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Theranostic Viral Nanoparticles for Autoimmune Diseases

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Abstract

Viral Nanoparticles (VNPs) as theranostic tools are a rapidly growing aspect of these particular types of nanoparticles. Among their multiple possible applications, their contribution in the field of autoimmune diseases has recently emerged, since they can increase the sensitivity of detection of autoantibody levels significantly allowing early diagnosis, prognosis and, consequently, the development of specific therapies. Based on the promising results obtained using nanoparticles derived from Turnip Mosaic Virus (TuMV) in an animal model of Inflammatory Bowel Disease (IBD), this mini review discusses the possibilities of development of this VNP as a power tool for diagnosis in immune-mediated diseases.

Keywords: Viral nanoparticles (VNPs) • Theranostic • Autoimmunity • Autoantibody

Introduction

Theranostic VNPs (Viral Nano Particles)

An important goal of current biomedical research is to develop good theranostic tools, amenable not only for good diagnostic practices but also for providing assistance to directed therapies. Nano biotechnology has supported many of these developments over recent years, ranging from nano devices or nano materials to individual nanoparticles of a great biotechnological interest [1-6]. Within the large collection of available nanoparticles, viral nanoparticles (VNPs) offer some specific characteristics turning them as an attractive tool for biomedical-related areas, including immunology. VNPs derive from the naturally occurring nanoparticles called virions, the encapsidated form of viruses [7-10]. Thus, VNPs offer a biocompatible and biodegradable nanoparticle option since they are mostly made of proteins [11]. In addition, a large diversity of virions usable as nanoparticles exists, all the way from small icosahedral ones with diameters of few nanometers to elongated flexuous particles which can be almost one-micron long. In any case, the viral capsid can be seen as a derivatizable scaffold, a multiway process including the genetic fusion of peptides or proteins [12-17], the chemical conjugation [18-20] or the encapsidation [21] of different kinds of molecules and amino acid residues.Combinations of derivatizing strategies are also possible, giving rise to multifunctionalization [20].

Biosafety is a central issue in biomedical-related biotechnologies. This also applies to VNPs, so their selection and design must take this into account. VNPs derived from plant viruses appear as an attractive alternative source since they are not pathogens of humans or higher animals [22-25]. In addition to this, the possibility of generating non-infectious Virus-Like Particles (VLPs), and a relatively easy and inexpensive scale-up, make of plant VNPs a good platform for theranostic developments [9,26-29]. Good examples of plant-derived VNPs are those developed from Turnip mosaic virus (TuMV), a flexuous elongated potyvirus. This virus has given rise to several VNPs, both derived from virions and from VLPs, which have shown to form a multi-functionalizable platform with different biomedical applications [15-17,20,30]. One of these implies their use for antibody sensing through the multimeric presentation of antigens on the particle external surface; such that a single particle can display up to approximately 2000 antigen copies [15-17]. This system allows to increase the sensitivity significantly with respect to conventional assays for autoantibody detection such as Enzyme-Linked ImmunoSorbent Assay (ELISA) and Immunofluorescence Assay (IFA), and it can be applied as a diagnostic tool in those pathologies associated to alterations in antibody levels.

The Relevance of Antibody and Autoantibody Sensing

Antibody sensing by highly sensitive tools allow an early prognosis, diagnosis and specific therapeutic approaches as well as the association of antibody levels and the pathological stage in different types of pathologies. VNPs as theranostic tool can be applicable to diseases that course with alterations in the antibody levels such as inflammatory and infectious diseases and cancer. This would be especially useful in pathologies in which change in antibody levels are subtle as occurs in autoimmune diseases [31-35] that course with an immune response directed towards self-molecules, the autoantigens, producing antibodies against them, the so-called autoantibodies.

