Oral Presentation

(8:35 AM)

INFLAMMATION AND FIBROSIS ON MOHS LEVELS, WHAT DOES IT MEAN?

Jillian Macdonald MD FRCPC, Jason Sneath MD, Bryce Cowan MD FRCSC, David Zloty MD FRCPC (University of British Columbia, Vancouver)

In Mohs micrographic surgery, many surgeons will take an additional level based solely on the presence of scar or inflammation. We sought to determine the frequency with which this occurs and parameters predicting tumor discovery on successive levels. A retrospective study was performed on 22, 419 lesions treated with Mohs micrographic surgery at a single institution between 1996 and 2011. An additional level was taken based on the presence of inflammation or fibrosis on 6233 lesions (27.8%). This resulted in detection of tumor on subsequent levels on 139 lesions (2.23%) in 137 patients (57 females, 82 males; age range 38-93 yrs). 92 lesions were basal cell carcinoma, 32 squamous cell carcinoma, 12 lentigo maligna, 1 sebaceous carcinoma, 1 atypical fibroxanthoma, and 1 dermatofibrosarcoma protuberans. The distribution of the tumors included: 40.3% on the nose, 15.1% forehead, 10.1% cheeks, 10.1% eyelids, 6.5% ears, 6.5% scalp, 2.9% perioral, and 8.6% were located on other body sites. Preliminary analysis of the data suggests that eccentrically placed first levels failing to completely encompass previous surgical scar, as well as the presence of dense inflammation particularly at the margins of the specimen, were more likely to predict tumor on subsequent levels. Several collision tumors were also detected. Additional data analysis is pending. Approximately 2.23% of levels prompted by the presence of inflammation or scar result in subsequent tumor detection. Taking an addition level may be warranted to ensure complete tumor removal and to maintain the low recurrence rates associated with Mohs surgery.

Category: Early experiments with well defined objectives/hypotheses

(8:46 AM)

THE PTEN/PI3 KINASE PATHWAY REGULATES THE EXPRESSION OF E- & N-CADHERIN IN MELANOMA VIA TRANSCRIPTION FACTORS TWIST AND SNAIL

Paul Kuzel[1], Li Hao[2], Elizabeth Garcia[2] and Sujata Persad[2]
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Introduction: To acquire motility and invasiveness, carcinoma cells must shed many epithelial phenotypes, detach from neighboring cells and undergo a series of drastic alterations known as the "Epithelial-Mesenchymal Transition (EMT)". In normal epithelium, E-cadherin provides high-affinity anchoring to neighboring cells, suppressing tumor progression. With malignant transformation, N-cadherin is upregulated. Method: Using a panel of five melanoma cell lines representing various phases of malignant transformation, we determined changes in the E- and N-cadherin profile during EMT progression. Results: As metastatic potential increased, we observed a switch from E- to N-cadherin expression. E-cadherin was expressed abundantly in primary melanocytes (HemaLP) with null expression in metastatic melanoma cells (A2058). In contrast, N-cadherin was expressed abundantly in A2058 cells, with null expression in HemaLP. There was also loss of the tumor suppressor PTEN in A2058 cells. PTEN transfection into A2058

cells resulted in re-expression of E-cadherin and decreased N-cadherin levels. The PTEN-modulated cadherin switch is regulated at the transcriptional level, involving the transcription factors Twist and Snail. Levels of both were greatest in A2058 cells and lowest in HemaLP. PTEN transfection into A2058 cells caused a decrease in Twist and Snail expression. Twist-knockout with shRNA in A2058 cells resulted in decreased N-cadherin expression, and E-cadherin re-expression. Over-expression of Twist in HemaLP caused an EMT-like cadherin switch. Conclusion/Clinical translation: We define a pathway that involves the regulation of E- & N-cadherin expression by PTEN. This may represent a key mechanism by which PTEN suppresses tumor progression, thus potentially representing a novel therapeutic target.

Category: Early experiment with well defined objectives/hypotheses

(8:57 AM)

IN VIVO MULTIPHOTON MICROSCOPY INSTRUMENT FOR DERMATOLOGY

Anthony Lee[1,2], Hequn Wang[1,3], Yingqiu Yu[1,4], Jianhua Zhao[1], Shuo Tang[4], Harvey Lui[1], David I. McLean[1], Haishan Zeng[1]
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Skin cancer is the most diagnosed form of cancer. As removal of skin lesions leads to scarring, it is highly desirable to have noninvasive diagnostic techniques that are able to distinguish cancerous from non-cancerous lesions without removing tissue. Here, we present the construction of a new multiphoton microscopy (MPM) instrument specifically for in vivo dermatology use. This instrument uses an ultrashort pulsed laser to excite fluorophores in the skin in a nonlinear process, providing cellular resolution and depth sectioning ability. The excitation powers used are low and do not cause damage to the skin. We observe two types of 2-photon excited signals, namely second harmonic generation (SHG) and two photon excited fluorescence (TPEF). SHG is sensitive to non-centrosymmetric structures in tissue such as collagen. TPEF is sensitive to endogenous fluorophores in the skin that absorb in our excitation region (360nm-475nm) such as elastin. In the future, we hope this instrument will allow dermatologists to perform so-called 'optical biopsies' to aid in determining tissue pathology during a patient's visit.

