Mechanism-guided novel therapies for treating inflammatory diseases

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Nowadays, pharmacologic treatments of inflammatory and autoimmune diseases are largely palliative rather than curative. They result in non-specific immunosuppression, which can be associated with disruption of natural and induced immunity with significant, sometimes dramatic, adverse effects. Among the novel strategies that are under development, tools that target specific molecular pathways and cells, and more precisely modulate the immune system to restore normal tolerance mechanisms, are central. In these approaches, peptides represent a class of therapeutic drugs that display many physicochemical advantages in terms of stability, toxicity, absence of immunogenicity and unwanted side effects. Peptides, however, display some inherent weakness, in particular their poor pharmacokinetic properties. These deficiencies can be overcome by different approaches, including the design of innovative bioactive peptide analogs and their presentation *via* delivery systems (e.g., nano-carriers) that allow to protect them, to bring them to their site of action in the tissues and to release them in a controlled manner.

Among peptide therapeutics of interest, the phosphopeptide P140 is very promising for treating patients with systemic lupus, and probably more largely patients with chronic inflammatory diseases. P140/Lupuzor is currently evaluated in phase III-clinical studies worldwide. This peptide targets key elements of chaperone-mediated autophagy, which are hyperactivated in lupus. The “correcting” effect of P140 on autophagy results in a weaker signaling of autoreactive T and B cells, leading to a significant improvement of physiopathological conditions. These findings open novel avenues of therapeutic intervention in pathological conditions in which reduction of autophagy activity is desired. Promising data have been obtained in animal models mimicking Sjögren’s syndrome, Crohn’s disease, neurological autoimmune diseases and asthma. After the era of drugs classified as “disease-modifying” therapeutics, a new type of “mechanism-guided” therapies starts to emerge for treating inflammatory diseases.