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Assessing transductional profiles from CLEC lesional skin and peripheral blood offers a comprehensive model of disease pathogenesis
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The importance of skin manifestations in lupus erythematosus (LE) makes it vital to investigate cutaneous disease based on molecular criteria. To this end, our strategy includes microarray-based gene expression analyses of lesional skin and blood of cutaneous lupus erythematous (CLE) patients to illuminate disease mechanisms and classify the molecular genetic basis of disease heterogeneity. Here, we integrate gene expression data from both environments and use a functional and genetic approach to better understand pathomechanisms of disease. There is a significant upregulation of apoptosis and interferon response in both skin and blood of CLE patients concomitant with reported findings in SLE supporting the hypothesis that these key pathways are relevant across the broad spectrum of lupus. Taken together, our data suggests a comprehensive model of systemic and local disturbances orchestrated as three distinct phases in the autoimmune response: 1) initiation, 2) amplification of the immune response, and 3) target damage. Of interest, we observe an enrichment for heightened immune surveillance/initiation related processes in lesional skin than in peripheral blood of CLE patients. Further, we identify seven regions of overlap between transcriptional and lesional skin, with several genes that do not correspond with reported SLE dysregulated genes or putative risk loci, thus potentially harboring susceptibility loci distinct for CLEC.

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Epigenetic modulation of skin equivalents by cosmetic ingredients
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Although diseases that involve alterations in epidermal growth and differentiation impact every one in five people, the basis for how epidermal progenitor cells suppress premature differentiation and maintain self-renewal is unknown. We hypothesized that DDx6 regulates cell self-renewal of the progenitor cells that reside in the basal layer of the epidermis. Depletion of DDx6 resulted in loss of progenitor cell function due to premature differentiation and loss of proliferation. Western blotting demonstrated that DDx6 suppressed expression of cell intrinsic mechanisms. Gene expression profiling revealed that DDx6 is necessary to sustain proliferation while actively suppressing differentiation. To promote proliferation and self-renewal, DDx6 facilitates the translation of regulators of proliferation (CDK1 and HMGB2) and epigenetic modifiers. Thus, DDx6 regulates the GC-rich region in the 5'UTR of KLF4, a transcription factor necessary for epidermal differentiation, and promotes its degrading through mediators of mRNA degradation such as EDC1. Collectively, our results suggest that DDx6 complexes maintain progenitor cell fate by facilitating the translation of mRNAs involved in proliferation and self-renewal while also targeting differentiation inducing mRNAs for degradation.

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Trans-ethnic genome-wide meta-analysis identifies multiple novel associations and reveals ethnic heterogeneity of psoriasis susceptibility

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In order to extensively identify the susceptibility genes and characterize the ethnic heterogeneity of psoriasis, we conducted the largest trans-ethnic genome-wide meta-analysis (GWAS) of psoriasis in 15,369 cases and 19,517 controls of Caucasian and Chinese ancestries. We identified four novel associations at rs9531862 (OR=1.12, P=7.5×10^-10), LOC144837 (OR=1.16, P=2.6×10^-10), CDG6 (OR=1.17, P=5.7×10^-10), and rs2125128 (OR=1.17, P=4.3×10^-10). These findings are consistent with previous GWAS results in both Caucasian and Chinese populations. In addition to common alleles, we report evidence of ethnic-specific or allelic heterogeneity for eleven loci, and these population-specific effects contribute significantly to the ethnic diversity of psoriasis prevalence. This study not only provides novel biological insights into the involvement of immune and keratinocyte development mechanism, but also demonstrates a complex and heterogeneous genetic architecture of psoriasis susceptibility across ethnic populations.

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DNA recognition motif of LEMD3 as a key player in the pathogenesis of Buschke–Ollendorff syndrome
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Buschke–Ollendorff syndrome (BOS) is an autosomal dominant disease characterized by dismorphic features, osteopoikilosis, and cutaneous lesions (nevi). These features appear early in life and are progressive. Genetic screening showed that the LEMD3 gene, encoding the leucine zipper and coiled-coil domain-containing protein LEMD3, is mutated in patients with BOS. Products of this protein are involved in the regulation of apoptosis and TGF-β signaling, which are both involved in the pathogenesis of BOS. In order to study the function of LEMD3, we generated and characterized LEMD3 knockdown (KD) and wild-type (WT) keratinocytes and primary fibroblasts. We showed that KD of LEMD3 results in increased cell death and decreased proliferation. Furthermore, we identified that the DNA recognition motif of LEMD3 is necessary for the function of LEMD3 in BOS patients. The results suggest that LEMD3 is a key player in the pathogenesis of BOS and may represent a novel therapeutic target for this disease.

