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Outsmarting CTCL Cells by Decoding the Language They Speak:

Focusing Past and Present Insights on Future Prospects

Richard L. Edelson, M.D.

Department of Dermatology, Yale University School of Medicine

Abstract

Since the term “Cutaneous T Cell Lymphoma” (CTCL) was introduced in 1974, investigation of the biology of the malignant T cells has contributed heavily to understanding of the clinically important biology of benign and neoplastic T cells. Availability of large numbers of clonal skin-homing CTCL cells facilitated the discovery of T cell-specific monoclonal antibodies and identification of “helper-T cells.” Tight linkage between the biology and clinical manifestations of CTCL cells has enabled major, and accelerating, scientific and practical advances. CTCL cells are now well defined by their distinctive features: membrane molecules which direct them to the skin; growth dependency on signaling from immature dendritic antigen presenting cells; origin from the large set of normal “cutaneous T cells” which recirculate between skin and blood; differentiation markers controlling the way they interact with antigen presenting cells, maintain memory for their cognate antigen and regulate normal T cells (CD4/CD45Ro/Treg); secretion of a Th2 set of cytokines; and surface expression of clinically targetable tumor distinctive antigens. CTCL provided the point of entry for now widely used biologically-based therapies: anti-lymphocyte antibodies to treat malignancies; cellular immunotherapy for cancer (Extracorporeal Photochemotherapy); IL2-diphtheria toxin fusion agent (Ontac); anti-cancer retinoid (Targretin); and anti-cancer inhibitors of histone deacetylase. On this rich foundation, we are now poised to resolve a next set of major questions. What are the skin-localized antigens that stimulate memory “cutaneous T cells” to clonally expand, prior to their malignant transformation? How can we best exploit the critical growth requirements and antigenicity of CTCL cells to develop even better therapies? Can we ultimately outsmart CTCL cells by interrupting their capacity to receive the growth stimulatory signals that they require to grow and spread?

Early History of CTCL

The term “Cutaneous T Cell Lymphoma” and its commonly used CTCL abbreviation were introduced in 1974 at a special National Institutes of Health Clinical Staff Conference, published in full the following year in the *Annals of Internal Medicine* (1). As this Summit strives to identify important future directions for research into the pathogenesis, diagnosis and treatment of those lymphomas that present through the skin, an assessment of how far we have come since that time provides a helpful context and perspective. Since I participated in the CTCL naming ceremony and hope to continue to contribute to the malignancy’s defeat, the organizers of the Summit have kindly asked me to frame the subject.

The reason that, of all of the cancers being investigated at the NIH in the mid-70s, CTCL was chosen as the focus of that conference was the excitement that its conception had generated. Human T cell biology had burst onto the scene precisely at that time, enabling the unifying discovery that those lymphomas presenting through skin infiltration were commonly cancers of T cells (2), regardless of the descriptive names attached to them (mycosis fungoides or MF, Sézary syndrome, reticulum cell sarcoma, lymphoma cutis, follicular mucinosis, etc). In stark contrast, those lymphocytic malignancies presenting in adults in the absence of skin infiltration, were most commonly of B cell origin. The impact of this dichotomy was enhanced by the clinical observation, in those days before the magic of chemotherapy was subdued by the realization of its toxicity and limitations (3), by the finding that intense pharmacologic therapy could convert MF and other skin lymphomas into Sézary Syndrome or vice versa.

Because leukapheresis was palliative for the leukemic phase of CTCL, enormous numbers of malignant T cells were being removed from high-count patients (4). The clonal nature of these cells made them exceptionally attractive research objects to virtually all NIH laboratories getting in on the ground floor of T cell biology. Over just three years, therefore, a huge amount of scientific information, from all available immunologic angles, became available to integrate with the burgeoning clinical recognition that majority of those lymphomas presenting through skin infiltration overlapped clinically and biologically. An invigorating view became prevalent: CTCL had become the first prominent example of the tight linkage between immunobiology and lymphoma manifestations, diagnosis and therapy.

It was from those breakthrough insights that the concept of CTCL emerged. Up until 1974, MF and Sézary Syndrome (SS) had been considered “pre-malignant” disorders that could develop into Hodgkin’s disease, lymphocytic leukemia or other established lymphocyte malignancies (5). Recognition that MF and SS are clonal malignancies (6), that they share distinctive histopathology (7) and cellular features and that they overlap clinically led us to the conclusion that old misconceptions needed to be replaced by a new unifying nomenclature. The term “Cutaneous T Cell Lymphoma” was therefore introduced, since patients needed to know that they had a genuine malignancy, requiring best available therapy. Bringing these skin-homing lymphomas under a single nomenclature also empowered cancer biologists to search for common biologic properties of the malignant cells.

