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Stabilized liposomes carrying bee venom new formulation is the breakthrough of pain and anaphylaxis and death in mice under venom immunotherapy

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Stings from bees, wasps, and ants produce a variety of clinical and histological manifestations. Anaphylaxis following an insect sting is the most serious complication. For individuals with a specific allergy to Hymenoptera venom, the venom immunotherapy (VIT) may be a relatively effective treatment. However, treatment failures occur and VIT may cause frequent systemic allergic side effects, mainly in honeybee allergic persons. The VIT is expensive and time consuming. New strategies to improve safety and efficacy of this treatment are therefore of general interest. We developed, step by step, a systematic approach to study the basic and biotechnological problems related to the design of a safe formulation of bee venom (BV) within liposomes to be used in VIT. It is known that mellitin (Mel) is the major toxic peptide in the European honey bee venom (50% of the wet weight) and that it has a powerful hemolytic activity and is responsible for local pain. Phospholipase A2, another BV component, also interacts and disrupts membranes. The inhibition of PLA2 and Mel activities through histidine alkylation, and or tryptophan oxidation (with pbb, para-bromo-phenacyl bromide and/or NBS- N-bromosuccinimide respectively) was envisaged to allow their encapsulations within stabilized liposomes. We strongly believed that this formulation (modified venom within stabilized liposomes) should be non toxic but immunogenic. The characterization of the total bee venom conformation, during and after chemical modification, as well as after interaction with liposomes, was undertaken using ultraviolet, circular dichroism and fluorescence spectroscopies. The PLA2 and Mel biological activities were measured indirectly by changes in liposomal turbidity measured at 400nm, rhodamine leak-out and haemolysis. The S-A-BV (Succinilated and alkylated BV) interacted with liposomal membranes without causing aggregation, leak-out or fusion (ILS, 2007). Here, we detailed (by confocal microscopy) the interaction between native or Mel or BV chemically modified with GUVs (Giant Unilamellar vesicles). These results were compared to freeze-fracture electron microscopy images, which corroborated the previously observed S-A-BV (succinilated and alkilated BV) or Mel/liposome interactions. A stable formulation composed of S-A-BV encapsulated within liposomes composed of SPC:Cho:pbb, 26:7:1 was employed. Large unilamellar vesicles of 202.5 nm with a negative surface charge (-24.29 mV) encapsulated 95% of S-A-BV. Mice injected with this formulation did not show venom toxicity signals. Two reasons could be ascribed to this effect: a. either, the Mel molecule or total BV lost their hemolytic activity through chemical modifications or b. the liposomal encapsulation avoided direct contact between animals with Mel or BV. Once more we observed that the liposomal vehicle has adjuvant properties. This formulation prevented anaphylaxis and death in mice during a challenge with native BV. The IgE was absent in these mice. This safe formulation can, now, be used in humans.

Biography

Maria Helena Bueno da Costa is a Scientific consultant (Toulouse- France). She obtained her titles of Pharmacy and Biochemistry from the UFMG (1972), Master in Biochemistry (ICB- UFMG, 1979) and PhD in Biochemistry from IQ-USP (1989). She did her Post- doctoral fellowships and Sabbatical year sat : Paul Scherrer Institute (Switzerland), Institut Pierre et Marie Curie, Universite Paris VI (France), Institut Pasteur (France), Universite Paris XI (France), Instituto Leloir (Argentine) and UNAM (Mexico). She is currebntly Researcher VI at the Butantan Institut (1987-2010). Her research areas are: Encapsulation of vaccines or animal venomsinto liposomes, biodegradable microspheres; supramolecular aggregates, controlled delivery systems and particulate adjuvants. Colaborations from: London University (UK) ; Universite Pierre et Marie Curie (France); Laboratoire de la Lumière Syncroton- Paul Scherrer Institut (Switzerland), Universidad de Quilmes (Argentina) ; Instituto Finlay ; Facultad de Ciencias y Tecnologias Nucleare sdel Instituto de Tecnologias e Ciencias Aplicadas e Universidad de La Habana (Cuba) ; Universidade del Pais Basco (Spain).

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