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The IncRNA FJ46906 alters expression of aging-associated proteins through binding to A1 and NB-5
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Aging is a complex biological process that affects all living organisms, and the skin is particularly affected by the aging process. In our study, we used high-throughput sequencing to identify long non-coding RNAs (lncRNAs) that are differentially expressed in aged skin compared to young skin. We found that the IncRNA FJ46906 was significantly upregulated in aged skin. Further analysis revealed that FJ46906 binds to the AP-1 transcription factor, which is known to play a role in skin aging. Using co-immunoprecipitation assays, we confirmed that FJ46906 bound to AP-1 in human keratinocytes. To investigate the biological function of FJ46906, we performed a series of functional assays. We found that overexpression of FJ46906 in keratinocytes resulted in reduced expression of several aging-associated proteins, including the matrix metalloproteinase-1 (MMP-1), collagen type I (COL1A1), and elastin (ELN). These results suggest that FJ46906 may play a role in skin aging by modulating the expression of aging-associated proteins.

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435 TALEN-induced mutations confirm Col17a1 as a genetic modifier of junctional epidermolysis bullosa in mice

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436 Somatic activating RAS mutations cause vascular tumors including pyogenic granuloma

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437 Gadermin A3 targets mitochondria to mediate keratinocyte necrosis and skin inflammation

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The epidermis forms a critical physical and immune barrier, which could be compromised by deregulated responses of keratinocytes to external stimuli and ensuing inappropriate cell death. GASDERMIN A (GSDMA) was involved in gastric epithelial apoptosis and has been implicated in inflammatory hyperresponsiveness. Its function in the skin was indicated by dominant mutations in gadermin A1 (GdmA), which caused inflammation-mediated epidermal hyperplasia and hair loss in mice. The mechanism of GdmA’s action and pathogenesis are unknown. Here, we showed that GdmA is regulated by intramolecular fold-back inhibition, which is disrupted by dominant mutations in the C-terminal domain. The unmasked N-terminal domain of GdmA then associates with Hsp90 and is delinked from mitochondrial membrane protein Tom70 to form the mitochondrial chaperone Trag1 and causes oxidative stress-mediated mitochondrial permeability transition and caspase-independent cell death. Using an inducible transgenic mouse model, we demonstrated that epidermis-specific expression of GdmA caused spontaneous keratinocyte necrosis and sterile skin inflammation in vivo. In primary keratinocytes isolated from the transgenic mice, GdmA expression caused mitochondrial oxidative stress and necrosis. We hypothesized that GdmA functions as a stress sensor, which regulates the susceptibility of keratinocytes to necrosis and its deregulation leads to chronic inflammatory skin diseases.

438 Genome wide association study of psoriasis in India

RP Nair1, LC Tsoi,2, M Ghosh,2 PE Stuart,1 M Kabra,1 T Tejasvi,1 JJ Voorhees,1 G Abecasis,2 VH Sharm1 and JT Elder1 1 Dermatology, University of Michigan, Ann Arbor, MI, 2 Biostatistics, University of Michigan, Ann Arbor, MI, 3 Pediatric Genetics, AlJMS, New Delhi, India, 4 Dermatology, AlJMS, New Delhi, India and 5 Ann Arbor Veterans Administration Hospital, Ann Arbor, MI

Genome-wide association studies (GWAS) have identified over 40 psoriasis susceptibility loci in European ancestry populations and 17 in Chinese. Suggestive of genetic heterogeneity, only 9 loci overlap between these two populations. We performed a GWAS of 953 psoriasis cases and 856 controls collected in India on the Illumina OmniExpressExome array. Principal component analysis showed that the samples are genetically similar to HapMap Gujarati Indian samples. We performed association testing using logistic regression after adjusting for the top 10 PCs. Only 5 loci achieved genome-wide significance (P<5E-8). The top 9 associated markers are located 10-143 kb telomeric of HLA-C, with the strongest associated marker, rs1265181 (OR=6.2, P=1.9E-103), located 81 kb telomeric. This is in contrast to Caucasian GWAS, where the strongest associated markers map centromeric of HLA-C. The second GW-significant signal was rs6887695 (OR=1.5, P=2.1E-12) near IL12B, an established psoriasis locus. In addition to these two loci, suggestive association signals (P(5E-8) were observed for 18 loci, including markers near RUNX3 and NFIB, two loci that have been associated with psoriatic arthritis and/or psoriatic arthritis in European-origin populations. These loci are currently undergoing additional refinement by imputation and will require verification using an expanded sample set.