So, in the compressed three time frame between the first application of T cell science to analysis of skin-homing malignant T cells to introduction of the term “CTCL,” several “translational” major clinically relevant insights accrued. CTCL cells were not only revealed to be malignant polyclonal “helper T cells,” (8), but they provided the first demonstration that human T cells can support normal B cell maturation. The specific accumulation of CTCL cells to those regions of lymph nodes and spleen where normal CD4 T cells localize, as well as their avoidance of bone marrow even under circumstances of extreme lymphocytosis, suggested that their distinguishing skin homing must reflect their generation from a subpopulation of normal “cutaneous T cells” (1). The immunosuppression that accompanied large tumor burdens of CTCL cells indicated that the malignant cells directly suppress normal immunologic function (1). A fast forward to current scientific

understanding in the next section reveals how prescient those collective early insights and suggestions were (Figure 1).

Common Scientific Denominators

Scientific advances made over the intervening years have markedly clarified the biologic boundaries of CTCL. Yet, the path to the present has been a two-way street, as CTCL cells, as a source of clonally derived T cells, have contributed immensely to the maturation of human immunobiology, in ways that have then further improved our understanding of CTCL. For example, the finding that anti-CD4 monoclonal antibodies bind to CTCL cells, while anti-CD8 monoclonal do not, revealed CD4 as a marker of helper-inducer T cells and CD8 as a marker of cytotoxic T cells (9)

Table 1 highlights ten particularly important distinguishing CTCL features and their biologic importance. Topping the list is the recognition that CTCL is a malignancy of CD4+ skin-homing T cells, whose clinical manifestations in the skin reflect subclone evolution towards populations that progressively lose their growth dependency on the epidermal environment. From the vantage point of physician-patient communication, it is particularly important that patients hear and understand the word “lymphoma” in the title of their disease, so that they do not underestimate the benefit of successful early therapeutic intervention and recognize that what they have is far more than merely a simple rash. The effectiveness of that communication has enabled such simple skin-directed treatments as ultraviolet light exposure to dramatically interrupt the natural progression of the malignancy and make CTCL one of the great stories of modern medicine.

The predilection of CTCL cells to localize in the epidermis and to accumulate in the pathognomonic Pautrier microabscesses is at the core of the disease’s pathogenesis. Since these collections are almost exclusively composed of malignant T cells and Langerhans cells, the dendritic antigen presenting cells (DC) of the epidermis (10–12), they form an exclusive club that likely offers a principal clue about the etiology of the lymphoma. The mandatory co-localization of these two cell types, along with the recognition that the epidermis is the early main site of CTCL proliferation (13) makes the CTCL cells highly vulnerable to skin-localized treatments for scientific reasons that will be discussed in the next section.

The discovery of Cutaneous Lymphoid Antigen (CLA) as both a marker of the large T cell subset (10–15 percent of circulating T cells) now conveniently labeled “Cutaneous T Cells” (14) has been pivotal in our understanding of CTCL’s origin, manifestations and biology. Elegant studies have revealed that CLA is a glycoprotein whose expression is by the conversion of naïve T cells into memory T cells, after their engagement of their cognate antigen in lymph nodes that drain skin (15,16). CLA, by binding to E-selectin, which is upregulated on papillary dermal endothelial cells in skin sites of inflammation, helps direct “cutaneous T cells” back to skin.

These discoveries provide extraordinary insights into the biology of CTCL. In the same way that melanoma is a malignant transformation of normal melanocytes, CTCL almost certainly derives from normal counterparts, the “Cutaneous T Cells.” Just as it does normally, CLA

helps direct CTCL cells back to skin, where as a neoplastic amplification they accumulate in the CTCL skin lesions. The exclusion of often dermally abundant normal reactive T cells from the CTCL cell-Langerhans cell liaison in lesional epidermis suggests that an additional factor preferentially attracts CTCL cells to the epidermis. Since CTCL cells differ from other memory CLA+ T cells in the specificity of the clonal T cell receptor for cognate antigen, a strong candidate for the selective attractant of CTCL cells to the epidermis is the as yet unidentified skin-localized antigen which originally converted their normal predecessors to memory T cell status. Therefore, I suggest that a key missing link to the pathogenesis of CTCL skin lesions, and even possibly to the malignancy's origin, is the identification of the original antigen. The tendency of CTCL skin lesions to occur in sun-shielded areas, and then to return in precisely the same locations and even with same lesion configuration, implies a role for a persistent local influence, quite possibly the original antigen, which may be altered by large doses of sunlight.

