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Cicatricial Alopecia Symposium 2011: Lipids, Inflammation and Stem Cells

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The 2011 Cicatricial Alopecia Symposium* was attended by approximately 90 members of the scientific community representing academia, industry, and government. The program was held over 2 days and included three keynote talks and six sessions: (i) Bench: "Mechanisms of inflammation"; (ii) Bedside: "Disease Presentation and Epidemiology"; (iii) Bench: "Nuclear Receptors and Lipids in Skin and Hair Disease"; (iv) Bedside: "Current and Emerging Therapies for Cicatricial Alopecia"; (v) Identifying Translational Opportunities in Cicatricial Alopecia; and (vi) Stem cells, Cicatricial Alopecia, and Hair Follicle Regeneration. In addition to major talks by invited speakers, the meeting included short talks selected from submitted abstracts, followed by panel discussions. The symposium culminated in a workshop composed of small discussion groups, each focusing on specific research questions and priorities.

Dr Stephen I Katz (NIAMS) discussed new directions at NIAMS and said that funding for hair research has steadily increased over the past 10 years. The symposium began with keynote addresses by David Norris (University of Colorado School of Medicine) and Frederick Miller (Environmental Autoimmunity Group, NIEHS). Dr Norris gave an overview of inflammatory alopecia and noted that alopecia areata and primary cicatricial alopecia (PCA) are the yin and yang of hair disorders. The inflammatory infiltrate targets the hair follicle (HF) bulb and spares the bulge stem cells in alopecia areata, whereas it targets the permanent, stem cell portion of the follicle in PCA, thereby making the hair loss permanent. He pointed out that factors driving the inflammatory reactions in PCA are poorly defined. He emphasized the recent associations reported in laboratory models of lipid abnormalities and hair loss. He noted that defined targets, such as peroxisome proliferator-activated receptor gamma (PPARγ) involvement in lichen planopilaris pathogenesis and treatment, have yet to be found in alopecia areata.

Dr Miller gave an overview of the role of environment in the pathogenesis of autoimmune diseases and emphasized the role of UV radiation in autoimmune diseases, which induces greater skin inflammation in female mice compared with male mice. His take-home message was that major risk factors for autoimmune diseases are both environmental and genetic, and that there is a clear gender bias in the prevalence of antinuclear antibodies and in the expression of estrogen and IFN-responsive genes. He suggested that it might be important to evaluate the incidence of each of the PCA subtypes in different parts of the world.

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*The Cicatricial Alopecia Symposium 2011, "Lipids, Inflammation and Stem Cells," was held in Bethesda, Maryland, USA, 27–28 October 2011. Information about the content and support of the symposium can be found at http://www.cicatricialalopecia.org.

Mechanisms of inflammation

John Ortaldo (Laboratory of Experimental Immunology, NCI) discussed the distinct features of natural killer and natural killer T cells, the pattern of their cytokine profiles, their activation, and their role in bridging the innate and adaptive immune responses. He noted that in the alopecia studies reported to date, there was little discrimination made between natural killer and natural killer T cells. Francisco Quintana (Harvard Medical School) showed that the interaction of Aryl-hydrocarbon receptor (AhR) with c-Maf is essential for the generation of mouse and human IL-10-secreting type 1 regulatory T cells that suppress inflammatory responses. His take-home message was that the *in vivo* immunological effects of AhR activation are tissue and ligand specific, and that in autoimmune disease, the outcome likely depends on the type of T-cell differentiation pathway activated by a given AhR ligand.

Matt Harries (University of Manchester) provided an overview of the HF, bulge stem cells, and the HF's immune privilege and how the immune properties of the HF are altered in lesional lichen planopilaris tissue. John Harris (University of Massachusetts) suggested a new method for approaching autoimmune diseases for the purposes of clinical treatment, drug development, and determination of pathogenesis based on cytokine profiles, clinical presentation, signs and symptoms, pathology, and epidemiology. He noted that diseases with similar profiles may respond to similar therapies.

