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Editorial

Special Issue: E3 ubiquitin ligases, the match makers and grim reapers of immune cells

Ubiquitylation regulates the levels and/or activity of virtually every protein in the cell, and thus plays an essential role in cell fate and function. Immune cells are no exception. Dysregulation of ubiquitin networks in many types of immune cells impairs immune function, leading to cancer, autoimmunity, and compromised pathogen defense. Over the past decade, many ubiquitin enzymes have been identified and categorized based on common structural features or conserved domains. Additionally, major advances have been made in detailing the biochemical properties of enzymatic function, and in defining ubiquitin chain diversity and topology. However, while over 700 ubiquitin pathway enzymes are encoded in the mammalian genome, only a fraction of those have thus far been linked to immune function, suggesting that our understanding of how ubiquitin regulates immunity is only beginning to be resolved. In this special edition of *Cellular Immunology*, we explore how ubiquitin pathway enzymes control immune cell function, disease susceptibility, and cancer.

Enzymes in the ubiquitin pathway are categorized into E1 ubiquitin activating enzymes, E2 ubiquitin conjugating enzymes, E3 ubiquitin ligases, and deubiquitylating enzymes (DUBs). E3 ubiquitin ligases catalyze or aid the transfer of ubiquitin onto substrate proteins, while DUBs are proteases that cleave ubiquitin from substrates. E3 ubiquitin ligases are subcategorized based on whether they are enzymatically inactive RING ligases, or enzymatically active HECT, or RING between RING (RBR), ligases. In contrast, DUBs are subcategorized based on their method of proteolysis. Of note, the enzyme A20, defies these classes and contains both E3 ubiquitin ligase and DUB activity [1]. Together, the enzymatic activity of E3 ligases and DUBs results in a highly complex ubiquitin network that controls cellular function by dynamic post-translational regulation of protein levels, location, and function.

Ubiquitin pathways regulate many aspects of immune cell development [2], host defense [3], and immune cell transformation [4]. Ubiquitylation promotes the degradation of key signaling intermediates to limit inflammatory signaling [1,5,6], and drives the degradation of transcription factors that control cell fate [2,7]. While much of what we know about ubiquitylation has focused on its ability to drive substrate degradation, we now know that the linkages of ubiquitin chains encode a degradative versus non-degradative outcome, and non-degradative consequences of ubiquitylation appear to be prominent in immune cells [8]. Nevertheless, with some exceptions, our understanding of how ubiquitin enzymes direct the formation of particular types of chains on their substrates to direct protein fate and ultimately impact biology is only beginning to be resolved. Furthermore, we have yet to understand how seemingly divergent pathways intersect through the concerted efforts of the enzymes involved.

While many questions remain, over the past decade, we have made major advances in understanding individual enzymes and the pathways they regulate. The review articles assembled here highlight the most recent advances in the understanding of ubiquitin in the immune system, including the function of newly identified ligases, ubiquitin linkages and chain types, and updates on some of the most well-characterized ligases, which serve as archetypes for how molecular regulation of protein ubiquitylation controls immune cell function and disease outcomes. We hope that this collection of reviews will inspire the reader to learn more about the central importance of the ubiquitin system in immunology.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cellimm.2019.103924.

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