

Guest Editorial

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Complement activation-related pseudoallergy: insights into a stress reaction to nanomedicines in blood

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The term “nanomedicine” is somewhat of a paradox. Although “nano” implies something very small, nanomedicines tend to be much larger than most medicines traditionally used in pharmacotherapy. The consequence of their larger size is that they are often mistaken by the immune system as pathogenic virus, an error that often sets off a defense reaction to eliminate the benevolent “intruder”. This unwarranted defense reaction may result not only in the loss of the medicine’s beneficial effect, but also in adverse effects on the patient.

The immune reaction against intravenously applied nanomedicines may involve a rapid inflammatory-like hypersensitivity reaction, also known as infusion reaction, and/or a slow specific response manifested in antibody formation against the drug. The latter “immunogenicity” may prevent the drug from carrying out its specific and reproducible therapeutic mission, transforming it into a vaccine. Thus, immunogenicity of nanomedicines and biologicals with formation of anti-drug antibodies represents a major problem in modern pharmacotherapy. Accordingly, the phenomenon has attracted significant attention in the fields of experimental and clinical immunology and pharmacology.

In contrast, the issue of infusion hypersensitivity reactions has received much less attention to date. One possible explanation for the difference is that immunogenicity prohibits the use of nanomedicines, while acute hypersensitivity reactions are in most cases preventable and manageable, their risk is accepted by the patient and the physician. Nevertheless, a small fraction of infusion reactions are not preventable, nor manageable, and cause life threatening or even fatal reactions. Due to this, hypersensitivity reactions represent a significant safety concern, for which testing in preclinical drug development is listed among the most recent regulatory recommendations.

It has been increasingly recognized over the past 20 years that a major cause of acute infusion reactions to liposome- and micelle-based nanomedicines is their

ability to activate the complement (C) system, which is the humoral arm of nonspecific immunity. This phenomenon was named C activation-related pseudoallergy or CARPA, a term that highlights the mechanism of the reaction. CARPA has been the subject of numerous studies and reviews to date, evolving into the broader claim that it is a manifestation of the commonly known “stress” phenomenon, wherein the body responds to external and internal noxious effects with a standard pattern of physiological changes. In the case of CARPA the noxious agents are nanoparticulate drugs mimicking viruses, the reaction proceeds via the anaphylatoxin-mast cell/macrophage axis rather than the hypothalamo-pituitary-adrenal one, and the effectors are allergy mediators rather than steroid hormones.

As a reflection of growing awareness towards CARPA, the current and the 2015 July issue of the *European Journal of Nanomedicine* presents a series of reviews and research papers on CARPA, providing an unprecedented spectrum of old and new information on the subject. The topics addressed in the two issues include a historic account of how the concept developed from a problem in liposome research to the daring claim that CARPA is a universal stress reaction that may afflict most or all animals that have C in their blood; the types of reactogenic drugs and drug carrier nanosystems; the symptoms and mechanism of CARPA; the role of PIM cells; in vitro tests and animal models, especially pigs and rodents; prediction of CARPA in patients and approaches to prevention, as well as various other aspects of C activation and function. The guest editors of this two-part series strongly hope that the compilation of papers on CARPA in these freely accessible issues of the *European Journal of Nanomedicine* will significantly contribute to greater understanding of this relatively neglected subject and to its further research.

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