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Dendritic Cells-A Potential tool in Piscine Immunology

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Abstract: Dendritic Cells (DC) are potent antigen-presenting cells responsible for the initiation of primary antigen-specific immune responses. It shows anti-tumor and anti-viral activities. It also carries the antigen and selects the lymphocyte that is clonally expanded. Maturation in the cells is conceived by initiation of immune responses by signals activation from pathogens or other activated immune cells. Immune tolerance is an important attribute exhibit by these cells. Potential of these cells can be utilized to develop vaccines. Dendritic cells link Metchnikov to Ehrlich and its awareness will fishes would form the basis of still unknown medical advances.

Keywords: Dendritic cells, Immune Response, Anti-viral Activity, Vaccine, Anti-tumor Activity.

1. INTRODUCTION

Ralph Steinman discovered dendritic cells which was key breakthrough in immunology. The dendritic cell discovery was brought together the work of Paul Ehrlich and Ilya Metchnikov, who shared the Nobel Prize in Physiology or Medicine in 1908 for their work on immunity. Dendritic cells are a part of the innate system and they orchestrate adaptive immunity. Burnet's theory says that when antigen comes into the system, it selects the right clone and that clone is expanded and memory is induced. Joshua Lederberg added to this idea by suggesting that any self reactive clones that arise during development would be deleted during encounters with self antigens (Lederberg, 1959). The most intriguing problem in immunology during the 1960s was how to create sufficient diversity to account for adaptive immunity. But neither Burnet nor Steinman was interested in this problem. Steinman wanted to learn how an immune response begins, and he believed that understanding this feature of immunity would make it possible to regulate immune responses, both to prevent autoimmunity and to create vaccines.

2. DISCOVERY

Breakthrough in immunology in 1967 was the development of a method to study specific immune responses in vitro. Mishell and Dutton, 1967 acknowledged the system developed by Robert Mishell and Richard Dutton involved mixing antigens with lymphocytes and measuring responses of antibody. The finding was that lymphocytes alone were not sufficient to produce immune responses and requirement of accessory cells were felt to initiate immunity. Steinman and Cohn, 1973 found through a phase contrast microscope was a different cell that has dendritic processes but no prominent phagocytic vacuoles; features that were distinct from typical macrophages and monocytes. This is the discovery that was honored with the 2011 Nobel Prize in Physiology or Medicine. The cells were elongated with tree-like processes that were constantly forming and retracting. Steinman named them dendritic cells, from the Greek word *dendreon* for tree. The dendritic cells also had a few, small lysosomes and lacked the typical membrane ruffling seen in phagocytes. With micro-cinematography they observed dendritic cell behavior that was dynamic and distinct from macrophages that were sedentary.

3. MIXED LEUKOCYTE REACTION

Nevertheless, most immunologists did not accept this conclusion as Paul, (2011) mentioned in Cell on the 2011 Nobel Prize in Physiology and Medicine: "This report was initially received with some skepticism, based on the widely held view that the major antigen presenting cells were the far more numerous macrophages and on the uncertainty that many immunologists had about the assay that Steinman and Cohn used to establish the function of their dendritic cells." It means that the MLR was not thought to be a typical adaptive immune response but like a spontaneous, innate response. Albeit, the precise nature of the antigen and the reacting cells were not well defined.

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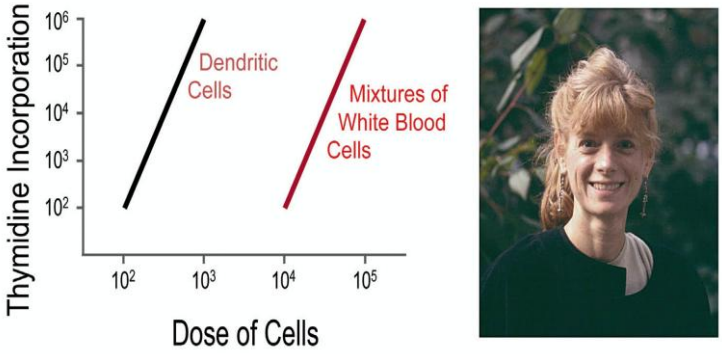

Fig 1: Dendritic cells are potent stimulators of the mixed leukocyte reaction (Steinman and Witmer, 1978). The graph shows a comparison of the stimulatory activity of dendritic cells and unfractionated spleen cells. The photograph shows Maggi Witmer-Pack, who worked with Ralph Steinman on these experiments.

