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AUTHOR'S VIEW

The thyroid hormone triiodothyronine reinvigorates dendritic cells and potentiates anti-tumor immunity

V.A. Alamino[a], M.M. Montesinos[a], G.A. Rabinovich[b], and C.G. Pellizas[a]

[a]Centro de Investigaciones en Bioquímica Clínica e Inmunología (CIBICI-CONICET) and Departamento de Bioquímica Clínica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Córdoba, Argentina; [b]Laboratorio de Inmunopatología, Instituto de Biología y Medicina Experimental (IBYME-CONICET) and Departamento de Química Biológica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Buenos Aires, Argentina

ABSTRACT
Dendritic cell (DC) cancer vaccines have shown limited clinical benefit. Thus, the identification of signals and molecular pathways that potentiate the immunogenicity of DCs has become a major challenge in cancer research. Our studies demonstrate that triiodothyronine endows DCs with enhanced ability to stimulate cytotoxic T-cell responses with implications in DC-based immunotherapy.

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The immune and endocrine systems are interconnected via bidirectional networks. This reciprocal cross-talk preserves homeostasis in physiological conditions. This communication is possible because both systems share common ligands (hormones and cytokines) and their specific receptors. This immune-endocrine circuit is evidenced by the immunological consequences of primary endocrine disorders as well as by the altered function of hormonal systems during immunopathology. However, it also offers additional opportunities for therapeutic intervention.[1]

Dendritic cells (DCs), the main antigen-presenting cells, are endowed with a unique capacity to recognize, process and present antigens to naive T cells tailoring adaptive immunity. Interestingly, DCs can process exogenous antigens and present them in the context of major histocompatibility complex (MHC) Class I molecules, a process termed "cross-presentation" crucial for the induction of protective immunity against tumors. DC-based cancer immunotherapeutic strategies have been widely used to engender $CD8^+$ T-cell responses using patients' own DCs loaded with tumor-associated antigens *ex vivo*. However, success of this therapeutic modality is still limited as activated DCs have a short half-life in lymph nodes, and antigen processing and presentation in tumor-associated lymph nodes may fuel tolerogenic rather than immunogenic T-cell programs. Therefore, increasing DC survival and immunogenicity represents a major challenge in vaccination strategies.[2]

Thyroid hormones (THs) are critical regulators of cellular differentiation, growth, and metabolism. Thyroid-related pathologies are the most common endocrine dysfunctions, and therefore the study of TH action in different target cells is of crucial interest. Cellular activity of THs usually requires the binding of the active TH triiodothyronine (T3) to its nuclear receptors (TRs) expressed as 4 major isoforms: TRα1, TRβ1, TRβ2 and TRβ3. However, nongenomic actions of THs have been recognized and include the involvement of cytoplasmic TRs. TRβ mutant knock-in mice harboring a frame-shift mutation in the last 14 carboxy-terminal amino acids of TRβ1 (termed TR^{PV}) showed a complete loss of T3-binding and transactivation activities. TR^{PV}, as well as other mouse models, has enabled the demonstration that normal TRβ could function as a tumor suppressor, avoiding cancer development, progression, and metastasis.[3]

The direct effects of THs on T cells have been largely studied in both primary T lymphocytes and lymphoma T-cell lines.[4] However, the impact of THs in the initiation of adaptive immune responses is poorly understood. We have shown that expression of TRs, surprisingly the cytoplasmic β1 isoform, contributes to DC maturation and Th1-type cytokine secretion induced by physiologic levels of T3. We found that T3-stimulated DCs favored IFN-γ secretion by $CD4^+$ and $CD4^-$ T cells.[5] These effects involved activation of Akt- and NF-kB-dependent pathways [6] and were counteracted by glucocorticoids.[7]

In a recent issue of *Cancer Research* [8] we demonstrated that the immunostimulatory effects of T3 were abrogated in DCs isolated from TR^{PV} mice, emphasizing the requirement for an intact TRβ-T3 signaling axis in T3-induced DC activation. Taken together, these findings, the tumor suppressor role of TRβ^3 and the increased IFNγ production by $CD4^-$ T cells induced by allogeneic T3-treated DCs [5], prompted us to investigate the role of T3 in tumor immunity.

Does T3 reshape DCs and modulate antigen-specific T-cell cytotoxicity?

In our recent study[8], we revealed that T3 instructs DCs to stimulate antigen-specific cytotoxic responses as shown by *in vivo*