439 Cutaneous neovascularization in mice with chronic proliferative dermatitis (Sharpirin®)

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Laboratory mice carrying a null mutation in the Sharpin gene develop a systemic hyperinflammatory syndrome with a severe inflammatory and hyperproliferative skin disease called chronic proliferative dermatitis. The inflammatory cells are mainly comprised of eosinophils with lesser numbers of macrophages and neutrophils and an increased number of mast cells. While the mutant mice appear clinically normal at birth, at about 4 weeks of age they begin to develop a rapidly progressive skin disease characterized by hair loss and thick and scaly skin. We evaluated the cutaneous vasculature in these mice from 2 to 10 weeks of age by histochemistry, immunohistochemistry, and transcriptome analyses. While there was no obvious change in the dermal lymphatics (using LyVE1 as a marker), histology and immunohistochemistry using CD31 and smooth muscle actin as markers revealed prominent neovascularization throughout the dermis and the hypodermal adipose tissue. There was progressive upregulation of Vegfa, Flt1, Ccr7, Cxcr4, Pdgf and Sema1a mRNAs while the expression of Cxcl12 and Nrp2 mRNA was decreased. Many of the proteins encoded by these genes interact to create a robust lympho-vascular network. UCAT1 is a major transcript in lymphatic endothelial cells, remained low consistent with no obvious histologic change. The increased expression of Vegfa mRNA in SHARPIN-deficient mice suggests that VEGFA contributes to the progressive dermal and hypodermal fat angiogenesis observed in these mice.

440 Analysis of long non-coding RNAs highlights tissue-specific expression patterns and epigenetic profiles in normal and psoriatic skin

JT Elder1,2, LC Tsoi,2 MK Iyer2, PE Stuart1, WR Swindell,1 JE Gudjonsson,1 T Tejasvi1, MK Sarkar1, B Li1, J Ding1, JJ Voorhees1, HM Kang1, RP Nair1, AM Chinmayan1 and G Abecasis1 1 Dermatology, Unives of Michigan, Ann Arbor, MI, 2 Ann Arbor VA Hosp, Ann Arbor, MI, 3 Biostatistics, Univ of Michigan, Ann Arbor, MI, 4 Bioinformatics, Univ of Michigan, Ann Arbor, MI, 5 Vanderbilt Univ, Nashville, TN, 6 Nat Inst Health, Bethesda, MD and 7 Pathology, Univ of Michigan, Ann Arbor, MI

Although analysis pipelines have been developed to use RNA-seq to identify long non-coding RNAs (lncRNAs), most transcriptome studies of autoimmune disease to date have assessed only protein-coding transcripts. To address this gap, we used RNA-seq data from 99 lesional psoriatic, 27 uninvolved psoriatic, and 90 normal skin biopsies, and currently undergoing additional refinement by imputation and will require verification using an expanded sample set.
MCP-1 is overexpressed by Tsc2-null skin fibroblasts in a mouse model of tuberous sclerosis with targeted disruption of Tsc2.

Meta-analysis of the TNPI1 region in pсорiasis identifies two independent association signals.

Analysis of transcription from palmoplantar pustulosis and palmoplantar pustular psoriasis suggests that the gene not be d08 psoriasis was nearly 2-fold thicker and had more F4/80-positive macrophages than control mice. These results suggest that MCP-1 may play important roles in TSC tumorigenesis and serve as a novel target for the treatment of TSC.

Dominant de novo GA1 mutations cause erythrodermatoderma variabilis.

Psoriasis drug development and GWAS interpretation through in silico analysis of transcription factor binding sites.

ABSTRACTS | Genetic Disease & Gene Regulation

441 MCP-1 is overexpressed by Tsc2-null skin fibroblasts in a mouse model of tuberous sclerosis with targeted disruption of Tsc2

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446 Psoriasis drug development and GWAS interpretation through in silico analysis of transcription factor binding sites.
Buschke-Ollendorff syndrome in the absence of LEMD3 mutation

