POSTER PRESENTATION

Poster 1

EXPERIENCE WITH USTEKINUMAB IN THE SETTING OF ANA+ PATIENTS WITH PSORIASIS

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Psoriasis is an autoimmune disease which can affect the skin, scalp, nails and joints. Treatment of extensive or recalcitrant psoriasis commonly involves the use of biologics such as TNF inhibitors (adalimumab, etanercept or infliximab). The use of TNF inhibitors in the setting of systemic lupus erythematosus (SLE) is controversial as these drugs have been reported to precipitate SLE and cutaneous lupus erythematosus. In this case-series, we reviewed our experience in the treatment of patients with SLE and concurrent severe psoriasis. We present 3 patients, 2 with prior SLE and 1 with a positive ANA. All patients were treated with ustekinumab (Stelara ®). Response to therapy in terms of psoriasis and SLE was followed. SLE activity remained stable and psoriasis improved. This series suggests that ustekinumab can be safely considered for patients with cutaneous psoriasis and positive ANA.

Poster 2

SOX4 MEDIATED DICER EXPRESSION IS CRITICAL FOR SUPPRESSION OF MELANOMA CELL INVASION

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Sry-related HMG-box4 (Sox4) is a transcription factor and its expression is lost in metastatic melanoma. Sox4 can bind to the promoter sequence of certain miRNA biogenesis factors such as Dicer. Interestingly, altered expression of Dicer was also observed in cancers. However, the potential mechanisms which regulate Dicer expression and its significance in melanoma progression are unknown. Our data revealed that Sox4 knockdown reduces Dicer expression, while Sox4 overexpression increased Dicer expression. We found that Dicer knockdown enhances melanoma cell invasion by at least 2-fold. In addition, we revealed that overexpression of Dicer reverts the enhanced melanoma cell invasion upon Sox4 knockdown. Furthermore, we examined the expression of Dicer protein in melanocytic lesions (n=504) at different stages by tissue microarray and found that Dicer expression is inversely correlated with melanoma progression ($P < 0.0001$). Consistently, reduced Dicer expression was correlated with a poorer overall and disease-specific 5-year survival of patients ($P = 0.015$ and 0.0029, respectively). In addition, we found a significant correlation between expression of Sox4 and Dicer proteins in melanoma biopsies ($P = 0.009$), further indicating the regulation of Dicer expression by Sox4. Finally, we revealed that knockdown of Sox4 induces a major change in the expression pattern of miRNAs in melanoma cells. Our results pinpoint the regulation of Dicer expression by Sox4 in melanoma and the critical role of Dicer in suppression of melanoma invasion. Our findings on Sox4 regulated miRNA biogenesis pathway may aid toward the development of novel targeted therapeutic approaches for melanoma.
Category: Applied/functional experiments (animal models of disease and *in vivo* studies, etc)

Poster 3

COOPERATION BETWEEN ING1B AND P53 IN UV-DAMAGED DNA RECOGNITION

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Being an essential prerequisite for repairing DNA induced by ultraviolet (UV), the recognition process, the time limiting step during the nucleotide excision repair (NER), has remained elusive. We previously found that inhibitor of growth (ING), both ING1b and ING2, play an important role in repairing UV-damaged DNA. So, in this study we firstly investigated the cooperation between ING1b and ING2 in NER. We found that ING1b knockdown (KD)/ING2-overexpression had a reduced removal rate of cyclobutane pyrimidine dimmers (CPDs) compared with ING2-overexpression alone at 12 hour after UV treatment. The fluorescent intensity of CPDs in ING1b KD/ ING2-overexpressing cells faded at a slower rate than that in ING2-overexpressing cells, which was consistent with the results from the slot-blot. The immuno- fluorescence results showed that ING1b and ING2 partially colocalized in nuclei after 12 hour UV treatment. Compared with ING2-overexpression, ING1b KD/ING2- overexpression impaired the recruitment of XPA to sites of damage and reduced the efficiency of DNA repair. As our previous research showed that p53 can vigorously alter chromatin accessibility to impact NER and the p53-dependency of ING1b- enhanced NER, we will next investigate how the interaction between ING1b and p53 enhances the repair of UV-damaged DNA through identifying the domain responsible for their interaction, their cooperation in DNA lesion recognition, and the relationship between ING1b-p53 interaction and NER. Understanding the exact molecular mechanism of NER may lead to the design of new prevention strategies for various UV-related skin diseases

Category: Early experiments with well defined objectives/hypotheses.