Category: Pilot/Exploratory Experiments

(9:08 AM)

CARDIOVASCULAR AND MORTALITY IMPACT OF DEPRESSION AMONG INDIVIDUALS WITH PSORIASIS AND PSORIATIC ARTHRITIS: A POPULATION-BASED STUDY

Authors: Burns LC[1,2], De Vera M[1,2], Bhole V[1], Choi H[1,2,3], Dutz J[1,2].
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Background: Psoriasis (PsO) and psoriatic arthritis (PsA) are chronic inflammatory diseases of the skin and joints, respectively. Limited clinical data indicate a high burden of depression among sufferers of PsO and PsA, yet population data are needed to delineate the impact of depression across the spectrum of these diseases relevant for resource allocation. Given the shared dysregulated inflammatory processes in PsO, PsA, and depression, an understanding of the impact of depression on critical outcomes (i.e., cardiovascular disease [CVD] and mortality) in PsO and PsA is needed. Hypotheses: 1) The burden (incidence and prevalence) of depression in PsO and PsA is high in British Columbia (BC); 2) Depression leads to excess risk of CVD and mortality in PsO and PsA. Data Source: Administrative health data from Population Data BC (PopData) have been used to create three study cohorts: PsO and PsA cohorts, consisting of all PsO and PsA cases in BC diagnosed between 1991 and 2006, and a non-PsO/PsA cohort comprised of 5 controls for each case, matched by age, sex, and length of available medical history. Analyses: The incidence and prevalence of depression across cohorts will be calculated. Cox proportional hazards models will measure the association between comorbid depression in PsO/PsA and the relative risks (RRs) of CVD and all-cause mortality. Significance: If the hypotheses are confirmed, these data may change the standards of clinical care for psoriatic patients, including comprehensive screening for depression in PsO and PsA, and when identified, more aggressive management of depression and cardiovascular risk factors.

Category: Early experiments with well-defined objectives/hypotheses

(9:19 AM)

CXCR3/LIGAND SIGNALING IS IMPORTANT FOR NON-MELANOMA SKIN CANCER KERATINOCYTES

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Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are the most common non-melanoma skin cancers (NMSCs). Previously, we showed that chemokine receptor CXCR3 signaling was an essential mediator for primary human BCC-derived cell growth *in vitro*. However, CXCR3 effects on SCC and its pre-cancerous forms are still not known. We hypothesized that CXCR3 signaling may be involved in the growth of NMSC including SCC. In this study, real-time RT-PCR (qPCR) revealed that expression of *CXCR3* and its ligands were upregulated at the highest levels in SCC among all NMSC lesions tested, which included SCC, BCC, seborrheic keratosis, actinic keratosis and Bowen's disease samples, as compared to non-lesional skin epithelium. Immunohistochemistry showed that CXCR3 colocalized with SCC

marker, cytokeratin 13 in SCC tumor masses. Blockade of CXCR3 signaling in HaCaT cells, a human immortalized keratinocyte cell line, via treatment with CXCR3 neutralizing antibody, resulted in substantially reduced cell growth and enhanced apoptosis. Treatment of HaCaT cells with anti-CXCR3 plus CXCL11 peptide led to similar results. Cells treated with CXCL11 only exhibited enhanced proliferation. Migration and invasion assays showed significantly increased percentages of HaCaT cells moving towards CXCL11 peptide in a dose dependent manner. Furthermore, qPCR revealed that among several *matrix metalloproteinases* (*MMPs*) tested, *MMP1* was upregulated significantly in CXCL11-treated HaCaT cells as compared to untreated cells. Taken together, CXCR3/ligand signaling may be important for cell growth and survival as well as invasive characteristics in cancerous keratinocytes, especially in SCC. KT: Targeting CXCR3/ligands may be effective in treating non-melanoma skin lesions.