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Buschke-Ollendorff syndrome (BOS) is a rare disorder that classically exhibits connective tissue nevi (collagenomas or elastomas) and osteopetrosis (OPK). BOS is highly penetrant, but exhibits variable expressivity, resulting in some patients with skin manifestations in the absence of OPK, especially prior to puberty. BOS is autosomal dominantly inherited, resulting from heterozygous loss-of-function mutations in LEMD3, an inner nuclear membrane protein that antagonizes transforming growth factor beta (TGF-β) and bone morphogenetic protein (BMP) signaling. We present an 11-year-old boy with multiple congenital anomalies and a mutation in LEMD3 (c.1331G>A, p.R444Q). The patient exhibits typical features of BOS including an osteopenic variant outside the HLA. The LEMD3 gene resides within a MHCI class I-related cluster and encodes ligands for the NKGD2 cytotoxic T cell receptor. We previously reported a striking upregulation of these ligands in both human and mouse AA hair follicles, and more recently, demonstrated that LEMD3 is a candidate gene for BOS. To identify functional variants at the LEMD3 locus, we performed targeted deep sequencing of this region on 124 AA patients and uncovered a small number of rare, non-coding variants enriched on AA risk haplotypes. Interestingly, 1 DNA add, 1 N Malchik, 1 O Isakov, 1 N Erez, 1 A Gat, 1 Goldberg, 1 N Shomron, 1 Schwartz, 1 M Moritz, 1 M de Guzman Strong, 1 Washington University SOM, St. Louis, MO, 2 Tel-Aviv University, Tel-Aviv, Israel, 3 Tel-Aviv University, Tel-Aviv, Israel, 4 Child and Family Research Institute, University of British Columbia, Vancouver, BC, Canada, and 5 UMDNJ, New Jersey, NJ

Multiple facial vellus hair cysts, ear pits, lipomas, macrocephaly, joint laxity and cardiac defects: A novel genodermatosis?

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Eruptive vellus hair cysts (EVHC) often occur on the trunk and limbs. Facial involvement is uncommon. Autosomal dominant inheritance has been described but associated extra-cutaneous anomalies have not. We describe a 4-patient kindred presenting with multiple facial vellus hair cysts, and an association of ear pits, lipomas, macrocephaly, joint laxity and cardiac defects. Patients were investigated, examined, and photographed with consent. Evaluations performed include skin biopsy (3 of 4 patients), echocardiogram, and electrocardiogram. Cutaneous histopathologic examination confirmed the diagnosis of vellus hair cysts in all 4 affected individuals. Data on clinical findings lipomas (3 of 4 patients), joint laxity (4 of 4 patients), ear pits (4 of 4 patients), cardiac defects (1 of 4 patients), macrocephaly (1 of 4 patients) were documented. We propose that facial EVHC may indicate the presence of a novel inherited autosomal dominant disorder with multisystemic manifestations.

The BAF/SWI/SNF complex controls genome accessibility to p63 during epidermal differentiation

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“Open” and “closed” chromatin states impact gene expression by rendering genomic regions either accessible for expression or by repressing them, respectively. Chromatin remodeling complexes, such as the BAF (SWI/SNF) complex, control the transition between these open and closed states. In epidermis, BAF catalytic subunit, Brm and Bren, are required for differentiation and are frequently mutagenically inactivated in SCC, however, how BAF acts to control differentiation in homeostasis and cancer is unknown. To address this, we mapped chromatin accessibility genome-wide in the presence or absence of functional BAF using ATAC-seq. We found that BAF is required to maintain accessibility of 6.6% of total open chromatin regions during epidermal differentiation. Motif searches of these BAF-dependent regions identified a striking enrichment of the p63 DNA binding motif (p=1X10^-8). mRNA profiling indicates a significant overlap between the target gene sets of p63 and BAF (p=2.6X10^-10) with the 424 co-regulated genes enriched for top gene ontology (GO) terms including “epidermal development” (p=3.9X10^-9) and “epidermal cell differentiation” (p=3.4X10^-7). Our ATAC-seq studies demonstrated that BAF loss led to loss of accessibility, at 40 basepair average compaction, selectively at p63 binding sites. Binding sites of other factors, such as H3K27Ac, p300, and RNA Pol II, at p63 binding sites, while increasing the repressive H3K27me3 mark at these sites. Therefore our data demonstrates that the BAF complex and p63 cooperatively bind to maintain open chromatin and promote epidermal differentiation.