4. ANTIGEN PRESENTATION

Michel Nussenzweig, developed an assay that utilized haptens as the antigens to elicit responses. The assay involved the cells modification with the nitrophenyl moiety and measures the development of cytotoxic or killer T lymphocytes. Nussenzweig *et al.,* 1980 compared responses of Dendritic cell to those of macrophages and other accessory cells. Results of these experiments showed that "dendritic cells are the critical accessory cells whereas macrophages regardless of source or Ia (MHCII) are without significant activity." With these experiments both has established the important principle that dendritic cells present antigen to T cells to initiate immunity. The 33D1 monoclonal antibody was distinguishable molecule of dendritic cells from other cells (Nussenzweigv *et al.,* 1982 and Steinman *et al.,* 1983).

How dendritic cells capture and process the antigen and present it to T cells?

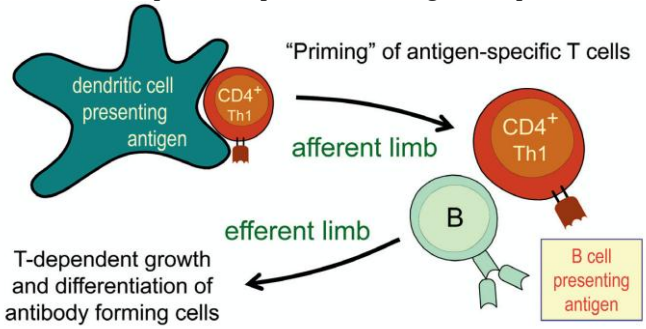

Fig 2: A model put forward by Ralph Steinman and his colleagues to explain the role of dendritic cells in inducing B cell antibody responses. Dendritic cells present antigen to and activate T cells which then interact with antigen specific B cells, by virtue of antigen presentation by the B cells.

Ground breaking experiment on anti-tumor and anti-viral activities of dendritic cells

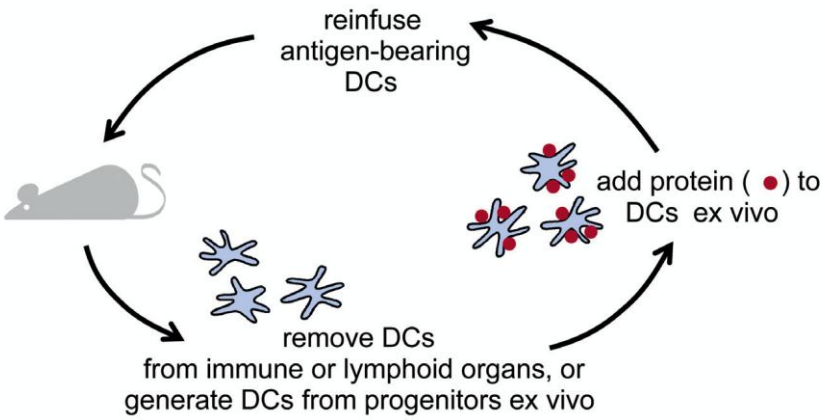

Fig 3: Diagram of the protocol for showing how antigen-loaded dendritic cells can be re-infused into mice to induce potent immune responses (Inaba *et al.,* 1990).

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Currently, immunotherapy is used in humans and has potential to be used in the fishes and shellfishes. This is the basis for the therapy of the first drug, Provenge, approved by the U.S. Food and Drug Administration to treat prostate cancer. This is also the basis for the therapy Steinman used to treat his own pancreatic cancer.
The new idea from clones of lymphoid cells with specific receptors to expand in response to the pathogen is that the response depends on antigen capture and presentation by an innate cell. An essential anticipating step in initiating immunity is that the dendritic cell carries the antigen and selects the lymphocyte that is clonally expanded.
Dendritic cells are present at all the interfaces between the body and environment: airway epithelium, skin, and mucosal surfaces. Metchnikov conceived that Dendritic cells are positioned as sentinels in the innate immune system, and Ehrlich conceived they are also positioned to connect with the adaptive immune system cells to initiate the responses by effector cells.

5. DENDRITIC CELL MATURATION

In order to initiate immune responses, they need to be activated by signals from pathogens or other activated immune cells. Steinman called this step maturation. Pierre *et al.,* 1997; showed that the switch between inactive and active states could in part be explained by re-distribution of MHC Class II molecules from lysosomes in immature dendritic cells to their cell surface during maturation where they would be recognized by T cells.

