Complement inhibition, an important tool in the treatment of human diseases In the perspective of nanomedicine

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Abstract

Complement system is part of our innate immune system and it is composed of more than 50 plasma proteins, circulating in their inactive forms as zymogens or proenzymes. Proteins of the complement cascade together form a key innate immune sensor that mediates immunosurveillance and tissue homeostasis by interacting with each other in a cascade like manner. The complement system is actually a very fine modulator of a lot of functions and biological processes that happen not only at the interface of innate and adaptive immunity, but it interacts with a lot of other biological pathways including the coagulation system, tissue remodelling and regeneration as well as other biological processes. It is observed that C3 and C5 proteins are specifically expressed in the regenerating zones of different organisms, starting from different species of low vertebrates (amphibians) to mammals.

There is a wide range of diseases caused by abnormal complement activation, including kidney disease like Paroxysmal Nocturnal Hemoglobinuria (PNH), Age-related Macular Degeneration (AMD), Systemic Lupus Erythematosus (SLE), etc. Convertase enzymes play a central role in complement activation by cleaving C3 and C5 and mediate nearly all complement effector functions, being so ideal targets for therapeutic complement inhibition. Targeting the complement system has been established for rare clinical disorders such as paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome and is a very promising solution to a wide group of diseases, including orphan diseases. The peptide Compstatin and the new analogs of this complement C3 inhibitor, inhibits all complement pathways. In the field of dental medicine, there is shown a very promising potential of these therapeutics to periodontal diseases and gingival inflammation. During the last years, several studies present the important role of these inhibitors in the treatment of covid-19 infection too.

Comstatin has a very good solubility profile and an exquisite plasma half-life which is quite long for peptide therapeutics and exceeds over 50 hours in plasma with favourable toxicology and safety profile. These facts and all the data from clinical studies to date in non-human primates and in first human studies on complement therapeutics are opening new perspectives for clinical application in various clinical conditions.

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