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Strategies to avoid shiga toxin effects

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Shiga toxin producing *Escherichia coli* (STEC) refers to a group of *E. coli* that produce Shiga Toxins (Stx). STEC strains are associated with a variety of disorders in humans such us hemorrhagic colitis (CH) and the systemic illness: hemolytic uremic syndrome (HUS).[1] These pathogens have several virulence traits however the most important are Shiga toxins encoded by *stx1* and *stx2* genes carried by lysogenic phages.[2,3] There are 2 serologically distinct groups of Stx: Stx1 and Stx2. Both Shiga toxin genes present variants although stx_2 is the most heterogeneous group. In contrast to Stx1, that possess stx1c, stx1d, and stx1 $_{EDL933}$ variants several subtypes of Stx2 have been identified, consisting of Stx2c, Stx2d, Stx2d$_{act}$, Stx2e, Stx2f, and Stx2g.[4,5] Stx belong to the family of AB5 protein with an enzymatically active A subunit, and a pentamer of B subunits responsible for binding to its cellular receptor (Gb3) located in several organs as kidney, brain, liver, and pancreas. Stx is absorbed form gut lumen to underlying tissues and then enters circulation. Then it is internalized to the cells that harbour Gb3. Once into de the cytosol it is transported through the Golgi complex to the endoplasmic reticulum, nuclear envelope and nucleus, resulting in the intoxication of sensitive cells.[6,7] Stx also initiates a cascade of responses leading to an increased expression of pro-apoptotic mediators, mitochondrial dysfunction and activation of caspase cascades with consequent cellular apoptosis.[8,9,10] Shiga toxins cause very important damage in glomerular endothelial cells with reduction in glomerular capillaries and the occlusion of microvasculature with platelets and fibrin clusters.[11] It is well known that the damage in the microvascular endothelium is responsible for acute renal failure and the development of HUS. Despite intensive research, currently there are no specific therapies to prevent or to ameliorate the disease course.[12]

It is necessary to developed some strategies to prevent the effect of Stx when they were released in the lumen at intestine and the entrance into circulation to prevent the develop of HUS. There have been some approaches in developing some strategies to prevent the development of HUS. An alternative was to use reagents which can neutralize toxins released as was the administration of a silicon diamine compound diatomaceous linked oligosaccharide chain (Synsorb PK®). However, the effects of the Synsorb Pk® were not beneficial in preventing extrarenal complications.[13] Another attempt was investigated by Paton et al.[14] who designed a recombinant bacterium displaying on its surface a Stx receptor mimic, which show a high affinity for Stx and can neutralize significant amounts of Stx in the intestine.

Analogs for the Stx receptor (Gb3) to be administered systemically are being developed, that is the example of the Starfish® which show an affinity for Stx1 and Stx2 higher than the Synsorb and protected mice when administered subcutaneously together a lethal dose of Stx1 but no to Stx2.[15]A modified version of Starfish, called Daisy®, protects mice against both, Stx1 and Stx2[16] Nishikawa et al. developed a series of polymers that have several Gb3 molecules called SUPER TWIGS. This compound has the capacity of forming complexes with both types of Stx in circulation[17]

Mohawok et al.found that Stx2-neutralizing antibodies administered passively to mice protect animals from death when challenged with an E. coli O157:H7 stx2 mutant.[18]

It is known that SIgA is efficient in preventing the entrance of pathognes thrugh de intestine.[19,20] Miyashita et al.[21] investigated the IgA production in response to a recombinant Stx1B (engineered by them) used as antigen. Imai et al[22] found that Stx1B has low immunogenicity, not enough to induce an specific IgA response efficiently in mice. Tanikawa et al[23] produce an IgA m Ab (G2G7) specific to Stx 1B that was not efficient in neutralizing the toxicity of the Stx1 holotoxin, it yes was neutralized by IgG mAb D11C6. Belonging to the same research group, Tobisawa et al.[24] produced a recombinant hybrid IgG/IgA, in which variable regions came from IgG mAb, while the heavy chain constant region was from IgA mAb. This hybrid IgG/IgA containig variable regions whith neutralizing activity and with the constant region of IgA neutralized the effect of Stx1 on Vero cells. Iwata et al[25] found that the dimeric hybrid-IgG/IgA is more effective than the monomeric form in neutralizing the toxin. Imai et al (this issue) compared the effectiveness of the hybrid IgG/IgA and parenteral IgG1 by observing apoptosis inhibition using different cells lines.[26] This study demonstrated that the hybrid IgG/IgA inhibits apoptosis more efficiently than the parenteral IgG on Ramos cells and the sane was observed in Vero cells. This study highlights the potential expansion of IgA repertoire by using high affinity binding sites as variable regions of IgA.

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