Category: Pilot/exploratory experiments

(9:30 AM)

AUTOMATED DETECTION AND ANALYSIS OF DERMOSCOPIC STRUCTURES ON DERMOSCOPY IMAGES

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With recent advances in skin imaging technologies there has been an increasing demand for image processing techniques in computer aided-diagnosis of pigmented skin lesions using dermoscopy images. Such diagnosis may involve the identification of over 100 cutaneous morphological features. Our work follows a relatively new trend in clinical dermatology to identify specific 'dermoscopic structures' such as streaks, scale, and pigment network which are used to aid skin cancer (Melanoma, Basal Cell Carcinoma, and Squamous Cell Carcinoma) diagnosis. We present a novel approach to detect and visualize streaks, scale, globules, and pigment network in dermascopic images, based on their clinical definitions. These dermoscopic structures are modeled based on the structural (shape), geometric (spatial arrangement), chromatic and textural features defined by experts in dermoscopy. Our approach has several steps; pre-processing that includes image enhancement and automatic skin lesion segmentation, object detection using morphologic techniques, and feature extraction and classification into cancerous or benign lesions. Our results over 500 images show an accuracy of 93% on pigment network detection, 82% on typical-atypical pigment network classification, 74% on streaks detection (experts had less than 91% agreement), and 84% on scale detection. Conclusion: Our method is a fully automated skin lesion analysis that successfully segments and analyzes the three important dermoscopic structures for Melanoma, Basal Cell Carcinoma, and Squamous Cell Carcinoma diagnosis. Clinical Significance and KT: This approach can be used as the core component for automated skin cancer diagnostic systems.

Category: Early experiments with well defined objectives/hypotheses.

HIGH EXPRESSION OF IMPACT PROTEIN PROMOTES RESISTANCE TO INDOLEAMINE 2,3 DIOXYGENASE-INDUCED CELL DEATH

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Introduction: We have previously used the immunosuppressive effects of Indoleamine 2,3-dioxygenase (IDO), a tryptophan-degrading enzyme, in the development of a non-rejectable skin substitute. We showed that IDO expression selectively induces apoptosis in immune cells rather than skin cells. However, the mechanism(s) underlying selective resistance of skin cells to IDO exposed environment is not elucidated. Here we asked whether the activity of general control nonderepressible-2(GCN2) kinase pathway and its known inhibitor, IMPACT protein, in immune and skin cells is differentially regulated in response to IDO. Methods: IDO-expressing fibroblasts were co-cultured with Jurkat cells, human CD3+ Tcells, fibroblasts or keratinocytes. Levels of phosphorylated GCN2, total GCN2 and IMPACT were evaluated by Western blot. MTT and viability assays were performed for IMPACT siRNA-knocked down fibroblasts. Proliferation assay was performed for IMPACT-overexpressing Jurkat cells. Results: GCN2 kinase pathway activation was significantly higher in immune cells exposed to IDO, relative to that of skin cells. In contrast, IMPACT protein was highly expressed in skin cells while its expression level was very low in T cells and undetectable in Jurkat cells. A significant IDO-induced suppressive as well as apoptotic effect was demonstrated in IMPACT-knocked down fibroblasts in the presence of IDO. Proliferation of IMPACT-overexpressing Jurkat cells was rescued significantly in tryptophan-deficient environment. Conclusion: High expression of IMPACT in non-immune cells acts as a protective mechanism against IDO-induced GCN2 activation. Clinical Significance/Knowledge Translation: This study revealed that IDO expression can function as a local immunosuppressive factor to protect the allograft skin without compromising skin cell viability.

Category: Early experiments with well defined objectives/hypotheses.

ROLE OF EIF5A2 IN HUMAN MELANOMA CELL MIGRATION, INVASION AND PATIENT SURVIVAL.

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Human eukaryotic initiation factor 5A2 (EIF5A2) has been shown to be associated with metastasis in multiple cancer types, including colon, ovarian, and bladder cancer. However, so far no work has been done to specifically study the role of EIF5A2 in melanoma. In this study we investigated the role of EIF5A2 in human melanoma pathogenesis. Using the tissue microarray technology we found that EIF5A2 expression is significantly increased in metastatic melanoma compared to normal nevi and dysplastic nevi as well as in primary melanoma compared to normal nevi. Increased EIF5A2 staining is associated with increased melanoma

thickness, presence of ulceration as well as poorer overall and disease-specific 5-year survival of primary melanoma patients. Cox regression analysis revealed that induced EIF5A2 staining is an independent factor for the poor prognosis of patients. Furthermore we found that knockdown of EIF5A2 did not have any effect on cell proliferation but decreased melanoma cell migration and invasion compared to control. Knockdown and overexpression of EIF5A2 also showed a decrease and increase in the level of p-AKT compared to respective controls. Taken together this study highlights the importance of EIF5A2 in melanoma pathogenesis and the possibility that EIF5A2 may serve as a promising prognostic marker and a potential therapeutic target for human melanoma.

Category: Early experiments with well defined objectives/hypotheses.