CONTACT C.G. Pellizas claudia@fcq.unc.edu.ar
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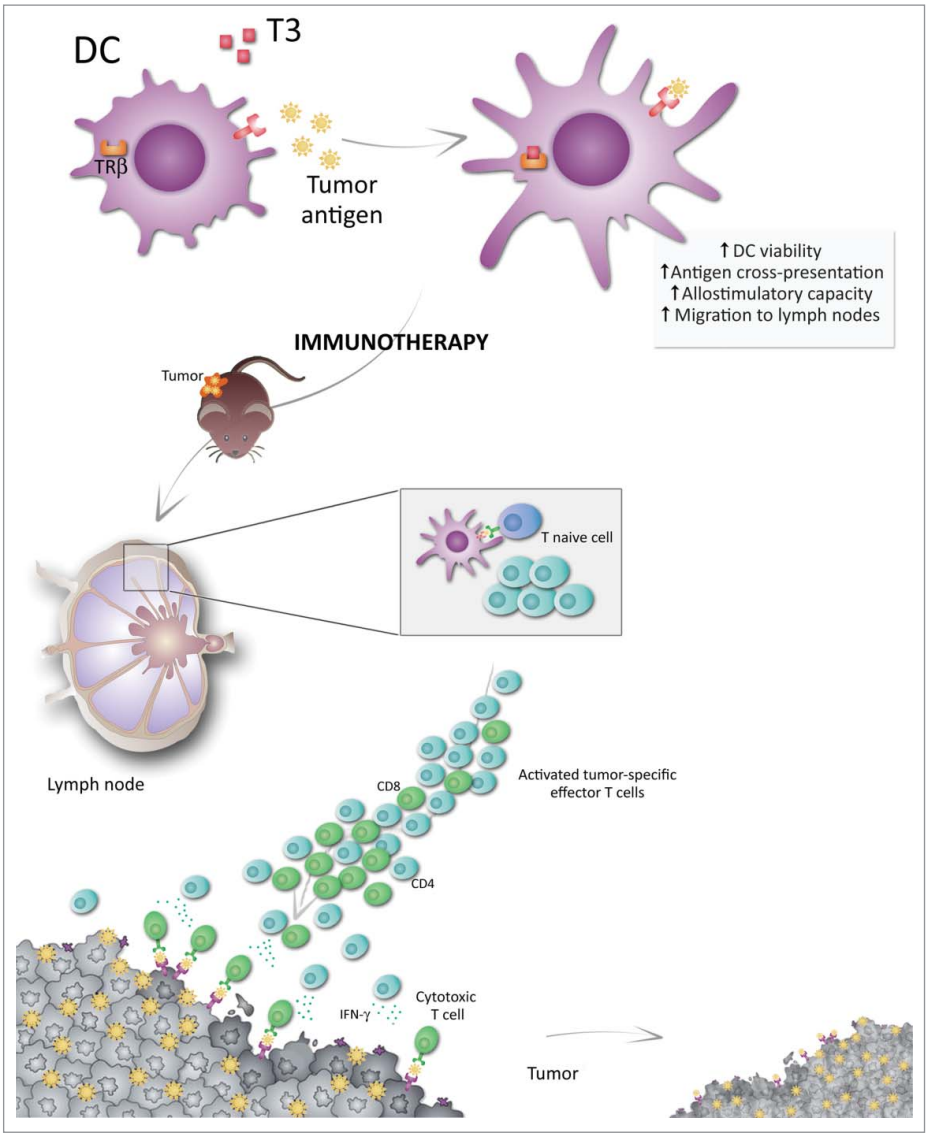

Figure 1. Triiodothyronine instructs DCs to stimulate T-cell mediated antitumor responses. Triiodothyronine (T3) binding to thyroid hormone receptor (TR)-β increases dendritic cell (DC) viability and T cell-stimulatory capacity, and potentiates the ability of DCs to cross-present antigens. In a mouse model of melanoma, vaccination with T3-stimulated DCs in the presence of a tumor antigen, favors the migratory capacity of these cells to lymph nodes where they present antigens to naïve T cells and promote the activation of tumor-specific effector T cells. These cells migrate into the tumor to boost the development of a specific cytotoxic immune response mediated by IFN-γ-producing CD8$^+$ T cells, which ultimately restrain tumor growth and prolong host survival.

cytotoxicity and *in vitro* antigen cross-presentation assays. These effects were accomplished by a T3-dependent increase in DC viability. This finding reinforces our previous results showing a T3-dependent induction of Akt activation in DCs [6], as Akt phosphorylation enhances DC survival. [9] In addition, our new studies revealed that T3 ameliorates the DC capacity to migrate to lymph nodes and favors the expression of CCR7, an essential receptor for DC homing to lymph nodes.[10] Altogether, these data demonstrate the ability of T3-conditioned DCs to potentiate antitumor immunotherapeutic strategies.

Finally, our report [8] showed that T3-conditioned OVA-pulsed DCs delayed growth of B16-OVA tumors *in vivo*, prolonged survival of tumor-bearing mice and increased the percentage of tumor-free mice, in part by promoting the expansion and/or differentiation of IFNγ-producing CD8$^+$ T cells at sites of tumor growth (Fig. 1).

In conclusion, our findings suggest a novel mechanism by which the T3-TRβ complex influences antitumor responses by bolstering DC-mediated T-cell activation during tumor growth. Although the influence of T3 on DC immunogenicity needs to be evaluated in other tumor models, our results establish the first evidence of an adjuvant effect of T3-TRβ signaling on DCs, suggesting an applicable method to empower DC vaccination either alone or in combination with other cancer immunotherapeutic strategies, including the blockade of inhibitory checkpoints (CTLA4, PD-1/PD-L1, LAG3, etc).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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