Variety, complexity, specificity... infinitively seductive ubiquitin

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I recently returned from the 2013 EMBO Conference on 'Ubiquitin and Ubiquitin-like proteins: from structure to function', where I once again marveled at the rapid pace of discovery. From one year to the next, many people have completely new stories to tell and the spirit of the field is one of openness and collegiality. The late Cecile Pickart, a pioneer in ubiquitin research, once referred to ubiquitin as infinitively seductive. I have to agree, in more ways than one. Not only is ubiquitin involved in virtually all aspects of cell biology, but the community goes about its business in a very positive and welcoming manner; an approach not always seen in other areas of the biomedical sciences.

Given the rate at which new knowledge is acquired, and seeing the wealth of primary research published, we were inspired last year to put together a Review Series on 'Ubiquitylation: mechanism and functions'. Some aspects of the latest research were not included—such as the role of ubiquitin in DNA repair, and the roles and regulation of deubiquitylating enzymes (DUBs)—as excellent recent reviews are already available, but we have captured much of what is exciting in this remarkable field. In the first review of the series, which we published this past December, Wade Harper and colleagues analyze how Cullin-RING E3 ubiquitin ligases (CRLs) are dynamically controlled, with an emphasis on neddylation cycles and substrate receptor exchange. In this issue of *EMBO reports*, Henning Walczak and colleagues provide a comprehensive overview of the role of ubiquitin in the innate immune system and autoimmunity. Future issues will include an analysis of the mechanism of action of RING-between-RING (RBR) E3 ligases from Judith Smit and Titia Sixma, and a review from Anna Plechanovová and Ron Hay on recent structural work that has revealed how ubiquitin is activated, how it is transferred onto the E2 and from E2s onto both HECT E3 ligases and

substrates. From a functional viewpoint, Mafalda Escobar-Henriques and Thomas Langer will assess the role of ubiquitin in mitochondrial dynamics, quality control and response to pathogens, and Ioannis Aifantis and colleagues will write about the role of ubiquitin in stem cells.

Most of the senior authors of the Reviews included in this series, as well as two of our Editorial Board members—Ivan Dikic and Micha Rape—gathered at the recent EMBO ubiquitin meeting. I therefore had the pleasure of interviewing them for an article that we also include in this issue. The excerpts of the stimulating conversations I had with them give a flavor of the most important recent developments in the field, what their labs are working on, the translational applications coming from ubiquitin research, and their impressions of working in the field. Particularly striking, given their different research backgrounds, is that all seven interviewees generally agreed that the most important concept stemming from recent research is the realization of the complexity and selectivity in the ubiquitin system, as well as the multitude of outcomes of ubiquitylation. Indeed, efforts are now focused on understanding the ubiquitylation cascade and the specificity of the enzymes for particular ubiquitin linkages, as well as for specific acceptor lysines. Mixed chains are also gaining recognition as new molecular signals. There is clearly a lot of work to be done to decipher the ubiquitin code and its biological significance, which is why the field is so open to newcomers with new ideas.

The ubiquitin field seems to be ever expanding. Each major discovery opens up new avenues for exploration from numerous angles—biochemistry and structural biology, molecular and cell biology, systems levels proteomics analyses, physiology,...—and the field benefits from the synergy between people with different backgrounds and expertise, who aim to understand the same

questions. This rapidly generates an understanding of many pathways that ubiquitin regulates or of how ubiquitylation is itself catalyzed, that goes from identifying a phenotype and the molecules involved, to an almost atomic-level understanding of the mechanisms at play. Such a sophisticated level of insight suggests that translation into therapeutic approaches is possible in the mid-term. It is now clear, for example, that compounds that modulate the activity of specific E3 ligases could have therapeutic value in diseases such as cancer, inflammation and autoimmune disorders, neurodegenerative diseases and even some infectious diseases. Notably, ubiquitylation regulates autophagy—another proteolytic pathway that is often dysregulated in disease—at multiple levels. Ubiquitin controls the stability of several components of the autophagy machinery and marks certain autophagy cargo—such as protein aggregates or incoming bacteria—for recognition by specific receptors that recruit it to the phagophore. Thus, modulation of the relevant E3 ligases would allow control over the amount of degradation and provide a therapeutic benefit.

Ubiquitin and the ubiquitin proteasome system have been recently linked to the regulation of pluripotency in stem cells, as Ioannis Aifantis and colleagues will discuss in this review series. Indeed, research in the ubiquitin field seems to be moving into more physiologically relevant models, and using induced pluripotent stem cells and controlled differentiation systems is a big part of that, as reflected in the interview.

We hope the reviews included in this *EMBO reports* series help our readers understand the complexity and functions of the ubiquitin system. With potential translational applications not far down the road, the future of the field is exciting indeed!

DOI 10.1002/embr.201338243