in order to study multi-cellular arrangement, cellular signalling and organismal development. I am still fascinated by this topic; however, I have further expanded my research focus to the study of cellular signalling in the context of cancer. With a thesis on this topic, I obtained my diploma degree from the University of Freiburg in 2014. The same year, I joined the group of Prof. Kathrin Thedieck as a PhD student at the University Medical Center in Groningen (UMCG, the Netherlands) to elucidate mTOR signalling under stress conditions in cancer cells. Complex signalling networks, intertwined signalling pathways, cellular localizations of protein complexes and molecular mechanisms have become part of my daily life. The more complex the interconnections, the more fun I have. In addition to my direct training in biochemistry and molecular biology, several collaborations and joined projects have helped me to gain insights into systems approaches and oncology. Therefore, I was very happy to join the MESI-STRAT project after my PhD, in order to unravel oncogenic signalling and breast cancer metabolism in regard to endocrine therapy. In 2019, I moved to Innsbruck and ever since, I have been closely involved with the MESI-STRAT consortium. I am proud of being a part of this collaborative effort to define a new concept of breast cancer patient stratification.

The MESI-STRAT NETLOGO application

Like so many other activities this year the Austrian Night of Science was organised as an online event. The University of Innsbruck participated together with the University of Newcastle with a livestream about the MESI-STRAT NETLOGO application. This interactive computational application developed by our partners in Newcastle aims to inform on aspects of the biology of breast cancer and different treatment strategies.

The model includes six different cell types (fat cells, milk ducts, lobules, blood vessels, immune cells, and cancer cells) and simulates their behaviour, growth and interactions under different treatments. Users can adjust the drugs, their doses and the interval they are administered and learn how they may influence tumour growth. Importantly the model is updated as new knowledge becomes available and every simulation run will also contribute to this knowledge.



Screenshot of NETLOGO MESI-STRAT breast cancer simulation

More than 30 people watched our livestream and gave us very positive and valuable input which we will use to further develop the app for educational purposes. If you are interested, a recording of our live stream and many other presentations of the Science Night are still available online here, until the end of 2020.

Visit www.mesi-strat.eu to learn more about our consortium and follow us on twitter @MesiStrat for the latest news of our project!

If you haven not done so yet, please subscribe to receive our newsletter twice a year.

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