Novel regulatory variants identified in adult atopic dermatitis by targeted deep sequencing of a candidate region

A Quiggle, 1 T Marfatia, 1 KJ Gulewicz, 1 A Shemer, 2 Z Goodwin, 1 W Jones, 1 E Guttman-Yassky 1 and C de Guzman Strong 1

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Eruptive vellus hair cysts (EVHC) often occur on the trunk and limbs. Facial involvement is uncommon. Autosomal dominant inheritance has been described but associated extra-cutaneous anomalies have not. We describe a 4-patient kindred presenting with multiple facial vellus hair cysts, and an association of ear pits, lipomas, macrocephaly, joint laxity and cardiac defects. Patients were investigated, examined, and photographed with consent. Evaluations performed include skin biopsy (3 of 4 patients), echocardiogram, and electrocardiogram. Cutaneous histopathologic examination confirmed the diagnosis of vellus hair cysts in all 4 affected individuals. Data on clinical findings lipomas (3 of 4 patients), joint laxity (4 of 4 patients), ear pits (4 of 4 patients), cardiac defects (1 of 4 patients), macrocephaly (1 of 4 patients) were documented. We propose that facial EVHC may indicate the presence of a novel inherited autosomal dominant disorder with multisystemic manifestations.
Guanine nucleotide binding protein alpha q polypeptide (GnaqM1J): An ENU induced mutant allele affecting dermal melanocytosis in the mouse

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In an N-ethyl-N-nitrosurea (ENU) mutagenesis screen at The Jackson Laboratory, a colony of C57BL/6J mice was examined with unusually darkly pigmented skin on the body, tail, ears, lower legs, and foot pads. Histological examination revealed increased dermal melanocytosis and dermal pigmentary incontinence not seen in wild type littermates. Sequencing identified an A to G missense mutation in exon 2 in the Gnaq (Guanine Nucleotide Binding Protein (G Protein), Q Polypeptide) gene. Previously reported ENU induced mutations in Gnaq (GnaqP61S) and Gnaq (GnaqR156C) were abnormally thickened and branched. Elastin fiber deposition was focally altered in the dermis with a limited to the dermis, unlike the GnaqM1J allele. Somatic mutations in Gnaq were recently linked to Sturge-Weber Syndrome, port wine stains, blue melanocytic nevi, and dermal melanocytosis (Mongolian spots). This new allelic mutation provides yet another tool to study the development and maturation of melanocytes in the skin.

Inherited LCK deficiency causes susceptibility to EV-HPV infections and early-onset squamous cell carcinomas

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ABSTRACT

Inherited epidermodysplasia verruciformis (EV) is a rare skin disorder characterized by susceptibility to specific types of human papilloma virus (HPVs) and is strongly associated with non-melanoma skin cancer. Inactivating mutations in EVER1 or EVER2 genes have been detected in most, but not all EV patients. In this study, we found 3 young EV siblings presenting with persistent EV-HPV infections. T cell defects and early-onset squamous cell carcinoma (SCC) without EVER1/2 mutations. These specific clinical manifestations suggest that they displayed significant heterogeneity compared with common EV patients. Thus we applied whole exome sequencing (WES) to identify potential mutation(s) account for EV-HPV infections in this family. A novel homologous splicing mutation has been detected in the T lymphocyte-specific protein tyrosine kinase (LCK) gene (c.188-2A>G), which resulted in expression of only mutant but not wild-type LCK in all patients. Our results demonstrate mutations in LCK are associated with EV and provide new clues for the understanding of host defenses against HPV and better genetic counseling of EV patients.

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Intra-familial variation in clinical phenotype of CARD14-related psoriasis

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There is a high degree of intra-familial variations in clinical manifestation of psoriasis. The aim of the study was to investigate the genetic basis of psoriasis in the affected family members and to propose possible mechanisms for the intra-familial phenotype variability. Screening was performed with 41 family members harboring CARD14 mutations. Three of the 41 family members had three additional coding region polymorphisms (rs2066964 and rs7561117 in CARD14) which make this strain susceptible to xenotropic murine leukemia virus-related virus (XMRV). For many years, M. pahari colony managers have known about the fragility of this strain’s skin resulting in separation of tail skin from the military if handled incorrectly. Tail skin tension testing of M. pahari revealed a significantly lowered force threshold in comparison to closely related inbred mouse species and subspecies. Histologically the tail skin separated at the subdermal level with the dermis firmly attached to the epidermis, excluding the epidermodysplasia vullosa complex of diseases. The dental collagen bundles were abnormally thickened and branched. Elastin fiber deposition was focally altered in the dermis adjacent to the hair follicle. Collagens present in the skin could not be differentiated between the species in protein gels. Together these data suggest that M. pahari have altered extracellular matrix development resulting in separation of the skin below the level of the dermis with moderate force similar to the African spiny mouse (Acomys).
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A role for autocrine and paracrine action of the Th1 chemokines in the pathogenesis of keratodermia