(11:31 AM)

DIFFERENTIATE SQUAMOUS CELL CARCINOMA CELL AND MELANOMA CELL FROM HACAT CELL AND MELANOCYTE USING MICRO-RAMAN SPECTROSCOPY GUIDED WITH CONFOCAL IMAGING
Hequn Wang[1,2], Tsung-Han Tsai[2], Jianhua Zhao[1,2], Anthony Lee[1,2], Blanche Ka Ki Lo[2], Mei Yu[2], Harvey Lui[1,2], David I. McLean[1,2], and Haishan Zeng[1,2*]
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Background/purpose: Skin cancer is the most common type of cancer. Current techniques for identifying normal and neoplastic tissues are either destructive or not sensitive enough. Optical techniques, such as Raman spectroscopy and confocal technique, may potentially obviate many of the limitations by providing non-invasive, high-resolution, real time morphological and biochemical analysis of living tissues and cells. Methods: *In vitro* cultured cells, including HaCaT cell, squamous cell carcinoma cell (SCC), melanocytes (MC), and melanoma (MM) cell, were trypsinized and measured using micro-Raman spectroscopy under the guidance of confocal imaging. Linear discriminant analysis (LDA) was employed to separate the 4 types of cells. Results: Significant differences were found in the mean spectra of HaCaT and SCC cell, MC and MM cell. Different types of normal cells and different types of tumor cells could also be differentiated. Combining HaCaT and MC cell as normal group, SCC and melanoma cell as tumor group, we also found significant differences in the mean spectra. About 90% sensitivity and specificity was achieved for all the separations that we performed. Conclusion: Our results demonstrated great capability of confocal Raman spectroscopy in separating different types of cells. We also recognized Raman spectra of major types of skin cells and their malignant counterparts, which would help interpreting Raman spectra of *in vivo* skin. This work should eventually help diagnosis of skin cancer and other skin disease in clinical dermatology.

Category: Early experiments with well defined objectives/hypotheses

(11:42 AM)

UVA1 THERAPY OF MORPHEA - THE VANCOUVER EXPERIENCE

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Background and Objective: UVA1 has been used in Europe for morphea with significant success, but the experience in North America is more limited. This study summarizes our preliminary experience with UVA1 for morphea. Methods: Fifteen patients (13 females, 2 males), aged 17-60 (median 50) with morphea were treated with UVA-1 between November 2009- December 2010. A whole-body, stand-up UVA1 ML24000 phototherapy unit (Daavlin Co., Bryan, OH) was used for treatment. Each patient received 20 sessions of "medium dose" UVA1 phototherapy at a dose of 60 J/cm^2, five times weekly for 4 weeks. Results: To date 11 patients have fully completed one 20-session treatment course. One patient discontinued treatment after 15 sessions because she felt that the skin tightening was getting worse, although the investigators did not notice this effect. Some degree of clinical improvement was observed in 9 patients. Improvement was manifested as resolving inflammation and/or decreasing induration. None of the patients had a complete response as defined by total normalization of affected skin. One patient exhibited no change with treatment and did not return for follow up. Side effects included pruritus (4/15), erythema (5/15), dryness (1/15), tanning (15/15), polymorphous light eruption (2/15) and UV-burn (2/15). UVA1 induced marked postinflammatory hyperpigmention within the affected plaques that persisted longer than the overall tanning effect. Conclusion: UVA1 has demonstrated some efficacy for patients with morphea that somewhat parallels the experience reported in the literature. The lack of validated outcome scoring system made it difficult to quantify the responses.

(11:53 AM)

ALOPECIA AREATA DEVELOPMENT MAY INDUCE ABNORMAL HEART PHYSIOLOGY

Eddy H.C. Wang[1], Katy Chong[1], David Granville[2], Jerry Shapiro[3], Kevin J. McElwee[1]
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Alopecia areata (AA), a non-scarring, inflammatory hair loss disease, is believed to involve an autoimmune mechanism. In other autoimmune skin conditions, such as psoriasis, there is evidence that affected individuals have an increased risk of heart disease and heart failure. We investigated the potential for a relationship between AA and heart disease. It was noted in passing that some of the mice with AA had heart hypertrophy compared to the normal haired littermates. Quantitative PCR (qPCR) analysis showed a significant increase in the expression of Interleukin 18 (IL18, 4.6 fold), IL18 receptor-1 (IL18r1, 2.8 fold) and IL18 binding protein (IL18bp, 5.2 fold) in the AA heart tissue compared to controls. In a time course study, significant increase of mRNA expression of IL18r1, IL18bp and Interleukin Converting Enzyme (ICE) were observed 10 weeks post skin graft but not IL18. Masson's Trichrome Stain for collagen

deposition revealed a significantly higher amount of collagen around the blood vessels within the heart of AA mice and the thickness of the endothelial layer of these blood vessels was significantly thinner. Immunohistochemistry analysis showed a localization of IL18 in the atria of AA mice that resembles a phenotype of atrial fibrillation. IL18r1 and IL18bp showed a more dispersed pattern covering the whole heart in both AA and controls. KT: the development of AA may result in an elevated IL18 activity that can lead to fibrosis of heart tissues and the intervention of this factor may be beneficial to hair re-growth and heart health.

