

THE AUTHOR FILE

Koraljka Husnjak

A “simple but a bit crazy idea” to tag ubiquitin and practice multilingual, multidisciplinary proteomics.

“Phosphorylation gone wild,” says Koraljka Husnjak, a researcher at Goethe University Medical School



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Koraljka Husnjak

in Frankfurt; that’s how ubiquitination is sometimes described. Both phosphorylation and ubiquitination are ways that proteins can be modified post-translationally, and both can lead to many types of activity in the cell. The cell ‘reads’ the modification and converts it into a function. When ubiquitin attaches to

a protein, the cell might read, “Please degrade me; I am ubiquitinated and ready to leave,” she says. Other possible messages are “Please perform DNA repair” or “Immune response, now!”

Ubiquitination can involve one molecule, a chain of several linked molecules, even branched structures. In each case, the process involves a lysine in a target protein and cellular decision-making that ensues upon protein attachment. The challenge has been that existing modes of studying linear ubiquitination do not work well, says Husnjak. With this specific ubiquitin chain that she studies, the N terminus and C terminus of ubiquitin have to be ‘free’ for a linear chain to form, which means that adding a tag at the N terminus and enriching with tag-specific antibodies won’t work. And other methods fail, too. As a solution, she had a “simple but a bit crazy idea” that she and her team have now published.

The researchers tagged ubiquitin internally: the tag is essentially a hook that hangs off of the ubiquitin molecule. The hook is placed so that it does not interfere with either formation of the ubiquitin chain or binding to ubiquitin receptors. When the time comes for linear ubiquitination, this internally tagged ubiquitin is integrated into the emerging linear chain along with regular ubiquitin in the cell. When the cells are then lysed, the ubiquitin ‘hooks’ are captured by affinity resins, and a mass spectrometer can detect these modified proteins.

Linear ubiquitination, the enzymes regulating it, and a few of the substrates involved with the process have been implicated in inflammation, T cell development, Parkinson’s disease and response to pathogens.

Husnjak and her team have identified new targets of linear ubiquitination. Their paper is a resource with interesting targets to functionally validate, she says. The researchers have started new collaborations to explore the biology behind linear ubiquitination and its broad biomedical influence. The new method will hopefully help labs identify more substrates related to this type of ubiquitination, and perhaps find new signaling pathways and, possibly, new drug targets, she says.

Husnjak describes herself as a molecular biologist who does biochemistry and who “pretends to know a bit of chemistry and structural biology.” The new paper is a group effort and, she says, multidisciplinary collaboration is key for investigating the types of biological questions and cellular processes related to diseases such as cancer that she pursues.

After finishing her PhD in molecular biology at the University of Zagreb, Husnjak completed a postdoctoral fellowship at Goethe University Medical School in Frankfurt, working with Ivan Đikić, and became a principal investigator there in 2010. Her parents and siblings live in Croatia, and she enjoys visiting them and her friends. She also has scientific collaborators in Croatia and says, “I find keeping connections with Croatian science very important.”

In the lab, she and Đikić, who is also Croatian, speak English as their common language, except in conversations about informal matters, when they speak Croatian. She speaks German with many of her colleagues. Her connections in Germany and around the world are helping her explore new professional opportunities. Her mother comments that scientists are always traveling. Husnjak says that is not far from the truth and says she also enjoys travel and exploring new places. “I used to hike a lot in Croatia, but here not so much.”

Husnjak likes discussing new ideas with colleagues. “Sometimes we just chat over coffee and cake and end up discussing science,” she says, and that often leads to collaboration. Her colleague Stefanie Oess, a biochemist also at Goethe University Medical School, likes Husnjak’s critical, independent, creative approach to science, her experimental expertise and perseverance, and “maybe to be admired most, a clear vision of where she wants her science to go.” Husnjak developed this new method to better study questions that piqued her curiosity. To her, science is about “always searching for new things to explore.” Being a scientist, she says, is “doing fun stuff while doing something useful.”

Vivien Marx

Kliza, K. *et al.* Internally tagged ubiquitin: a tool to identify linear polyubiquitin-modified proteins by mass spectrometry. *Nat. Methods* **14**, 504–512 (2017).

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