Disease presentation and epidemiology

Vera Price (University of California, San Francisco) discussed the NAHRS classification of cicatricial alopecia, the demographics of patients, and the clinical features of the different subtypes of PCA. Len Sperling (Uniformed Services University) spoke of the controversy in the identification of different cicatricial alopecia subtypes and discussed an alternate classification for the disease. He suggested five fairly distinct types of cicatricial alopecia: (1) chronic cutaneous lupus erythematosus (discoid LE); (2) lichen planopilaris; (3) dissecting cellulitis (perifolliculitis abscedens et suffodiens); (4) acne keloidalis; and (5) central centrifugal scarring alopecia (follicular degeneration syndrome, folliculitis decalvans, pseudopelade). Elise Olsen (Duke University Medical Center) discussed the incidence, potential risk factors, and a new photographic scale for exploring etiological factors in central hair loss in African-American women.

Nuclear receptors and lipids in skin and hair disease

Beatrice Desvergne (University of Lausanne, Switzerland) described a global knockout mouse model of PPARγ that shows disrupted HFs, lack of sebaceous glands, and absent subcutaneous fat. Starting at postnatal day 28, HF disruption, massive inflammatory infiltration, and scarring were observed. Bret Evers (University of Texas Southwestern Medical Center) described hair growth defects in an insulin-induced gene 1 (Insig1)-deficient mouse model. The mice displayed defects in postnatal HF cycling because of cholesterol precursor accumulation that could be rescued after treatment with Simvastatin.

Pratima Karnik (Case Western Reserve University) presented gene expression profiles of lymphocytic and neutrophilic PCA to show that lipid metabolic changes are a hallmark of all PCA subtypes and that altered lipids underlie the pathogenesis of this group of alopecia. She emphasized the central role of PPARγ and other nuclear receptors in the pathogenesis of PCA. PPARγ is a transcription factor that belongs to the nuclear receptor family and has emerged as an important regulator of lipid metabolic and inflammatory genes. Dr Karnik presented data from the PPARγ knockout and AhR transgenic mouse models of scarring

alopecia to demonstrate that lipid metabolic changes precede inflammatory changes and are caused by altered PPARγ signaling in HFs and sebaceous glands.

Current and emerging therapies for cicatricial alopecia

Jerry Shapiro (New York University, University of British Columbia) reviewed the current treatments for cicatricial alopecia and outlined how he would treat each subtype. Paradi Mirmirani (The Permanente Medical Group) discussed emerging therapies, including her experience in treating lichen planopilaris patients with Pioglitazone (a PPARγ agonist).

Dr Mirmirani reported that 50% of the patients responded to the treatment as determined by reduced inflammatory cells on hematoxylin and eosin sections and by a reduction in clinical itch and inflammation. Dr Wilma Bergfeld (The Cleveland Clinic Foundation) described her experience with Pioglitazone and reported a positive response in 67% of treated patients, with resultant hair regrowth in two of the patients. Because of the reported incidence of bladder cancer in rodents on systemic therapy, topical treatment with Pioglitazone was discussed as a possible alternative to oral treatment. John Varga (Northwestern University) reported that PPARγ expression and activity is decreased in scleroderma patients with early-stage disease and that this correlates inversely with skin fibrosis. His studies showed that treatment of mice with bortezomib, a proteosomal inhibitor, resulted in upregulation of tissue PPARγ and resistance to bleomycin-induced skin and lung fibrosis. Dr Varga pointed out that scleroderma and PCA have common histopathological features and a shared pathomechanism—that is, a defect in local PPARγ function. These intriguing commonalities point to the possibility of common therapeutic approaches for these two disparate conditions.

The Dinner Speaker on Day 1 was Jean-Hilaire Saurat (University of Geneva, Switzerland). Dr Saurat reviewed the effects of high doses of dioxin on the skin of his patients. Although toxic doses of dioxin did not cause clinical hair loss, they did result in histological loss of sebaceous glands and formation of cystic hamartomas. He emphasized the need for new biomarkers of dioxin toxicity.

The second day began with a keynote talk by Christopher Austin (NIH Center for Translational Therapeutics) who defined rare and neglected diseases and gave an overview of the congressionally mandated program to speed the development of new drugs for these diseases. He cited specific examples of successful collaborations between the NIH Therapeutics for Rare and Neglected Diseases program, big pharma, biotechnology companies, and universities.