Poster 4

SUNBURNS AND SUNSCREEN USAGE TRENDS IN CANADA

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Canadian educational campaigns have been conducted in an attempt to educate people about the potential hazards of excess sun exposure. Using cross-sectional data from the 2006 Canadian Community Health Survey (CCHS), a population based national survey that provides detailed information on sunburns and sun protection behaviours. The Canadian Community Health Survey is conducted by Statistics Canada and collects responses from household interviews from persons aged 12 or older, which covers private occupied dwellings in 122 health regions covering all provinces and territories, which represents 98% of the Canadian population aged 12 or older. In this study we compared sun protection behaviours from 2007/2008 from 2005. The primary outcome variable for level of sun exposure was measured by assessing the presence or absence of any sunburn over the last twelve months. Secondary variables were also assessed that included behaviors practiced to prevent the occurrences of sunburns such as duration of sun exposure, wearing protective clothing, and wearing sunscreens. SAS 9.3.2 (SAS institute, Cary NC) was used to analyze and run models on data collected. In 2005, 792 of 2031 individuals (39.0%) experienced a sunburn in the past 12 months, compared to 893 of 2303 individuals (38.7%) in 2007/2008. These trends show that significant changes have not been observed in changing sun protection behavior over time. Further studies are needed to confirm these findings.

Category: Epidemiology study

Poster 5

PREVENTION AND TREATMENT OF ALOPECIA AREATA VIA RE-ESTABLISHING IMMUNE PRIVILEGE

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Alopecia Areata (AA) is characterized by tissue-specific hair loss and caused by a suspected autoimmune disorder in hair follicles (HF). It is a common disease with a lifetime risk of 1.7%. Although it is not fatal, patients experience extreme stress from their hair loss. Currently, there is no cure for AA. Previous studies show that normal HF exhibit immune privilege and loss of immune privilege may trigger AA. We hypothesize that promotion of immune privilege can prevent or treat AA. First, we proposed to identify immune privilege related genes expressed in HF by quantitative PCR (qPCR). Compared to fibroblasts, an upregulation of immune privilege associated genes (activin A, αMSH, and TGF-β2 showed a 3.0-, 12.6-, and 3.2-fold increase, respectively) and downregulation of MHC class I molecules (HLA-A, B, and C showed a 4.6-, 2-, 4.8-fold decrease, respectively) were observed in HF cells. Next, we established a valid assay for identification of the factors linked to immune privilege. HF significantly inhibited allogeneic responses in human peripheral blood mononuclear cells (PBMCs, as responders) when co-cultured with purified human islets (as stimulators), the secretion of IFNg from PBMCs was significantly reduced in the presence of HF (23.0 vs. 5.7 pg/ml, $p<0.01$) or HF-conditioned medium (18.5 vs. 2.15 pg/ml, $p<0.04$). We will further identify factors in our established assay and then validate *in vivo* using the C3H/HeJ AA mouse model. The result of this study will provide new strategies for the treatment of AA.
Category: Early experiments with well defined objectives/hypotheses

Poster 6

MMP2 EXPRESSION IS A PROGNOSTIC MARKER FOR PRIMARY MELANOMA PATIENTS

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Matrix metalloproteinase 2 (MMP2) is a collagenase, which aids tumor growth and invasion by digesting the extracellular matrix surrounding the tumor tissue. Our study examined MMP2 expression in various stages of melanoma progression and tested if the prognostic significance of MMP2 expression is dependent on tumor thickness and ulceration. We also analyzed the correlation between p-Akt status and MMP2 expression in melanoma patients. Using tissue microarray (TMA) and immunohistochemistry, melanoma (330 primary and 152 metastatic) tumor biopsies were analysed and MMP2 expression was correlated with melanoma progression. Kaplan-Meier survival curve and multivariate Cox regression analysis were applied to verify if the correlation between MMP2 expression and patient outcome was independent of tumor thickness and ulceration status. The results showed that strong MMP2 expression was significantly increased in primary and metastatic melanoma compared to normal and dysplastic nevi. Patients with strong MMP2 had significantly poorer survival compared to those with negative-to-moderate MMP2 expression. MMP2 expression could predict the patient survival independent of tumor thickness and ulceration. Furthermore, MMP2 expression positively correlated with p-Akt status and influenced the effect of p-Akt on patient survival. To summarize, strong MMP2 staining is associated with worse survival of melanoma patients and is an independent molecular prognostic factor for primary melanoma. The immunohistochemical staining of the tissue samples we describe here is a simple technique to perform and thus our study could form a practical approach to identify the high risk primary melanoma patients who could have a worse prognosis.
Category: Applied and Functional experiments