Category: Early experiments with well defined objectives/hypotheses.

(12:04 PM)

CLINICAL HETEROGENEITY OF PRIMARY FOCAL HYPERHIDROSIS
Yuanshen Huang, Yin Yao, Christina Scali, Christina Han, Ming-wan Su and Youwen Zhou Department of Dermatology and Skin Science, University of British Columbia; Molecular Medicine Laboratory and Chieng Genomics Center, Vancouver Coastal Health Research Institute.

Background and objectives Primary focal hyperhidrosis (PH) is characterized by unprovoked and uncontrollable perspiration, which causes significant social and psychological burden to the affected individuals. Although anatomic subtypes have been described, little is known about the age of onset, genetic predisposition and prevalence in ethnical groups. In this study, we aim to investigate the clinical features of various anatomic PH subtypes. Method Four hundred and forty nine consecutive subjects assessed at the Vancouver General Hospital Hyperhidrosis Clinic June 1 2004-November 1, 2009 were included. Each subject filled out a detailed questionnaire on the onset and distribution of excessive sweating, together with family history and association with other conditions, such as anxiety. The patients were classified into subtypes based on their anatomic sites of perspiration. For each subtype, the gender distribution, age of onset, ethnic composition, family history and association with anxiety were analyzed. χ^2-test and t test were performed using SPSS with significance set at two-sided 5% error level. Results Four distinct anatomic subtypes can be recognized: PH-1: palmoplantar; PH-2: axillary; PH-3: mixed palmoplantar and axillary; PH-4, face with or without torso affected. These subtypes differ from each other significantly in age of onset, anxiety association, gender distribution, ethnic prevalence and familial clustering, suggesting that they are distinct subtypes. Conclusion With four distinct anatomic subtypes, primary focal hyperhidrosis is highly heterogeneous. Further investigations are warranted to uncover the genetic basis of the clinical heterogeneity. Interpretation Our findings highlight the need to individualize management for each patient with PH.

Category: Pilot/exploratory experiments

(12:15 PM)

EVALUATION OF AN *IN-SITU* GELLING MATRIX TO SERVE AS A PATIENT-READY SKIN SUBSTITUTE IN THE TREATMENT OF DIABETIC WOUNDS

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With nearly 20 million cases each year, diabetic wounds continue to be among the most difficult to treat. Autografts and biological dressings can provide wound coverage and promote healing yet have limitations. Ideally the use of a patient-ready, non-rejectable, non-autologous engineered skin substitute would be advantageous. Previously we demonstrated that Indoleamine 2, 3 dioxygenase (IDO), an essential immune modulating enzyme, is able to suppresses Tcell infiltration into solid skin substitutes. Nonetheless, one unattractive limitation of solid scaffolds is the length of time that they required to prepare. It is our hypothesis that an in-situ gelling scaffold comprising non-autologous IDO expressing fibroblasts will provide rapid, integrative wound coverage and promote healing without rejection. Methods: To investigate this hypothesis a novel crosslinked, collagen-glycosaminoglycan (GAG) scaffold was developed comprising a rapid-temperature and pH sensitive hydrogel. Physical testing assessed: Physical testing assessed: strength, degradation and gelation rate. In-vitro cell culture and preparation of a skin substitute evaluated tissue architecture, in addition to cellular viability and proliferation. Results demonstrated that the novel composite scaffold exhibited not only faster gelation ($p<0.01$) but also improved mechanical strength ($p<0.05$). It further demonstrated reduced contracture ($p<0.05$) and cellularity ($p<0.05$) at day 10 without compromising cell viability ($p>0.05$). In conclusion, the combination of our hydrogel system within a crosslinked collagen gel produced an in-situ gelling scaffold that could be used to deliver IDO expressing cells to diabetic wounds and promote healing. The abstract fits somewhere between these two criteria (as components of it are under review for publication, and others have already been published): Early experiments with well defined objectives/hypotheses; Applied/functional experiments (animal models of disease and in vivo studies, etc)

(12:26 PM)

