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Exosomes that target antigen specifically and deliver dsRNA of choice for physiologic and exquisitely specific siRNA therapy

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We have discovered a new form of immunological regulation. Suppressive CD8+ T cells from high dose antigen tolerized mice release physiologic nanovesicle exosomes containing inhibitory miRNA. The suppressive exosomes are present in the plasma of the tolerized donors and thus disperse in a systemic endocrine manner. The exosomes target and then suppress distant effector T cells by delivering inhibitory miRNA we have identified. They likely act in our system by binding to antigen bearing dendritic cells that suppress companion antigen specific effector CD4+ T cells. In mice deficient in the involved miRNA, and thus had no suppressive function, transfection with the specific miRNA and not controls or mimics, reconstituted suppression. We have discovered that the suppressive miRNA exosomes act antigen-specifically. This is via a coating of antigen-specific immunoglobulin chains demonstrated by flow cytometry, likely derived from a B cell subpopulation activated during the tolerizing protocol. Consequently, tolerized pan immunoglobulin deficient mice cannot generate suppressive exosomes, but if antigen-specific antibody chains are added their suppression is reconstituted. The exososmes protect the miRNA in transit and act Ag-specifically to deliver the inhibitory miRNA to target effector T cells antigen-specifically. This is the first example of T cell regulation via inhibitory miRNA passing from cell to cell via exosomes and acting antigen-specifically in vivo in a systemic endocrine manner. This work offers new and novel approaches of Ag-specific T cell regulation via transfer of genetic instructions to achieve entirely unique new translational possibilities for the therapy of immunological and other diseases, like cancers. Exososmes can be activated for surface coating with antibody of choice and easily transfected with dsRNA of choice. The result is the construction of therapeutic exosomes as natural physiologic nanoparticles carrying siRNA of choice, delivered antigen specifically to targeted cells via an Ag-specific antibody coating.

Biography

Dr Askenase graduated from Brown University and then Yale Medical School, was a Resident at the Harvard Unit of the Boston City Hospital, and a fellow at the NIH (NHLI and NIAMD), and then the Clinical Research Center at Northwick Park and NIMR Mill Hill in London, before returning to Yale to become Professor and Chief of Allergy and Clinical Immunology. He has published 275 original articles, many in first ranking journals, relevant to basic understanding of the regulation of allergic disease responses by T cells, mast cells, basophils, complement, NKT and NK cells.

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