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Capability of a Single Antigen to Induce Both Protective and Disease Enhancing Antibody: An Obstacle in the Creation of Vaccines and Passive Immunotherapies

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Abstract : This study was conducted by taking B. anthracis as a model pathogen. On infecting a host, B. anthracis secretes three proteins, namely, protective antigen (PA, 83kDa), edema factor (EF, 89 kDa) and lethal factor (LF, 90 kDa). These three proteins are the components of two anthrax toxins. PA binds to the cell surface receptors, namely, tumor endothelial marker (TEM) 8 and capillary morphogenesis protein (CMG) 2. TEM8 and CMG2 interact with LDL-receptor related protein (LRP) 6 for endocytosis of EF and LF. On entering the cell, EF acts as a calmodulin-dependent adenylate cyclase that causes a prolonged increase of cytosolic cyclic adenosine monophosphate (cAMP). LF is a metalloprotease that cleaves most isoforms of mitogen-activated protein kinase kinases (MAPKK/MEK) close to their N-terminus. By secreting these two toxins, B.anthracis ascertains death of the host. Once the systemic levels of the toxins rise, antibiotics alone cannot save the host. Therefore, toxin-specific inhibitors have to be developed. In this wake, monoclonal antibodies have been developed for the neutralization of toxic effects of anthrax toxins. We created hybridomas by using spleen of mice that were actively immunized with rLFn (recombinant N-terminal domain of lethal factor of B. anthracis) to obtain anti-toxin antibodies. Later on, separate group of mice were immunized with rLFn to obtain a polyclonal control for passive immunization studies of monoclonal antibodies. This led to the identification of one cohort of rLFn-immunized mice that harboured disease-enhancing polyclonal antibodies. At the same time, the monoclonal antibodies from all the hybridomas were being tested. Two hybridomas secreted monoclonal antibodies (H8 and H10) that were cross-reactive with EF (edema factor) and LF (lethal factor), while the other two hybridomas secreted LF-specific antibodies (H7 and H11). The protective efficacy of H7, H8, H10 and H11 was investigated. H7, H8 and H10 were found to be protective. H11 was found to have disease enhancing characteristics in-vitro and in mouse model of challenge with B. anthracis. In this study the disease enhancing character of H11 monoclonal antibody and anti-rLFn polyclonal sera was investigated. Combination of H11 with protective monoclonal antibodies (H8 and H10) reduced its disease enhancing nature both in-vitro and in-vivo. But combination of H11 with LETscFv (an scFv with VH and VL identical to H10 but lacking Fc region) could not abrogate the disease-enhancing character of H11 mAb. Therefore it was concluded that for suppression of disease enhancement, Fc portion was absolutely essential for interaction of H10 with H11. Our study indicates that the protective potential of an antibody depends equally on its idiotype/ antigen specificity and its isotype. A number of monoclonal and engineered antibodies are being explored as immunotherapeutics but it is absolutely essential to characterize each one for their individual and combined protective potential. Although new in the sphere of toxin-based diseases, it is extremely important to characterize the disease-enhancing nature of polyclonal as well as monoclonal antibodies. This is because several anti-viral therapeutics and vaccines have failed in the face of this phenomenon. The passive –immunotherapy thus needs to be well formulated to avoid any contraindications.

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