PHYSICIAN FACTORS AND THEIR INFLUENCE ON BIOPSYING ATYPICAL PIGMENTED LESIONS

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Background: Biopsies of atypical melanocytic lesions are subject to histopathologic analysis. For melanoma, this is the gold standard for obtaining information pertinent to diagnosis, staging and prognosis. Method: 787 pathology cases were retrospectively reviewed. Data included biopsy technique, outcomes (diagnostic ability, definitive treatment), medical school graduation year, post-graduate training, and location of training. Results: 1) Medical training location: 77.5% of South African (SA)-trained physicians performed elliptical excisional biopsies, compared to 66.0% of Canadian-trained physicians. 2.2% and 9.1% performed shave biopsies, respectively. In comparison to 10.2% of Canadian-trained physicians, only 6.7% of SA-trained physicians performed biopsies that were neither diagnostic nor provided definitive treatment. 2) Post-graduate training: 90.2% of biopsies sampled by Plastic Surgeons were elliptical excisions, compared to 43.7% and 67.5% by Dermatologists and Family Physicians, respectively. Although Dermatologists and Family Physicians performed a comparable percentage of punch biopsies, the former performed 76.8% of all excisional punch biopsies, while the latter performed 77.6% of all partial punch biopsies. Plastic surgeons were significantly more likely to perform biopsies resulting in both definitive diagnosis and treatment. 3) Clinical experience: No difference in biopsy outcomes. Conclusion: SA-trained physicians and Plastic Surgeons were more likely to use elliptical excision biopsy techniques, and had improved diagnostic and treatment outcomes. Years of clinical experience did not affect biopsy outcome. These results may reflect differences in educational training, established patterns of practice, referral patterns, or resource availability. Improvements to biopsy outcomes are possible through awareness of outcomes associated with particular techniques and judicious choice of technique.

Category: Early experiments with well defined objectives/hypotheses.

(1:30 PM)

ACCINATION VIA THE SKIN PROVIDES ACUTE PROTECTION AGAINST BOTH BACTERIAL AND VIRAL INFECTIONS

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Infectious diseases are the leading cause of death and disability in humans. Although immunization is the most cost-effective health interventions against infectious diseases, current vaccines remain inefficient specifically because they are ineffective in eliciting protective CD8 cytotoxic T cells (CTLs). Using the skin as an adjuvant administration route, we hypothesize topical Toll-like receptor 9 (TLR9) agonists safely optimize standard vaccines by activating both skin stromal cells and hematopoietic-derived cells, which in turn increase antigen-specific CTL frequency. We have demonstrated that topical administration of a DNA sequence (CpG ODN 1826), a TLR9 agonist, with a subcutaneous protein antigen is superior in inducing antigen-specific CTLs and antibody responses compared to parenteral routes in the absence of adjuvant toxicity in a mouse model. We determined whether hosts obtain increased ability to combat bacterial (*Listeria monocytogenes*) and viral (influenza A) infections (acute protection). Immunized mice with adjuvant dramatically decreased bacterial load compared to antigen alone three days post systemic infection in liver ($5.4 \pm 1.9 \times 10^5$ to 0 CFU*) and spleen ($2.0 \pm 0.7 \times 10^6$ to $1.4 \pm 1.3 \times 10^1$ CFU*), or the viral burden of influenza A three days post intranasal

infection in the lung ($3.4 \pm 0.6 \times 10^3$ to $1.0 \pm 0.8 \times 10^3$ PFU*). Our immunization strategy enhances host ability to combat infections, which potentially leads to safer and more effective vaccines without re-formulation and re-licensure that will have an impact on human health and in alleviating social economic burden globally. (Errors in SEM, * P <0.05)

Category: Applied/functional experiments

(1:41 PM)

DIFFERENTIAL POLARISATION PROPERTIES OF MELANOMA VERSUS BENIGN PIGMENTED LESIONS

Gurbir Dhadwal[1], Lioudmila Tchvialeva[1], Harvey Lui[1,2], David I. McLean[1], Tim K. Lee[1,2,3]
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Background: When skin is illuminated with polarised light, the light becomes partially depolarized. The amount of light maintaining its original linear polarisation state can be quantified by capturing two images with polarisation filters oriented perpendicular to each other and expressed as the degree of linear polarisation (DOLP). Our objective is to determine if there are differences in the DOLP between melanomas and benign pigmented lesions. Methods: A device was built which can illuminate an area of skin with polarised red or blue laser light and capture polarised images. A convenience sample of patients attending a dermatology clinic was obtained. The mean DOLP of 15 melanomas was compared with the benign group with a t-test and then compared individually to 66 seborrheic keratoses, 15 acquired nevi and 25 atypical nevi using Dunnett's method. Results: We found a significant difference in the mean DOLP of melanomas and the benign lesions taken as a group with blue light (0.68 +/- 0.05(SEM) vs 0.55 +/- 0.02, p=0.021) but not red light. On subgroup analysis we found that there was a significant difference between melanomas and seborrheic keratoses using blue light (0.68+/- 0.05 vs 0.51+/- 0.02, p<0.05) and red light (0.61 +/-0.03 vs 0.53+/-0.01, p<0.05). Conclusions: We were able to find significant differences between melanomas and benign skin lesions, and on subgroup analysis find a significant difference between melanomas and seborrheic keratoses. There is a potential that the DOLP could be used to aid in the non-invasive diagnosis of melanoma.