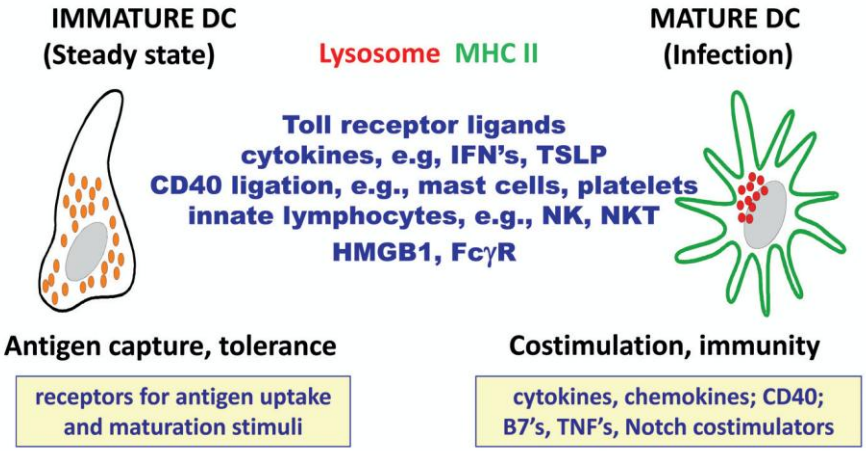

Fig 4: The diagram summarizes the idea that dendritic cells act as sensors which can be induced to undergo maturation as a result of Toll like receptor signaling or signaling by a number of other pathways. In the immature state dendritic cells are specialized for antigen capture, and in the mature state they up-regulate surface molecules required for T cell activation and polarization.

When a dendritic cell at a body surface receives an innate signal from the incoming pathogen by virtue of, for example, Toll receptor ligation, it becomes activated or mature. The mature dendritic cell then migrates to the local lymph node to join the networks of dendritic cells that contact migrating T and B cells. In addition to presenting antigen, the dendritic cell orchestrates the adaptive immune response by activating effector T cells. The activated T cells then leave the dendritic cell network in the lymphoid organ and patrol the body for invading pathogens.

6. IMMUNE TOLERANCE

Hawiger *et al.,* 2001 devised a system to test dendritic cell function in vivo by delivering antigen to these cells in situ. What he did was to engineer a monoclonal antibody specific to a molecule on dendritic cells, DEC-205, that would then serve as a specific delivery vehicle to carry the antigen to the dendritic cell. When injected into a mouse, the chimeric antibody bound to dendritic cells and thereby delivered the antigen. Antigen delivered to dendritic cells in this manner was far more efficient than soluble antigen in inducing T cell responses. Moreover, Bonifaz *et al.,* 2004 acknowledged long half-life of antibodies and their targeting, of dendritic cells lasted for days, and there were prolonged T cell responses with immunity strong enough to reject tumors or handle a viral infection.
Hawiger *et al.,* 2001 reported when dendritic cells were activated by Toll receptor ligation or some other stimulus by giving antigen along with a maturation stimulus, the result was robust immunity. But when the antigen was administered alone, T cells, instead of becoming effector cells for immune responses, were stopped from responding by one of a number of different mechanisms. They were either deleted, silenced (anergized), or actively induced to become regulatory T cells (Hawiger *et al.,* 2001; Hawiger *et al.,* 2004; Kretschmer *et al.,* 2005). This important experiment added an unanticipated role of dendritic cells to maintain tolerance.

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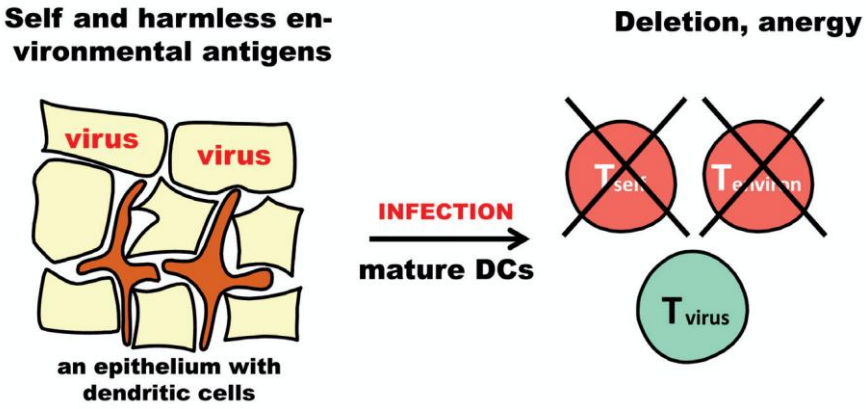

Fig 5: Induction of T cell tolerance by steady state DCs is required to prevent anti-self reactivity during immune responses to pathogens. Steady state dendritic cells capture, process and present self-antigen to T cells resulting in tolerance. The same self-antigens are also processed and presented by dendritic cells when they capture pathogen-infected cells, but the immune response is focused on the pathogen because the anti-self reactive T cells were previously silenced in the steady state (Steinman and Nussenzweig, 2002).