Identifying translational opportunities in cicatricial alopecia

Donna Mendrick (National Center for Toxicological Research, FDA) emphasized the need for new biomarkers of disease diagnosis and drug efficacy. She suggested that, to enable their use in the clinic, noninvasive biomarkers in body fluids and bioimaging are needed. David Margolis (University of Pennsylvania) explained the differences between comparative effectiveness (use in general practice) and comparative efficacy (use in an ideal setting), and discussed methods to conduct comparative effectiveness research. He said that as PCA is a rare disease, the study population and disease population may be largely the same. His suggestion was to prove effectiveness in the basic population and thus define who to treat and how to use observational, proof-of-concept, and translational studies.

Stem cells, cicatricial alopecia, and HF regeneration

Luis Garza (Johns Hopkins University School of Medicine) described a role for prostaglandin D2 and its receptor DP-2 in the development of androgenetic alopecia, thereby providing another lipid-based target as a hair loss treatment. Isaac Brownell (NCI, NIH) described studies to show that Sonic hedgehog secreted by sensory neurons signals to a population of cells in the telogen bulge marked by the Hedgehog response gene *Gli1*.The perineural stem cell niche is necessary to maintain bulge cells capable of becoming epidermal stem cells but, interestingly, is dispensable for follicle contributions to acute wound healing and hair homeostasis. George Cotsarelis (University of Pennsylvania) discussed the role of HF bulge stem cells in wound healing. He suggested that understanding the regeneration of HFs after wounding is the first step toward developing new treatments for scarring alopecias.

Workshop and breakout sessions

David Norris, Kevin D Cooper, Matt Harries, John Harris, and Francisco Quintana led discussions on “Mechanisms of Inflammation”. Vera Price, Elise Olsen, Paradi Mirmirani, Amy McMichael led discussions on “Clinical Aspects, Disease Presentation and Epidemiology.” Pratima Karnik, Bret Evers, Lloyd King, Beatrice Desvergne led the discussions on “Environmental Influences, Nuclear Receptors and Lipids.” George Cotsarelis, Kurt Stenn, Isaac Brownell, Ken Washenik led the discussions on “Stem Cells and Hair Follicle Regeneration”.

Several themes became apparent from these discussions. One theme dealt with classification: Do the PCAs represent one or a family of disorders with different etiologies and pathogenetic mechanisms? Although the histology of these diseases suggests some commonality, the clinical presentations suggest differences. A second theme focused on the role of immunity and inflammation during the course of the disease. Is the inflammatory reaction primary or secondary? How much of the inflammatory reaction reflects an autoimmune process? It was generally believed that the argument for a strong autoimmune component has not yet been put forth, although that possibility has not been entirely excluded. A third theme was the novel association of lipid pathways in hair biology. Most attendees were influenced by the generally unrecognized impact that lipid pathways and the sebaceous gland have in the normal health of the HF, as well their role in the pathogenesis of several laboratory models and clinical systems. The description of lipid metabolic pathways, such as the PPARγ target genes, sterol intermediates in PCA, and prostaglandins in lichen planopilaris and androgenetic alopecia, was most insightful. Current evidence suggests that the sebaceous gland in the PPARγ knockout and AhR transgenic mouse models disappears before the infiltration of inflammatory infiltrate. This observation raises several questions. Is it that the sebaceous gland is highly sensitive to the destructive etiologic agent, or does the loss of the sebaceous gland cause the loss of HFs? What is the role of the sebaceous gland in hair biology, anyway? The data presented suggesting some role for PPARγ and AhR in these disorders are, at present, compelling and cannot be easily be disregarded. In fact, the action of these molecules at this time offers the best mechanistic explanation, and perhaps the best therapeutic targets.

Marked progress has been made in this field since the last NIH Colloquium (October 2005). In the future and in subsequent meetings, we hope certain projects will be tackled. (1) We need a more extensive record of PCA patients with family and environmental histories, by initiating a central database that physicians around the world can contribute to and utilize. (2) We need better definition of each of the PCA entities by differentiating the time course of the disease at all levels and some definition of the conditions associated with the onset.

(3) We need a direct and focused attempt to elucidate the role of the sebaceous gland in hair biology by, for example, using such tools as conditional sebaceous gland knockout models. (4) Finally, we need a greater understanding of the role of lipids in the pathogenesis of these disease, and in particular, aggressive dissection of the PPARγ signaling pathway and the potential role it might have in the development of each of the sundry PCA presentations. Much needs to be done, but the future looks surprisingly bright regarding a confident understanding of and effective treatments for this long neglected group of hair disorders.

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