Category: Applied/functional experiments (animal models of disease and in vivo studies, etc)

(1:52 PM)

INVESTIGATING METHOTREXATE USE AMONGST DERMATOLOGISTS AND RHEUMATOLOGISTS IN CANADA

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Background: Methotrexate (MTX) is commonly used by dermatologists in the treatment of psoriasis and by rheumatologists for psoriatic arthritis (PsA) and rheumatoid arthritis (RA). Treatment guidelines on MTX use have been published in both specialties yet current use patterns remain largely unknown. This study examined MTX use amongst Canadian dermatologists and rheumatologists. Methods: An online survey was made available to 414 Canadian dermatologists and 415 Canadian rheumatologists in September 2010. The 56-question survey asked about MTX use in the treatment of psoriasis, PsA and RA with topics specific to administration and use with biologics. Results: 27.2% of rheumatologists and 16.4% of dermatologists responded to the survey. Both rheumatologists (80.0%) and dermatologists (96.8%) initiated MTX therapy with oral tablets in psoriasis. More rheumatologists (95.7%) than dermatologists (49.2%) reported switching to parenteral MTX and to subcutaneous (SC) injections. When adding biologics, rheumatologists (75.6%) did not change the MTX dose while dermatologists (81.1%) discontinued MTX. In PsA, both rheumatologists (82.0%) and dermatologists (100%) initiated MTX therapy with oral tablets. More rheumatologists (100%) than dermatologists (68.8%) switched to parenteral MTX, specifically to SC injections. When adding biologics, rheumatologists (70.4%) did not change the MTX dose while dermatologists (43.8%) discontinued MTX. Few dermatologists reported treating RA. Conclusion: Results demonstrate that dermatologists and rheumatologists are similar in their initial use of MTX in psoriasis and PsA but differ in how they proceed with the therapy. Clinical significance and KT: This study provides insight into how Canadian dermatologists and rheumatologists compare in the use of MTX therapy.

(2:03 PM)

GRANZYME B CONTRIBUTES TO EXTRACELLULAR MATRIX REMODELING AND SKIN AGING IN APOLIPOPROTEIN E KNOCKOUT MICE

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Granzyme B (GrB) is a serine protease expressed by immune cells with an ability to degrade the extracellular matrix (ECM) component decorin, a key mediator of collagen structure. Apolipoprotein E knockout (apoE-KO) mice display an aged and inflamed skin phenotype susceptible to disease featuring collagen remodeling. The purpose of this study is to examine the role of GrB in aging and disease of the skin in apoE-KO mice. Wild type (WT), apoE-KO and GrB/apoE double knockout (DKO) mouse skin was examined using H&E, picrosirius red and luna stains to assess morphology and ECM changes in formalin fixed skin sections. Multi-photon microscopy was also used to examine collagen organization in mouse skin samples. ApoE-KO mice demonstrate frailty, increased morbidity, skin thinning and a loss of dermal collagen density. DKO mice showed protection against these deleterious changes. ApoE-KO mice also showed reduced decorin levels in the skin, while DKO mice showed increased decorin. In conclusion, apoE-KO mice display features of premature aging skin, a phenotype that is reduced when knocking out GrB suggesting GrB plays a role in skin aging and collagen disorganization, possibly through the cleavage of decorin. These results help in our understanding of possible mechanisms of aging skin and identify new potential therapeutic targets to treat patients suffering from premature aging or diseased skin.
Category: Applied/functional experiments

(2:14 PM)

TRENDS IN SUNBURN RATES AT A NATIONAL LEVEL

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Skin cancer, the most common type of cancer continues to be a major concern with increasing numbers of skin cancers being detected. A variety of campaigns have targeted the Canadian population to educate the public about the importance of reducing sun exposure. Although studies have shown that these campaigns have increased the knowledge of the importance of sun protection and sun avoidance, limited studies have evaluated the effect on behavior.The National Population Health Survey (NPHS) conducted by Statistics Canada has followed the same cohort of people across Canada over several years, targeting over 98% of the Canadian population. The NPHS has evaluated different sun protection behaviors, such as the presence or absence of sunburn(s) within the last twelve months. This study compared the rates of sunburn in 2006-2007 to 2000-2001. Correlations with demographic variables were computed. Simple logistic regression analysis was performed using Statistical Analysis Software (SAS) version 9.2, and those variables that were statistically significant were included in multiple logistic regression analysis. The response rates for the NPHS have varied over the years from 80-85%. In 2000-2001, 2914 of 11290 individuals experienced a sunburn within the past twelve months (25.8%), compared to 3123 of 12160 (25.7%) in 2006-2007. These changes show that minimal change has been observed with sunburn rates in the Canadian population. The trend shown in this study may indicate that educational campaigns have not yet been successful in changing sun exposure behavior patterns. Similar trends have been found in another national survey, the Canadian Community Health Survey, however further studies are needed to confirm these findings.