Poster 7

REGULATION OF NF-κB PATHWAY BY TRANSCRIPTION FACTOR SOX4 IN UVB-INDUCED SKIN PHOTOAGING

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Ultraviolet (UV) exposure is one of the main causes of skin photoaging. Although degradation and decreased production of collagen are among the main UV-induced changes in the skin, the exact mechanism of this process is still unknown. Nuclear Factor κB (NF-κB) is believed to be activated by UV exposure and enhances the expression of matrix metaloproteinase-1 (MMP-1) which in turn can degrade collagen. We recently showed that the expression of NF-κB p50 is suppressed by the transcription factor Sox4. In this study we evaluated the role of Sox4 in regulation of UVB-induced activation of NF-κB pathway. We analyzed the expression of Sox4, p50 and MMP-1 after different doses of UVB in human dermal fibroblast. Sox4 expression decreased by 80% in low UVB dose and then increased in higher dosages in a dose dependent manner (P=0.001). However, expression of p50 and MMP-1 increased and dicreased at low and high UVB doses, respectively. In addition, overexpression of Sox4 led to a remarkable decrease in MMP-1 and p50 gene expression. In conclusion, we demonstrated that NF-κB pathway is regulated by Sox4. In the next phase of this study we will investigate the expression pattern of collagen and fibroblast growth rate upon UV stress after Sox4 knockdown or overexpression. This study will explore molecular mechanism of UVB-induced photoaging which may lead to more effective preventive and/or therapeutic modalities.

Category: Pilot/exploratory experiments

Poster 8

SKINSAFE: A REPORT OF THE EARLY SUCCESS OF A PROVINCE-WIDE SUN SAFETY AND SKIN CANCER EDUCATION CAMPAIGN

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Skin cancer is the most commonly diagnosed cancer in both the U.S. and Canada and annual incidence rates have been on the rise. It is estimated that up to 50% of a person's lifetime sun exposure occurs before 18-21 years of age and societal messages concerning sun safety have oftentimes conflicted. Given the significant contribution of ultraviolet (UV) radiation to the cancer development pathway and the existence of diverse protective measures to limit UV exposure, skin cancer mortality and morbidity rates have the potential to be dramatically reduced. Accordingly, we have designed and implemented a province-wide education campaign directed towards high school students. The goal of this initiative, entitled SkinSafe, has been to educate teenagers about skin health and disease through presentations on topics such as sun safety; skin cancer pathogenesis, detection and prevention; and the dangers of excessive UV exposure. We report the early success of this community intervention, which has reached out to thousands of students across British Columbia, as well as the preliminary data that we have gathered concerning baseline knowledge, attitudes, and behaviours relating to skin cancer and UV protection among SkinSafe participants. The long-term impact of the SkinSafe program on participants' health practices will be monitored and the knowledge gained from this study will prove critical to our understanding of how community interventions can best be applied to reduce the burden of skin cancer.

Category: Pilot/exploratory experiments (for study design, hypotheses creation, etc)

Poster 9

QUANTIFICATION IN DERMATOLOGY WITH CLINICAL IMAGES

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The purpose of the study will be to evaluate dermatology residents accuracy in estimating size, number, and surface area using clinical images and detailed synthetic charts. In our previous study using synthetic charts in the form of grids and pictures of household objects, participants significantly underestimated size for small objects such as coins ($p<.01$). There was a trend towards underestimation of size with large objects such as a journal; however, this was not statistically significant. Surface area was overestimated by participants ($p<.01$). Participants were most accurate at estimating number, with no bias toward underestimation or overestimation. This study will assess residents accuracy in estimating size, number, and surface area using images that will more accurately reflect the real life settings in which dermatologists estimate these parameters. In order to accomplish this, a series of 60 clinical images and 60 detailed synthetic charts will be presented in a PowerPoint presentation for 10 seconds each. The synthetic charts will have curved borders, and the areas to be estimated within them will have irregular or circular borders to represent true clinical examination situations more realistically. The clinical images will consist of ranges of size, number, and surface area of nevi on patients backs. Participants will be asked to estimate either size, number, or surface area for each of the slides. The accuracy of these estimates will be compared to true values.

Poster 10

USEFULNESS OF A 2 MM PUNCH BIOPSY IN THE DIAGNOSIS OF DIFFERENT SKIN DISEASES: A PROSPECTIVE STUDY

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Background: The punch biopsy is a simple procedure commonly used for the diagnosis of different skin diseases. There is a wide range of sizes of biopsy punches, with the 3 mm and 4 mm punches being the most commonly used. The 2 mm punch biopsies are done less often. This is due to the fear that the size of the specimen will not be adequate to reach a diagnosis. The 2 mm punch biopsy has the advantage of not requiring suturing of the biopsy site and providing a better cosmetic result. There are no studies evaluating the diagnostic accuracy of the 2 mm punch biopsy compared to other punch biopsy sizes. The aim of this study is to determine the diagnostic accuracy of the 2 mm punch biopsy in the diagnosis of different skin diseases compared to the standard punch biopsies done in the dermatology practice. **Methods:** Patients seen in an inpatient setting at Vancouver General Hospital who agreed to undergo a diagnostic punch biopsy are being recruited. Baseline demographic data are collected from each patient. The size and site of the standard biopsy are determined by the primary dermatology team. The 2 mm punch biopsy is taken from either the same lesion as the standard biopsy or a similar lesion within the same anatomic area. One of two dermatopathologists review the 2 mm punch biopsy first and record the findings then review the standard punch biopsy. The data include the histologic features, ability to reach a diagnosis, diagnosis (if can be reached), and need for special stains. **Results:** This is an ongoing study. Preliminary results will be presented