It is known that many autoimmune diseases are caused by loss of immunologic self tolerance that generates chronic inflammation [33]. A precise and sensitive detection of autoantibodies in autoimmune diseases would help significantly in the understanding of the underlying mechanisms

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of the inflammatory processes as well as in the prognosis, diagnosis and the most suitable treatment. However, conventional antibody detection systems such as ELISA and IFA are not sensitive enough for the detection of very low levels of autoantibodies, which are extremely low during the first stages of these diseases [36-41].

A Case Study: Plant VNPs for Anti-HSP60 Detection in the Intestinal Bowel Disease

A study has been recently conducted in order to assess the use of VNPs as a tool in the diagnosis of autoimmunity-related inflammatory pathologies, using an animal model of inflammatory bowel disease (IBD) [15]. The selected autoantigen was Heat Shock Protein 60 (Hsp60), a chaperonin involved in the regulation of inflammation that has already been described to play a key role in several inflammatory and/or autoimmune pathologies [42-46]. Since Hsp60 is a very large protein, it was chosen a 21-amino acid epitope which has been previously described as an autoantigen in multiple sclerosis to functionalize VNPs [47]. Results of the study showed that TuMV-derived VNPs functionalized with Hsp60 peptide were able to detect differences in Hsp60 autoantibody levels in the peripheral blood which were not detectable by the conventional ELISA assay by neither the free peptidic antigen, nor by the whole protein. They also showed that, in the IBD animal model, the higher levels of the autoantibodies against Hsp60 protein were observed in the previous non-pathological stage and diminished with the inflammation development evaluated by the weight loss and the increase of granulocyte levels in peripheral blood [15]. Thus, the high sensitivity achieved by these VNP tools allowed the detection of changes in autoantibody levels, not detectable by conventional assays such as ELISA opening venues for the study of unknown mechanisms in the regulation of the inflammation processes. These results indicate Hsp60 autoantibody levels as a marker of a non-pathological physiological state involved in maintaining the immune homeostasis ('immunomodulator'), also described as 'immununculus' ('immune homunculus') [48], proposed already for other molecules and autoantibodies [38]. These results support previous investigations which revealed that the administration of antibodies directed towards Hsp60 [42, 49], or the immunization with the protein itself [50-53] improves the symptomatology associated to autoimmune inflammatory pathologies, including studies involving Hsp60 in IBD [46].

The Importance of Highly Sensitive Tool for Autoantibody Sensing in Disease and Non-Disease Scenarios

Although autoantibodies are key biomarkers of autoimmune diseases, they are not exclusive of these pathologies, since they have also been found associated to other diseases such as cancer associated to the neoantigen generation [36]. In addition, they are also present in healthy individuals [38]. The presence of autoantibodies in disease and non-disease scenarios and their age-associated changes highlight the need of deeper knowledge and understanding of the mechanisms governing their production and regulation which is difficulted by the great variability between different sensing methodologies and the insufficient sensitive of conventional methods for antibody detection in these scenarios with low levels of autoantibodies (first stages of the disease and healthy individuals) [31,37,39,54]. Also worth considering is the fact that there is not a universal autoantigen, each scenario goes associated to certain autoantigens, and vice versa. In summary, autoantibodies have been proposed not only as role players in the induction of inflammation but also as regulators of the inflammation such as the Hsp60 autoantibodies and the catalytic antibodies (abzymes) [34,38,54-57]. Highly sensitive procedures to assess the different autoantibody levels during the progression of the disease as pre-clinical and clinical markers and their likely physiological role in healthy individuals are most needed [37-39].

Conclusion

VNPs show themselves as potent tools for the early diagnosis and prognosis of autoimmune pathologies, in which the extremely low autoantibody levels during the earliest stages hinder their detection. This diagnostic tool opens the door not only for the study of the role of the autoantibodies in the inflammation mechanisms improving the diagnosis, prognosis, and specific treatment but also the role of autoantibodies as homeostasis regulators. VNPs also have the potential of becoming treatment tools through immunization, a clear example of their theranostic potential. Taking all the previous considerations together, we believe that further technological VNP development in this area has the potential to provide a significant leap forward in autoimmunity.

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