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Atherosclerosis is a chronic inflammatory disease of the arteries that can lead to thrombosis, infarction and stroke, underlying the first cause of mortality worldwide. Adaptive immunity plays critical roles in atherosclerosis, and numerous studies have ascribed both atheroprotective and atherogenic functions to specific subsets of T and B cells. However, less is known on how antigen specificity determines the protective or adverse outcome of such adaptive responses. Understanding antigen triggers in atherosclerosis is crucial to delve deeper into mechanisms of disease initiation and progression and to implement specific immunotherapeutic approaches, including vaccination strategies. Here we review the role of adaptive immunity in atherosclerosis and the insights that single-cell technology has provided into the function of distinct immune cell subsets. We outline the most relevant atherosclerosis antigens and antibodies reported to date and examine their immunotherapeutic potential. Finally, we review the most promising vaccination-based clinical trials targeting the adaptive immune system.