Poster 11

INVESTIGATION OF *ADAM10* MUTATIONS IN MELANOMA

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Different members of the ADAM (a disintegrin and metalloproteinases) family are involved in signaling events that are dysregulated in cancers and/or during tumor progression.In many cancers, ADAMs areupregulated and several recent studies have highlighted the potential of targeting ADAM family members as a new approach for antitumor therapy. The disintegrin–metalloproteinase ADAM has been found to be upregulated in ovarian, colon, gastric and prostate cancers. In addition, ADAM proteins were shown to be important in pigmentary pathways in mice. Thus, we postulated that ADAM mutation may play an important role in the pathogenesis of primary malignant melanomas. A library of nodular, superficial spreading, and mucosal melanomas was prepared and searched for the presence of ADAM mutations. None of the samples screened showed alterations in the ADAM protein. Additional studies will be required to demonstrate the role of ADAM family of proteins in the pathogenesis of both primary and metastatic melanomas.

Category: early experiments with well-defined objectives/hypothesis

Poster 12

ROLE OF FIBROBLAST PHENOTYPE AND PERICELLULAR MATRIX IN WOUND HEALING

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Scar formation as a result of wound healing in skin is associated with an increased deposition of extracellular matrix (ECM) by fibroblasts. Wounds in the skin heal with scar formation while in the human oral mucosa (OM) they heal without scars. The ECM niche that surrounds fibroblasts has a profound effect on their function and differentiation. Comparing fibroblast functions and interactions with their three-dimensional (3D) ECM niche in OM and skin may provide novel information about the factors that regulate scar formation. Therefore, we hypothesized that ECM produced by skin (SFBL) and gingival fibroblastsfrom oral mucosa (GFBL) are inherently distinct and determine the woundhealing outcome. Primary fibroblasts isolated from human skin (breast) and OM (attached gingiva) were cultured in high density for up to 14 days. The 3D ECM generated by SFBL and GFBL was characterized and expression of key genes involved in wound healing and scar formation was analyzed. Results showed that GFBL had a significantly faster proliferation rate during the 3D ECM generation but showed similar capacity to deposit total proteins into the 3D ECM as SFBL. SFBLshowed significantly higher expression of certain profibrotic growth factors and ECM proteins, while GFBL displayed a higher expression of MMPs. The distinct phenotype of fibroblasts and composition of the ECM produced by these cells may contribute to the different wound healing outcomes in skin and OM.Our research will help understand the molecular mechanisms in scar formation and contribute to the development of novel anti-scarring therapies.

Category: Applied/functional experiments

Poster 13

ING1b REGULATES CLASPIN AT TRANSCRIPTIONAL LEVEL

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DNA damaging agent causes lesions in DNA. If these lesions remain unrepaired, replication of DNA is stalled and leads to serious consequences such as replication collapse, DNA double-strand breaks, recombination and genomic instability. Recovery of stalled replication is achieved by replication bypass mechanisms such as the error-prone translesion DNA synthesis or the error-free template switching pathway that are regulated by monoubiquitination or polyubiquitination of proliferating cell nuclear antigen (PCNA), respectively. The human inhibitor of growth (ING1b) has been shown to have significant physiological role in the recovery from replication blockage through regulation of PCNA ubiquitination mediated lesion bypass mechanism and implicated in maintaining genomic stability. Claspin is an adaptor protein that binds to both Chk1 and ATR (ATM and Rad3-realated), and is necessary for ATR-dependent phosphorylation of Chk1. Claspin has also been shown to have a role in PCNA ubiquitination. Chk1, the kinase crucial for genomic integrity and an effector of ATR in DNA damage response, was also reported to regulate PCNA ubiquitination through stabilizing Claspin. Altogether, these data suggest that the regulation of PCNA ubiquitination is achieved through the coordinated action of ING1b, Claspin and Chk1. Interestingly, our preliminary data indicates that ING1b regulates Claspin expression at transcriptional level. When ING1b is knocked down, both protein and mRNA level are reduced as shown by immunoblot and quantitative PCR. Therefore, considering that both ING1b and Claspin are involved in PCNA ubiquitination, we will further study how ING1b regulates Claspin expression transcriptionally and regulates ubiquitination of PCNA to maintain genomic stability.