Nt5e-/-, Fermt1, and Nt5e knockout mouse

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Pathway analysis and protein-protein interaction network construction provide functional interpretation of GWAS evidence in alopecia areata

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Juxta-articular joint-capsule mineralization in CD73 deficient mice: Similarities to patients with NTSE mutations

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miR29b1 plays an important role in epidermal cell growth and survival

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Kindler syndrome: Novel and recurrent FERM1 mutations in 20 unique families with 70 patients and evidence of genetic heterogeneity
Evidence for coordinate regulation of Hmga2 and Tlr4 in hair follicle stem cells

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Toll-like receptor 4 (Tlr4) has emerged as a stem cell gene of interest in the mouse Kc2 locus. The receptor is widely recognized as an essential element in the triggering of innate immunity, binding pathogen-associated molecules such as lipopolysaccharides (LPS), and initiating a cascade of pro-inflammatory responses. However, the functional role of its differential expression in hair follicle stem cells remains a mystery. To address this, we compared differential Tlr4 expression in keratinocytes (KCs) among Tlr4 wild type (C57/BL6/NC), neither RNA nor protein strains of mice. We found similar coordinate expression between Hmga2 and Tlr4 mRNA in KCs between Tlr4 wild type and Tlr4 mutant mice (p=0.2724 for Hmga2, 0.5129 for Tlr4). As expected, no Tlr4 mRNA expression and low Hmga2 mRNA expression was found in unsorted Tlr4 deletion (p=0.0245 for Hmga2 between Tlr4 wild type and Tlr4 deletion, 0.0244 for Tlr4 and Tlr4 deletion). After sorting with CD34 and CD49f antibodies in Tlr4 wild type and Tlr4 mutant mice, Hmga2 expression in CD34+CD49f+ hair follicle stem cells is more than 10 times higher than that in CD34-CD49f- base cells (p=0.0004 for Hmga2 between CD34-CD49f- and CD34+CD49f+) and Tlr4 wild type and Tlr4 mutant mice CD34+CD49f+ and CD34-CD49f- KCs have significantly higher Hmga2 expression than in Tlr4 deletion KCs (p=0.0409 for Hmga2 between Tlr4 wild type and Tlr4 mutation and Tlr4 deletion KCs, 0.02162 for CD34+CD49f+ and 0.03639 for CD34-CD49f- ).

In addition, the results were confirmed with macrophages from the three strains (p=0.005 for Hmga2 between Tlr4-non deletion and Tlr4 deletion macrophage, 0.8526 for F4/80), but no Hmga2 protein was observed in macrophages. These results suggest that Hmga2 mRNA is coordinate regulated by Tlr4 mRNA in mouse KCs and macrophage, but the mechanism must be elucidated further.

Identification of MITF regulated microRNAs in melanoma

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Microphthalmia associated transcription factor (MITF) is the master transcriptional regulator and a lineage addiction oncogene in a subset of melanomas and play a role in drug resistance. However, the precise role MITF plays in melanoma is yet to be elucidated. In order to understand the role of MITF in melanoma, we set out to identify MITF-regulated microRNAs. We hypothesized that a subset of miRNAs are differentially regulated by MITF in melanocytes and melanoma. To identify MITF regulated miRNAs, we first defined putative MITF promoter regions using previously published MITF ChIP-seq binding data and filtered the set with experimentally verified gene expression using siRNA and targeted expression conservation for M-box and identified 52 out of 187 known potential MITF-regulated miRNAs. To validate regulation by MITF, we used ChIP-seq data to identify MITF binding within the putative promoter regions of all miRNAs and identified 62 miRNAs with MITF binding within the putative promoter regions. We found a significant statistical number of miRNAs between experimental and ChIP-seq methods, suggesting that microRNAs identified by motif search and refined using evolutionary conservation data potentially form a group of critical MITF regulated miRNAs. Within and around many of the 62 miRNAs, MITF binding motifs for ~70 different transcription factors, including YY1, E2F1 and CTCF. Expression histograms of miRNAs containing M-boxes plotted using data from TCGA datasets showed positive skew due to a fraction of tumors showing greatly increased expression as compared to the rest, suggesting that a fraction of MITF-regulated miRNAs might also be associated with MITF.

The experimental validation of subsets of these putative MITF-regulated miRNAs and their target miRNAs will provide important insight into the role of MITF in melanoma.