Thus, the dendritic cell discovery and its role in directing both tolerance and immunity not only connects innate and adaptive immune responses but also helps to explain how self-reactivity is removed from the adaptive repertoire to prevent autoimmunity, or Ehrlich's horror autotoxicus.

7. DENDRITIC CELL LINEAGE AND DEVELOPMENT

Geissman defined a bone marrow progenitor that was restricted to producing dendritic cells and monocytes, but not lymphoid cells or granulocytes (Fogg *et al.*, 2006).

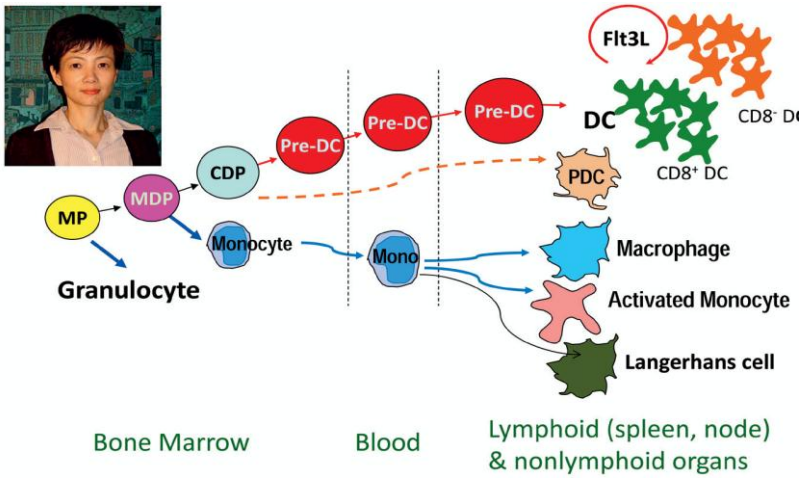

Fig 6: Dendritic cell development. Kang Liu (photograph left) and a diagram of the cellular intermediates in the dendritic cell development pathway in the bone marrow blood and tissues. The dendritic cell pathway splits from the monocyte pathway in the bone marrow after the common macrophage and dendritic cell precursor state. Predendritic cells leave the bone marrow and enter the tissues (Liu *et al.*, 2009). MP is myeloid progenitor, MDP is monocyte-dendritic cell progenitor, CDP is common dendritic cell progenitor, and PDC is plamacytoid dendritic cell.

8. DENDRITIC CELL-BASED VACCINES

Steinman emphasized that vaccines by and large have not been created by immunologists. Instead microbiologists, like Pasteur, used attenuated microbes to stimulate the immune system. Immunology to create vaccines by using the features of dendritic cells to exploit to produce immunity were 1) specific receptors for antigen uptake and processing, such as DEC-205; 2) pattern recognition receptors that activate or mature dendritic cells, such as the Toll like receptor ligand; and 3) the various pathways of dendritic cell development into their different subsets.

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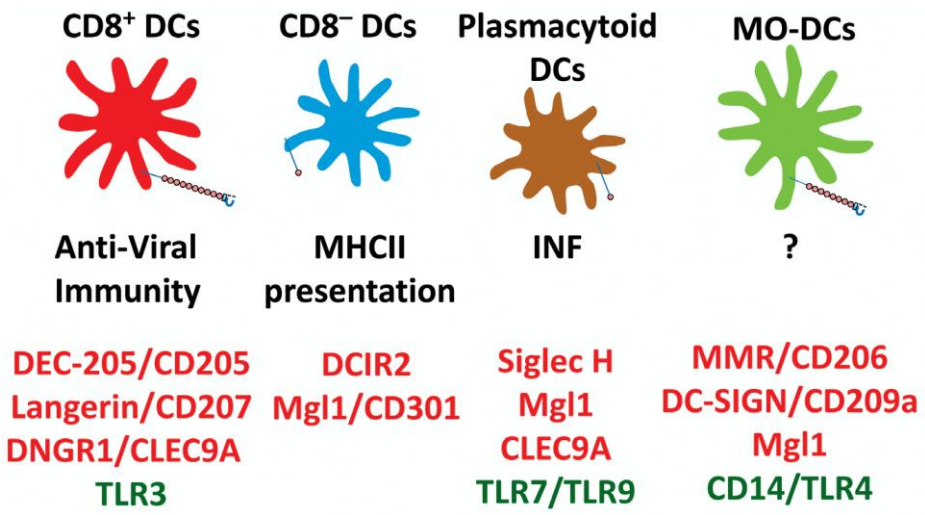

Fig 7: Subsets of dendritic cells, their functional specializations, and receptors that might be used to target or activate each one specifically.