Poster 14

NOTCH- RBP-J-MEDIATED SIGNALING IS INVOLVED IN BASAL CELL CARCINOMA GROWTH

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Hair follicles (HF) and basal cell carcinomas (BCCs) can be regarded as ordered and disordered skin appendages respectively. Multiple reports suggest that a significant subset of BCCs is directly HF-derived. They may utilize similar molecular mechanisms of growth. We examined the similarities and differences in gene expression between Nodular BCCs and HFs, including the bulge region which has been identified as a potential primary source of BCCs derived from HF, by microarrays. We want to define common and unique signaling pathways that distinguish an ordered skin appendage from a disordered skin growth. We validated the potential molecular expression using quantitative PCR, immunohistochemistry and in vitro studies. Two differentially expressed gene sets were identified by significance analysis of microarray in BCC and HF versus skin epithelium respectively. Subsequently, multiple signaling pathway analyses were conducted. The results indicated specific molecular mechanisms involved in the process of self renewal, such as Notch and Hedgehog pathways, were active in the growth of both HF and BCCs. However, the Notch signaling pathway, including receptors and ligands, all showed significant differential expression in BCCs compared to HF; the downstream components that code for “HFs” was suppressed in BCCs. We found that Jag1- induced notch signaling pathway activation increased HF keratinocyte proliferation and differentiation via a RBP-J -dependent pathway in vitro. Our data suggest that RBP-J, which is important for appropriately regulated HF formation, serves as a tumor suppressor in BCC. Modulation of the Notch pathway may be a focus for the development of BCC treatment.

Poster 15

LOW-DOSE METHOTREXATE DECREASES COLLAGEN AND INCREASES MMP-1 EXPRESION BY FIBROBLAST IN VITRO

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Methotrexate (MTX) is commonly used for the treatment of cancer, autoimmune diseases, psoriasis and ectopic pregnancy. Low dose MTX is recommended as a first-line drug in the management of early and established rheumatoid arthritis (RA). The low dose regimen is also used in psoriatic patients when topical agents or phototherapy prove ineffective. Although, the side effects of high dose MTX are related to its folic acid antagonism, the underlying mechanism of liver and pulmonary fibrosis, seen in patients on long- term, low dose MTX, has not been established yet. Preliminary study by our group showed that low dose MTX increases the proliferation of fibroblasts in vitro. We hypothesized that low-dose MTX increases collagen expression as well. Methods: Human skin fibroblasts were treated with 50ng/ml of MTX for 24 hours. Levels of collagen and MMP-1 were evaluated by western blot. MTT assay was performed to examine the viability of the fibroblasts. Results: The level of collagen expression decreased 65% ±15 after treatment with 50ng/ml MTX compared to control group. On the other hand, MMP-1 expression showed two fold increases following treatment. MTT assay revealed no significant difference between control and treated group. Conclusion: Our results suggest that liver and pulmonary fibrosis, seen after long term low-dose MTX therapy, cannot be explained by direct effect of MTX on fibroblast. On the contrary, due to the safety and tolerability of low-dose MTX, it has potential to be used as anti-fibrotic drug in fibroproliferative disorders such as hypertrophic scar and keloid.
Category: Early experiments with well defined objectives/hypotheses

Poster 16

CONNEXINS REGULATE FIBROBLAST GENE EXPRESSION

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Objectives: Fibroblasts communicate via cell-cell adhesions called gap junctions (GJ) that are composed of connexins. Interestingly, functional blockage of connexin43 (Cx43) accelerates granulation tissue formation during wound healing, but little is known about the mechanisms involved. Our goal is to find the mechanisms by which connexins promote wound healing. We hypothesized that Cx43 regulates expression of genes that play a critical role in healing. **Methods:** Human gingival fibroblasts were cultured in high (HD) and low densities (LD). expression of connexins was analyzed by real-time PCR, immunoblotting and immunostaining. To unravel whether Cx43 regulates fibroblast phenotype, HD-cells were treated with peptides GAP27 or GAP26 that block Cx43 by distinct mechanisms or with carbenoxolone or meclofenamic acid, which non-specifically block connexin function. Expression of key genes was then analyzed as above. **Results:** Fibroblasts expressed Cx43 as their major GJ protein with moderate levels of Cx45, low level of Cx32, and no expression of Cx40. At HD, Cx43 was functional, as indicated by its localization and distinct phosphorylation of its cytoplasmic tail compared to LD cultures. Blocking of connexin function at HD regulated expression of several wound healing related profibrotic and antifibrotic genes, including MMPs, extracellular matrix proteins and growth factors. **Conclusion:** In fibroblasts cell-cell communication mediated by Cx43 regulates expression of key genes involved in wound healing. This information can be used to better understand the mechanisms involved in normal and aberrant wound healing (extensive scarring and non-healing chronic wounds) and to develop novel strategies to prevent wound healing problems.
Category: Early experiments with well defined objectives/hypotheses