Category: Epidemiology Study for Skin Cancer Prevention

(2:25 PM)

ING1B MAINTAINS GENOMIC STABILITY UPON REPLICATION STRESS

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Although it is well known that ultraviolet radiation is the major environment risk factor for skin cancer, the genetic factors that are involved in the development of cancer due to UV is not clear. The expression of tumor suppressor Inhibitor of Growth 1b (ING1b) has been shown to be reduced or mislocalized in various cancers. We showed that ING1b is mutated in 20% of melanoma. Previously, we demonstrated that ING1b deficient cells are hypersensitive to UV and displayed enhanced genomic instability. We further showed that ING1b is required for monoubiquitination of Proliferating Cell Nuclear Antigen (PCNA) which plays an important role in the lesion bypass pathway. In this study, we further investigated the mechanism by which ING1b maintains genomic stability. We found that ING1b depleted cells displayed

hypoacetylation of histone H4 at S phase and treatment with class I and II histone deacetylase inhibitors restored histone H4 acetylation and PCNA monoubiquitination in ING1b knockdown cells. Moreover, restoration of histone H4 acetylation alleviated UV-induced DNA DSBs and cell death in ING1b knockdown cells. These data suggest that ING1b regulates PCNA monoubiquitination through histone H4 acetylation to facilitate lesion bypass and recovery from replication blockage. Clinical significance and KT: This study leads to a better understanding of the genetic factors that are required for preservation of genomic stability upon UV induced replication stress. It sheds light on identifying cancer susceptible pathways for skin cancer therapy.

Category: Applied / functional experiments

(2:36 PM)

REPIGMENTATION OF VITILIGO-ASSOCIATED LEUKOTRICHIA AFTER AUTOLOGOUS, NONCULTURED MELANOCYTE-KERATINOCYTE TRANSPLANTATION

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Leukotrichia is associated with many cases of vitiligo. Hair follicles are believed to be the source of melanocytes for skin repigmentation using standard medical therapy for vitiligo. Vitiliginous areas with overlying leukotrichia usually fail to achieve repigmentation by conventional medical treatments due to a deficient melanocyte resevoir. Even after successful repigmentation of vitiliginous skin by medical therapies, the leukotrichic hairs may remain depigmented causing a major psychological impact to the patient. In such cases, surgical treatments may help repigmentation of leukotrichia. There are only a few reports of successful repigmentation of leukotrichia after using different surgical treatments for vitiligo. We report 4 cases of successful repigmentation of vitiligo-associated leukotrichia after autologous noncultured melanocyte-keratinocyte transplantation.

(2:47 PM)

IS BORDER IRREGULARITY USEFUL FOR MELANOMA DIAGNOSIS?

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For computer aided skin lesion diagnosis systems, the lesion must first be outlined (segmented) and then the lesion characteristics quantified. Border irregularity measures quantify the degree of the irregularity of the structural indentations and protrusions along the lesion border. The objective of this work is to study the border irregularity features and their effect on melanoma diagnosis in computer aided systems. In this work, two irregularity features are extracted and their power in distinction between melanoma and non-melanoma lesions is tested. We used 83 lesion images from a dermoscopy atlas and extracted their borders using a threshold algorithm

on image intensities. We eliminated imprecise borders from our dataset by visual inspection; thus, our dataset size retained 63 lesions, 11 malignant (Melanoma and Basal Cell Carcinoma) and 52 benign. We have computed two different irregularity measures called Most Significant Irregularity Index (MSII) and Overall Irregularity Index (OII). MSII indicates the largest indentation or protrusion segment of the border irregularity index, while OII is calculated by summing up all individual indices over the entire lesion border. These features have been used in different diagnostic algorithms. In the first method, we used only MSII and we obtained 54.27% accuracy in classifying into malignant and benign lesions. Using only OII as a feature, we have obtained 62.75% accuracy. Combining OII and MSII resulted in 81.27% accuracy. Conclusion: Lesion border irregularity indices can be used as highly distinctive features in diagnosis of skin lesions.

Category: Early experiments with well defined objectives/hypotheses