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Sommario/riassunto

Inflammation is a fundamental protective mechanism and at the same time the driving force of a variety of major diseases in humans. Indeed, acute self-resolving inflammation usually plays a positive role for the host, as exemplified by infectious diseases where its positive role is well established and testified by its perception as innate immunity. On the other hand, non-resolving inflammation and consequent chronicization is a key determinant of immunopathology and clinical manifestations of most major diseases in humans. As a consequence, it is increasing appreciated that the problem with inflammation is not how often it starts, but how often it fails to resolve. Appropriate resolution of inflammatory responses, which also drives activation of tissue damage repair mechanisms and return of local tissues to homeostasis, is a necessary process for ongoing health. Interestingly, cells sustaining these processes are also key to the proinflammatory responses, and the underlying “pro-resolving” molecular pathways are triggered as part of the pro-inflammatory response. This clearly indicates resolution of inflammation as an active process requiring functional repolarization of inflammatory cells that calls our attention on the underlying molecular mechanisms. The increasing number of anti-inflammatory drugs best-sellers in the pharma market is a clear indication of the relevance of having inflammation under check; nonetheless, there is still a great need for better acting pharmacological tools for the control of inflammation. Indeed, the

remarkable success of biological drugs targeting proinflammatory cytokines has indicates that tools able to block proinflammatory mediators have promising applications, but at the same time has made clear that there are intrinsic limitations to this approach which frequently vanish undermine the activity of single targeting drugs, including the well-known redundancy of inflammatory mediators. Under self-limiting conditions inflammation spontaneously resolves in an active process. Some cellular and molecular mechanisms involved in inflammation resolution have been uncovered in the recent past, and include generation of specific cytokines, apoptosis of inflammatory leukocytes, lipid mediators, macrophage repolarization and others are likely to be revealed in the next future, since loss-of-function mutations of an increasing number of genes results in the development of spontaneous inflammation in experimental animals. We argue that “pushing for“ inflammation resolution by exploiting active naturally-occurring pro-resolving processes may have significant advantages over the attempt to simply “push back” inflammation by passive blockade of proinflammatory mediators. At present the research in the field of inflammation aims at identifying and validates new molecules involved in the resolution of inflammation as a basis for the development of innovative therapeutic strategies in chronic inflammatory and autoimmune diseases. This involves the discovery of new natural or synthetic “pro-resolving” molecules from plant and animals and the investigation of endogenous inflammation “pro-resolving” mechanisms, including atypical chemokine receptors, decoy receptors, and microRNA. An extensive effort is focused on the regulation by “pro-resolving” agents on two molecular systems of key relevance in inflammation: the chemokine system, which regulates recruitment, permanence and egress of leukocyte in tissues; and the Toll Like Receptor (TLR)/IL-1R system, which is central for the activation of infiltrating leukocytes.