Unlike other vaccines, this one would be delivered to dendritic cells throughout the body because the antibody would carry the antigen to all dendritic cells. The idea was that by using different receptors to target different dendritic cells and different innate stimuli, these vaccines could activate different types of immunity.

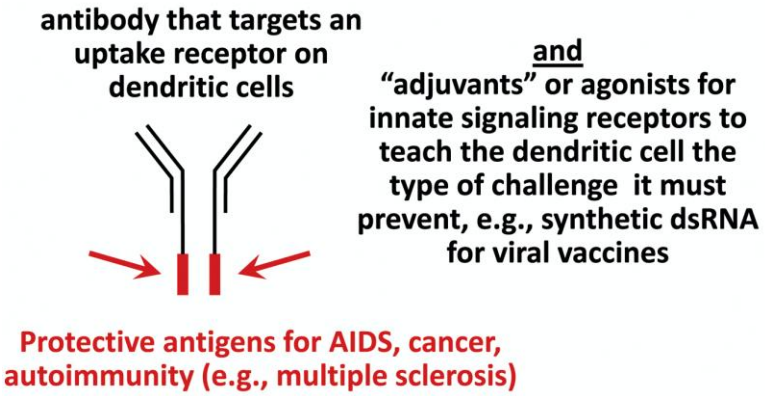

Fig 8: Suggested approach to dendritic cell-based vaccines for humans. Antibodies to endocytic receptors on dendritic cells are used as fusion proteins to target antigens to specific dendritic cells in vivo (left). Toll receptor ligands or other agents activate dendritic cells in specific ways (right).

9. CONCLUSION

Ralph Steinman created a revolution in immunology when he discovered a beautiful cell by just looking through a microscope. He showed that dendritic cells are critical for initiating the most important immune responses. He described their three central features. Dendritic cells are "Sentinels" that capture pathogens, as Metchnikov suggested. They are "Sensors" for infection that use their cell surface pattern recognition receptors like Toll to become activated. And, once activated, they become "Conductors" of the immune orchestra whose individual cells play harmonious roles to protect and regulate the body's immune system. Dendritic cells link Metchnikov to Ehrlich.

In fishes there is presumptive interdigitating/ dendritic cells appear occasionally in the medulla and corticomedullary border of the dogfish, Mustelus manazo (Zapata *et al.*, 1996). Other authors have suggested and demonstrated their presence in the thymus of young dogfish (Navarro, 1997) and wild brown trout (Alvarez 1993). Awareness of Dendritic cells in fishes would form the basis of still unknown medical advances.

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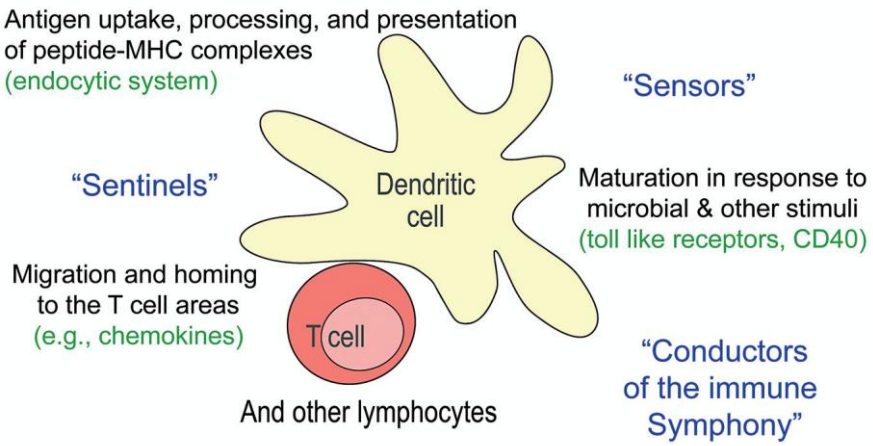

Fig 9: Dendritic cells are innate cells that activate adaptive responses. The diagram shows that dendritic cells are sentinels positioned in tissues to detect pathogens or inflammation; they act as sensors by virtue of expression of receptors that detect pathogens or other inflammatory signals; and they are conductors of the immune symphony as they process and present antigen to activate adaptive immune responses.

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