Patch, and early plaque, stage CTCL lesions commonly contain remarkably few epidermally-concentrated CTCL cells, which elicit a marked dermal inflammatory infiltrate (17). This finding reveals that the clinically evident erythema actually represents the host response, rather the malignant cells themselves. Hence, caution must be exercised in considering loss of erythema a genuine clinical response.

Tale of Two Cells

The tight relationship between Langerhans and CTCL cells extends to dendritic antigen cells (DC) in general. Initially, our group demonstrated that CTCL infiltrates regularly include evenly dispersed DC, most clearly demonstrated in cutaneous tumors (18). That phenomenon is such a regular feature of CTCL that the abundant presence of DC is a useful means of microscopically distinguishing cutaneous B cell lymphoma infiltrates from those of CTCL.

This finding, along with the composition of Pautrier microabscesses, suggested to us that DC provide in vivo growth signals to CTCL cells. Although it has long been known that CTCL cells are difficult to propagate in tissue culture, we found that co-cultivation of CTCL cells with autologous immature DC facilitated marked CTCL cell replication (19). This nurturing effect required that the DC be kept immature, by addition of IL-10. If the DC were permitted to mature, the cultured CTCL cells died.

This system permitted us to establish that the DC-CTCL interaction was mediated by the engagement of the CTCL T cell receptor by the class II major histocompatibility complex (MHC) of the cultured DC. DC present processed antigen to CD4 T cells through precisely that type of cell-to-cell contact. Hence, the possibility must be considered that CTCL cells may be stimulated to proliferate by DC through an interaction reminiscent of classical antigen presentation. Since the culture system employed does not provide access to antigen derived from lesional skin, if antigen participates in this phenomenon it must be either a self antigen or one associated with the CTCL cells themselves.

Although fundamental aspects of the DC-CTCL interaction remain to be determined, it is clear that CTCL cells have a rigid *in vitro* requirement for the nurturing effects of DC. The

probability that this requirement exists *in vivo* as well raises the intriguing possibility that the exquisite sensitivity of CTCL plaques to ultraviolet therapy may result from the known sensitivity of DC to both ultraviolet-B and ultraviolet-A-activated psoralens in PUVA therapy. This observation provides an attractive potential explanation for why ultraviolet therapy, administered as infrequently as at three month intervals, can maintain CTCL remissions. DC that are periodically depleted by such therapy must be repopulated over months. Therefore, periodic depletion of epidermal DC likely interrupts the growth signaling.

Further studies of the interplay between DC and CTCL cells should provide answers to these questions. The early intervention in CTCL lesions that has become standard care is the most logical explanation about why the prognosis of the malignancy has been so enormously improved over the past two decades. This clinical success ranks as one of the most impressive advances in the clinical care of serious cancers and offers hope that, with continued deciphering of CTCL growth requirements, malignant cell vulnerabilities can be exploited even further.

Future Prospects

Although major questions remain about the etiology and pathogenesis of CTCL, enormous progress has been made on these fronts over the three decades since it was first recognized as a broad entity. Many CTCL clinicians have long suspected that the malignancy is far more common than indicated by national registry data, and recent information has revealed that it is at least eight times as common as previously known. More homogeneity of nomenclature and improved registering of cases will probably increase that estimated incidence further.

With the number of strong research groups studying the biology of CTCL increasing, application of technical advances in molecular immunology and genetics should accelerate our decoding of the language that CTCL cells speak. I am personally very optimistic that the next decade will give us tools to treat advanced CTCL as well as we can now so safely and effectively do for the early stages.

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Figure 1.

Figure 2.

Table 1

		Key CTCL Features	Biologic Relevance
****	Migration	CD4 T Cell Malignancy	Potential Lethal Clonal Evolution
		Regional, Epidermal Predilections	Biologic Basis of Pautrier Collections
		Co-Localization with DC	Required Cellular Interaction
		Skin Homing Th2 cells	Origin from Distinctive T Cell Subset
	Distinctive Features	Derivation from Memory T Cells	Identification of Inductive Antigen
		T _{reg} Properties	Systemic Immunosuppression
		Immature DC Growth Requirement	Therapeutic Vulnerability
		Global Assault on T Cell Repertoire	Rearrangement of Immune System
		Requirement for IL7	Specific Factor Dependency
	Clinical	Dominant Early Infiltrate Benign	Initial Anti-CTCL Response
		Responsiveness to ECP	Distinctive Immunogenicity