Poster 17

DEVELOPMENT AND APPLICATION OF NANOFIBER RELEASING ANTI-FIBROGENIC FACTORS FOR TREATMENT OF DERMAL FIBROSIS

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Wound healing is a dynamic process that strikes a fine balance between synthesis and degradation of extracellular matrix (ECM). Non-healing and over-healing are two extreme cases in which the biomechanical processes of normal tissue are disturbed due to abnormalities in ECM production or remodeling. Although the promotion of healing in patients is clearly desirable, its cessation is equally important. Over healing processes in skin are disfiguring and devastating resulting in bulky, itchy and inelastic scars that are detrimental for millions of burn and trauma patients. As with any dynamic biological process, there must be a set of factors that gradually slow down and/or terminate the wound healing process. We recently identified a naturally keratinocyte derived-anti-fibrogenic factor (KDAF), later defined as stratifin. Our previous studies demonstrated that KDAF could serve as a stop signal for the healing process by stimulating matrix-degrading enzymes known as matrix metalloproteinases (MPPs). In spite of its anti-fibrogenic efficacy, delivery of KDAF directly to the wound poses finite challenges. First, most patients with severe trauma, require dressings that are changed every 3-5 days preventing frequent application of KDAF. Secondly, proteolytic enzymes are present at the wound site and a burst release of KDAF may offset the normal early-stage healing events. Therefore in this project we studied the formulation and application of KDAF slow releasing wound dressing, strips and sutures in order to improve and/or prevent dermal fibrosis. In addition, the effects of releasable KDAF on the expression of ECM components such as MMPs and collagen were evaluated.
Category: Applied/functional experiments (animal models of disease and *in vivo* studies, etc)

Poster 18

JWA REGULATES MELANOMA ANGIOGENESIS VIA ILK/NF-ΚB/STAT3/VEGF SIGNALING PATHWAY

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JWA, a microtubule-associated protein (MAP) and a tumor suppressor, plays important roles in apoptosis, motility and metastasis of tumor cells. However, the impact of JWA on tumor angiogenesis is currently unknown. In this study, we investigated the role of JWA in melanoma angiogenesis and its molecular mechanisms. The results showed that JWA overexpression strongly suppressed the growth of human umbilical vein endothelial cells (HUVECs) and their ability to form tubular structure in vitro. Moreover, we found that integrin-linked kinase (ILK), a proto- oncogene, is the downstream target of JWA in melanoma cells. JWA overexpression suppressed, whereas silencing of JWA increased ILK expression at both messenger RNA and protein levels. ILK in turn regulates melanoma angiogenesis by activating NF-κB/STAT3/VEGF signaling pathway. Furthermore, we found that the expression of JWA was induced by inhibitor of growth 4 (ING4), a tumor suppressor that inhibits melanoma angiogenesis. ING4 overexpression increased JWA, whereas knockdown ING4 decreased JWA expression. Further experiments will examine if JWA knockdown abrogates the suppressive effect of ING4 on HUVEC growth, and if JWA overexpression inhibits ING4 knockdown-induced angiogenesis, to validate that JWA is a downstream target of ING4 in the regulation of tumor angiogenesis. Collectively, our findings indicate that JWA, regulated by ING4 at transcriptional level, inhibits melanoma angiogenesis by suppressing ILK/NF-κB/STAT3/VEGF signaling pathway. Restoration of JWA function offers a potential novel strategy for the treatment of human melanoma.
Category: Early experiments with well defined objectives/hypotheses.

Poster 19

RETROSPECTIVE REVIEW OF FOLLICULITIS DECALVANS IN 21 PATIENTS WITH COURSE AND TREATMENT ANALYSIS OF LONG STANDING CASES

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Folliculitis Decalvans is a rare type of cicatricial alopecia mainly affecting the scalp. The goal in treatment of the condition is to stabilize the condition to prevent further irreversible scarring of hair follicles. The records of 21 patients with Folliculitis Decalvans who were seen at our institution from 1998 to 2011 were retrospectively analyzed with added data review done on the course and treatment of long standing cases. There were 15 males and 6 females with ages ranging from 12-42 and 36-74years, respectively. The main clinical features seen were pustules with crusting and erythema. Majority of patients had lesions located over the vertex and occipital region. Four patients had added midscalp involvement. Duration of the disease prior to consultation ranged from 9months to 10 years. Initial management consisted mostly of intralesional triamcinolone acetonide injection (10mg /cc), clobetasol lotion and either cephalexin, minocycline, doxycycline or tetracycline. Alternative medications consisted of isotretinoin, rifampicin, clindamycin and ciprofloxacin. Stabilization of the condition was achieved in few weeks to several months in more than half of the patients (4 weeks to 8months). The late responders (1-2years before significant improvement) had protracted course characterized by temporary improvement and worsening before significant stabilization was achieved. For majority of patients, medications had to be continued for several months to years to maintain stabilization of the disease activity. Long standing disease with on going follow up at our institution was seen in 11 patients with disease duration from the time of diagnosis ranging from 2-13 years.

