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Editorial

Immunogenicity of DNA Damage by Free Radicals and Carbonyls: A Probable Bio-marker for the Auto-immune Diseases

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Editorial

Immunogenicity is the ability of a particular substance, such as an antigen or epitope, to provoke an immune response in the body of a human or an animal. In other words, the ability of an antigen to elicit immune responses is known as immunogenicity, which can be humeral and/or cell-mediated immune responses. Differentiation has to be made between wanted and unwanted immunogenicity. Wanted immunogenicity is typically related with vaccines, where the injection of an antigen (the vaccine) provokes an immune response against the pathogen (virus, bacteria) aiming at protecting the organism. Unwanted immunogenicity is when the organism mounts an immune response against a therapeutic antigen (e.g. recombinant protein or monoclonal antibody). This reaction leads to production of anti-drug-antibodies (ADAs) inactivating the therapeutic effects of the treatment and, in rare cases, inducing adverse effects. The prediction of the immunogenic potential of novel protein therapeutics is thus a challenge in biotherapy.

There has been a recent development in the study of the immunologic behaviour of the modified DNA and proteins in the induction and furtherance of immunogenicity [1, 2]. The auto-antibodies formed in the experimental animals against the modified DNA are the subject of study in context of glycation reaction too. Anti-DNA auto-antibodies permanently attract the attention of researchers. In spite of numerous investigations aimed to determine their potential targets and role in the disease, origins of anti-DNA auto-antibodies and their pathological role remains to be established. Moreover, taking into account of such newly described features of anti-DNA antibodies as the ability to penetrate into the living cell and DNA-hydrolyzing activity, one may underestimate pathogenic potential of DNA-specific auto-antibodies. In general, antibodies that bind DNA do not display strict disease specificity. It is, however, widely accepted that healthy individuals usually express low-affinity antibodies with specificity to the single-stranded DNA, while presumably pathogenic high-affinity auto-antibodies to the double-stranded DNA are frequently over represented on the background of systemic autoimmune abnormalities and their presence appears a diagnostic criterion for SLE. Some blood tumours and even AIDS are also characterized by the increase in production of DNA-specific antibodies. The major known pathogenic process induced by anti-DNA antibodies is the inflammatory response due to their deposition in kidney in form of the immune complexes [3]. However, DNA specific auto-antibodies can also trigger apoptosis in cultured mesangial and endothelial cells and are cytotoxic to the primary cultures of lymphocytes. Non-immunogenic status of native DNA has led to the assumption that natural anti-DNA antibodies may be formed against DNA–protein complexes, such as nucleosomes, persisting in blood as a result of disease mediated increase in cellular destruction. Cross reactivity with proteinaceous nuclear antigens, displayed by anti-DNA antibodies, contributed to this hypothesis and even allowed to specify a pool of anti-nuclear antibodies (ANA). The cross-reactivity of anti-DNA antibodies with membrane antigens may potentially result in triggering of certain cellular responses through signal transduction pathways. Poly specificity of anti-DNA antibodies was also shown to favour to their capacity of penetration into living cell. Entry of anti-DNA auto-antibodies into living cell is shown to be accompanied by certain cellular dysfunctions. In some cases, penetration of antibodies into the cells is connected with either induction or suppression of a poptosis; however, precise consequences of antibody entry into the cell and its pathogenic significance remain to be determined.

Reactive oxygen species (ROS) and Reactive carbonyl species (RCS) are in the forefront of DNA immunogenicity studies. Amongst RCS, methylglyoxal and glyoxal are most common which forms advanced glycation end-products (AGEs) with the DNA leading to structural perturbations thus resulting into its immunogenic behaviour. Our Research group has shown that advanced glycation end-products (AGEs) plays a major role in the structural perturbations of DNA, LDL and as well as HSA biological macromolecules [4-9]. Glucose reacts non-enzymatically with protein amino groups to initiate glycation, the early stage of the Maillard reaction and forms AGEs [10, 11]. The AGEs thus formed has several roles in the development of pathological conditions like, diabetes mellitus, arthritis, ageing, and neurological disorders like Alzheimer's and Parkinson's diseases. One possibility to inhibit this glycation reaction is by means of anti-AGE antibody.

The problem of how an individual can immunologically distinguish between self and non self has fascinated and perplexed immunologists. When this distinction cannot be made, autoimmune diseases such as type I diabetes mellitus and rheumatoid arthritis occur and are associated with the appearance of large amounts of auto-antibodies. Studies on the antigenic specificity of anti-DNA antibodies have enforced the view that DNA is immunologically 'simple and bland'. It has been well established that native DNA in B-conformation is not immunogenic [2]. Nevertheless, various modified forms of DNA, DNA in complexes with DNA-binding

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proteins are immunogenic and induce antibodies. Origin of anti-dsDNA auto-antibodies in cancer patients and tumour-bearing mice has been demonstrated. Exogenous native B-DNA has not been found immunogenic in experimental animals. Mammalian DNA elicits poor responses to single stranded DNA and fails to induce antibodies against native or double stranded DNA. DNA modified with carbonyl species, free radicals, carcinogens etc, has been reported to induce antibodies against the immunogenic [12]. There has been also a recent report from our group showing the presence of DNA auto-antibodies against the glycated conformer in the diabetes patients as well [13, 14]. We have previously demonstrated that reactive oxygen species generated from carcinogens leads to the disestablishment of DNA [3, 4]. There is also direct effect of free radicals on some proteins like collagen and which gets swiftly altered under oxidative stress conditions [1]. Recently, the role of carbonyl species modified human placental DNA in the induction of circulating cancer auto-antibodies has also been reported [15]. Therefore, in my opinion the auto-antibodies against the damaged DNA might be used for the early detection of the disease, caused by reactive species. Furthermore, I would end up saying that the need of the hour is to stop or quench these reactive species to get rid of the ill effects on biologically important macromolecule like, DNA.

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