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Editorial

Complement: More than killing

"If you do not expect the unexpected you will not find it, for it is not to be reached by search or trail"—Heraclitus of Ephesus (535–475 BC)

More than a century after *Jules Bordet's* seminal observations introduced complement as a discrete entity in immunology and *Paul Ehrlich's* assignment of the term 'complement', our understanding of this innate immune system has been profoundly reshaped. Indeed, through an unprecedented surge of novel findings and associations, it has become irrefutably evident that the term 'complement' does not pay full tribute to the versatility of this intricate innate immune system, falling short of its expanding role as a gatekeeper of immune homeostasis.

Indeed, over the last two decades, the historical perception of complement as a 'helping hand' for antibody-mediated opsonophagocytosis and pathogen clearance has been drastically challenged by mounting evidence that points to novel and unexpected functions that largely exceed the defensive role of this system. Complement is now recognized as an elaborate network of soluble or surface-bound effector proteins and regulators that patrol our circulation, sense danger signals, safeguard host tissues from microbial intruders and autologous activation, and regulate other immune and non-immune systems through crosstalk interactions. In this regard, complement is now known to be involved in a wide range of biological processes, including the tailoring of adaptive immune responses, T*reg* development, transplantation tolerance, lipid metabolism, tumorigenesis, tissue regeneration and homeostasis, stem cell biology and progenitor cell modulation. It is not surprising therefore that complement dysfunction has been associated with an expanding list of infectious, inflammatory, and degenerative pathologies.

In resonance with this emerging paradigm shift in immunological research, we present in this issue of *Seminars in Immunology* a series of review articles that reposition complement-modulated pathways at the crossroads of tissue homeostasis and immunosurveillance and at the center of orchestration of adaptive immune responses, embryonic development, and progenitor/stem cell biology. The selected reviews discuss critical insights and perspectives of the emerging crosstalk of complement with a plethora of signaling pathways and cellular networks. This highly interactive, complement-driven molecular circuitry appears to modulate fine developmental processes, complex and dynamic morphogenetic programs, as well as tissue-regenerative and repair processes that bear the mark of local inflammation. Furthermore, the fine-tuning role of distinct complement fragments and downstream signaling pathways is discussed at the interface of innate and adaptive immune responses and potential implications for therapeutic intervention in the context of human pathophysiology are also highlighted.

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