Poster 20

THE ROLE OF TUMOR SUPPRESSOR BIN1 IN REGULATING PROLIFERATION AND APOPTOSIS OF HUMAN CUTANEOUS T-CELL LYMPHOMA CELLS

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AHI-1 is an oncogene that is highly deregulated in several leukemia and lymphoma cell lines, including the cutaneous T-cell lymphoma (CTCL) cell lines Hut78 and Hut102. Hut78 is derived from a patient with Sezary syndrome, a leukemic variant of CTCL. We recently demonstrated aberrant expression of AHI-1 in primary $CD4^+CD7^-$ Sezary cells. In AHI-1-suppressed Hut78 cells (AHI-1/sh4), suppressed using retroviral-mediated RNA interference, we identified several new differentially expressed genes by microarray analysis. One candidate is the tumor suppressor BIN1 which is upregulated at RNA and protein levels in AHI-1/sh4 cells and is downregulated in primary $CD4^+CD7^-$ Sezary cells. Four isoforms of BIN1 have been identified in Hut78 and primary $CD4^+CD7^-$ Sezary cells: two wild-type isoforms with tumor suppressor activities and two cancer-specific isoforms with no known tumor suppressor function in solid tumors. However, the role of BIN1 in regulation of normal hematopoiesis and lymphomagenesis remains unknown. To investigate the tumor suppressor activity of BIN1 in Sezary cells and its potential molecular connection to AHI-1, the wild-type BIN1 was overexpressed in Hut78 (BIN1/Hut78) and AHI-1/sh4 cells using a lentiviral vector. Increased transcript levels and protein expression of BIN1 were confirmed in transduced cells as compared to the control cells by Q-RT-PCR and Western analysis. Interestingly, more than 50% reduction in cell proliferation was observed in BIN1/Hut78 cells compared to controls using both the colony forming cell (CFC) assays and the 3H- Thymidine uptake assay. Furthermore, a significant increase in the number of apoptotic cells was observed in BIN1/Hut78 cells compared to controls after culturing the cells for 72 hours using 7-amino-actinomycin D and PE-conjugated AnnexinV antibody staining. However, no difference was observed in BIN-1-transduced AHI-1/sh4 cells compared to controls, possibly due to relatively high expression of endogenous level of BIN1 in these cells. These findings suggest anti-proliferative and pro-apoptotic roles for BIN1 in human CTCL cells.

Poster 21

SCREENING FOR AUTOANTIGEN EPITOPE TARGETS IN ALOPECIA AREATA

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Alopecia areata (AA), a non-scarring, inflammatory hair loss disease, is believed to involve an autoimmune mechanism. Both human studies and rodent models have shown that CD4 T cells and cytotoxic CD8 T cells (CTLs) play a crucial role in the development of AA. It is suspected that antigen epitopes originating in hair follicle (HF) keratinocytes and/or melanocytes may be CTL targets. However, the exact epitopes targeted by auto-reactive CTLs in AA have not yet been identified. We investigated the potential of a panel of epitopes expressed by human HF keratinocytes and melanocytes to induce activation of CTLs. Peripheral blood mononuclear cell (PBMC) populations isolated from AA affected and healthy subjects with HLA-A2 serotypes were cultured with synthesized peptides (HLA-A2 specific) with specific sequences for trichohyalin, keratin-16 (K16), tyrosinase, tyrosinase related protein, melanin, MELAN-A, and GP100. The frequency of CTL activation in the PBMC population was measured using an enzyme-linked immunosorbent spot (ELISpot) assay where reactive interferon gamma (IFNg) secreting cells are visible as spots. Specific trichohyalin epitopes induced significantly greater responses in human AA CTLs compared to healthy controls. The reactivity of AA affected C3H/HeJ mouse lymph node cells to an equivalent panel of mouse antigen epitopes displayed significantly increased responses against K16 epitopes in addition to trichohyalin versus no responses from healthy controls' CTLs, a potential indication of multiple targets in AA from keratinocytes. KT: Although the primary target in AA remains to be determined the identification of antigen epitopes can be beneficial to the generation of therapies.
Early experiments with well defined objectives/hypotheses.

Poster 22

EXTRACUTANEOUS MELANOMAS AND THE RISK OF A SECOND PRIMARY MELANOCYTIC MALIGNANCY IN THE CANADIAN POPULATION

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Extracutaneous melanomas are rare malignancies comprising 5% of all primary melanomas. The eye is the most common site for extracutaneous melanomas while mucosal melanomas include lesions of the head and neck, uro-genital, gastrointestinal and respiratory tracts. Because of the hidden nature of these tumors the diagnosis is often incidental and the tumors are identified at a late stage and have a poor prognosis. Screening for extracutaneous melanomas is complicated by the lack of firm associations with UV light exposure, precursor nevi or a family history. In addition, well-established surveillance guidelines for cutaneous melanomas are not applicable to the occult extracutaneous tumors. Still, largely on an empirical basis patients with a prior history of extracutaneous melanoma present to dermatologists for annual cutaneous examinations. This study establishes the rates and patterns of primary cutaneous melanomas in Canadian patients with a prior diagnosis of extracutaneous melanoma. Canadian Cancer Registry 1992-2006 data identifying subsets of patients with second primary cutaneous melanomas is presented and the rates of developing subsequent melanomas are reported. The hazard ratio of the extracutaneous melanoma group is compared with lung, breast and prostate cancer patients. The relationship between Breslow depth and the risk of a subsequent cutaneous melanoma is also examined. Our data will enhance patient care by estimating the risk of developing a second primary melanocytic tumor after the diagnosis of an extracutaneous melanoma. It may guide the development of screening guidelines specific to this subset of melanoma patients, and improve identification of second malignancies in this unique group.
Category: Pilot/exploratory experiments

