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Editorial

Bacillus Thuringiensis Cry Proteins: The Status of Their Therapeutic Potential in Infectious Diseases

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Introduction

Bacillus thuringiensis Cry proteins has been the subject of intense research in the last three decades. Cry proteins are highly specific towards different orders of insects [1,2]. Bt Cry proteins are a multigenic family. It can be distinguished two main families: Cyt (cytolitic) and Cry (Crystal) protein [1,2]. The protoxins or inmature proteins weights 130 kDa. To be active, protoxins should be processed by the C-terminal region, producing the fragment toxic of 60-70 kDa. The three-dimensional structure of the Cry1Aa, Cry3A toxins has been elucidated [1,2]. In general Cry toxins are formed by three domains [1,2]. Domain I, formed by a bundle of alpha –seven helix, domain II or the binding domain formed by anti-parallel beta-sheet and the domain III formed also by a sandwich of beta-pledged sheets [3,4] By another hand, it has been described the immunogenic and adjuvants properties of the protoxin Cry1Ac [5,6]. The study has been extended to other members of the Cry family, like the protoxins Cry1Aa, Cry1Ab, Cry3A as well as to the Cry1A a, Cry1Ab and Cry3A toxins [7].

We have learned from all the studies performed in vitro as well as in vivo that Cry proteins are as strong immunogens as cholera toxin produced by *Vibrio cholerae* and enterotoxins from *Eshcerichia coli*, to induce immune responses of antibodies (IgA in serum and mucosal fluids) and to cause several effects in the different cell populations [8,9]. Despite of this the mechanism of immunogenicity and adjuvanticity remains to be understood. Protective adjuvant properties studies have been performed in the mouse model as for example, *Naegleria fowleri* [10], *Plasmodium falciparum* [11], *Murine cisticercosis* [12] *Brucella abortus* [13] and in a recent paper by us, a co-administration with M. bovis *Bacillus Calmette Güerin* (BCG vaccine) elicted isotypes and IgG subclass Abs as well as type Th1 cytokines (IFN-g) and Th17 type cytokines (IL-17) [14]. Furthermore, Bt Cry proteins adjuvant properties could also involve other important innate immune interactions such a those that play a key role against intracelular pathogens such as *M tuberculosis* oxide nitric synthase (iNOS, NO production), pro-inflammatory cytokines, IL-6, IL1-beta, TNF-alpha, IL-23-IL17 autophagy pathways [Guerrero et al., 2019; Juárez et al., in preparation 2019].

Under these experimental settings *in vivo* as well as *in vitro*, Cry proteins represent a viable and safe alternative against mycobacteia of the MTB complex [14]. Despite this the mechanism of immunogenicity and adjuvanticity remains to be understood to further. explore their therapeutic potential in clinic (infectious, chronic diseases) in mammals. At this point, it is worthy to mention those studies that have addressed, whether or not these properties depend of an interaction with molecules like receptors. Thus, it has been shown that pCry1Ac binds to microvellosity of intestinal mouse epithelium [15] and it seems that monocytes elicited a higher expression of FcRn receptor after immunized with pCry1Ac [16], regionalization of pIgR [17]. Moreover, macrophage pCry1Ac induced activation involves interaction with HSP70 and ERK1/2 and p38 pathways [18]. Although there still some concerns regarding the toxicity of the Cry toxins [19,20] we think that experimental settings should be carefully followed [21,22] and the status as an adjuvant for therapeutic issues remains promisorious, Furthermore, the immunobiology of the Bt Cry proteins in evolutive biology per se represent a challenging opportunity to gain insight about: What is the role of Bt Cry proteins in nature, in particularly in mammals?. Is the structural information playing a dual role to be functional in animal health including man?. The hypothesis is that Bt Cry proteins are a remarkable biological system designed to interact either with the insects as and with the host immune system. In the first case, is to species conservation (Bt spore germination), while in the second, to function as an mucosal adjuvant for example i.e. in chronic infectious diseases (bacterial, viral).

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