Poster 23

PROGNOSTIC SIGNIFICANCE OF KAI1/CD82 IN HUMAN MELANOMA AND ITS ROLE IN CELL MIGRATION AND ANGIOGENESIS

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KAI1/CD82 is a member of the transmembrane 4 superfamily and it was first identified as a metastasis suppressorfor prostate cancer. The expression of KAI1 was found to be reduced in many types of cancers, including prostate, breast, ovarian, cervical, and endometrial cancer. However, the role of KAI1 in melanoma pathogenesis is not known. In this study, we investigated the expression level of KAI1in a large set of melanocytic lesions at different stages. We found that the expression of KAI1 is significantly decreased during melanoma progression.In fact, KAI1 expression is drastically reduced in primary melanoma compared todysplastic nevi (1.8×10^{-4}, χ^2 test) and further reduced in metastatic melanoma comparedto primary melanoma (9.4×10^{-15}, χ^2 test). Moreover,decreased KAI1 stainingis strongly correlated with a worse 5-year patient survival. Also, multivariate Cox regression analysis showed that KAI1 is also an independent prognostic factor. In addition, we found that overexpression of KAI1 significantly reduced the ability of melanoma cell migration. Furthermore, we found that KAI1 overexpression significantly inhibited the growth and tube formation of endothelial cells, indicating that KAI1 also plays an important role in melanoma angiogenesis. Taken together, our data suggest that KAI1 may be used as a promising prognostic marker and a possible therapeutic target for human melanoma.

Poster 24

OSTEOMA CUTIS SECONDARY TO ACNE VULGARIS; CASE SERIES, LITERATURE REVIEW AND TREATMENT GUIDELINES

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Osteoma cutis (OC) is focal cutaneous ossification in the dermis and subcutaneous tissue, and may be primary or more commonly secondary to an underlying disease of the skin. Acne vulgaris is the most frequent cause of secondary OC, often presenting as multiple military osteoma cutis (MMOC) subtype which present as multiple hard, non-tender papules often with blue to slate-gray discolouration, usually 1-2 mm in diameter predominantly on the cheeks. The lesions may resemble comedones, therefore the condition is frequently misdiagnosed and treated as acne. We present our series of 3 cases of MMOC secondary to acne vulgaris which were successfully managed with needle extraction. Additionally, we provide a review of 19 cases from an extensive literature search of both for cases of OC which developed in patients with acne vulgaris. All patients were found to be female with a mean age of 32 (range 17-57 years) at the time of lesion development. Appropriate treatment of OC secondary to acne is challenging; however, surgical and pharmacological treatment modalities are available. Because of the relative rarity of the condition and subsequent paucity of published treatment modalities, we propose an algorithmic approach to help guide physicians in the management of OC secondary to acne. As a practical approach, we recommend beginning treatment with a 3-4 month trial of topical retinoid therapy; followed by surgical excision in cases with a few nodules versus needle microincision and forcep extripation in cases of multiple minute lesions of MMOC subtype.

Category: Early experiments with well defined objectives/hypotheses

Poster 25

DNA REPLICATION CHECKPOINT REGULATES ING1B IN GENOME STABILITY UPON REPLICATION STRESS

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DNA replication checkpoint plays a pivotal role in maintaining genome integrity to prevent cancer occurrence. This is exemplified by the fact that patients carrying mutations in DNA damage response genes are prone to cancer development. Previously, we showed that the tumor suppressor Inhibitor of Growth 1b (ING1b) is involved in the regulation of translesion DNA synthesis (TLS) which protects cells from genomic instability upon ultraviolet (UV) radiation-induced replication stress. In this study, we further characterized the upstream regulator of ING1 in such process. We found that ING1b interacted with the E3 ligase Rad18 which monoubiquitinates the proliferating cell nuclear antigen (PCNA) to facilitate TLS, and such interaction was induced after UV. Furthermore, we found that induction of ING1b-Rad18 interaction upon UV required the activation of the DNA replication checkpoint. We previously showed that ATR/Chk1 phosphorylates ING1b at S126 residue. Interestingly, we found that cells expressing the phosphorylation-defective mutant ING1b-S126A, showed reduced TLS and enhanced chromosomal aberrations. This suggests that DNA replication checkpoint regulates ING1b to modulate TLS and maintain genome stability. UV is the major environment risk factor for skin cancer development. Our finding sheds light on the mechanism leading to tumor suppression upon UV-induced replication stress which provide basis for designing new strategy for skin cancer prevention and therapy.
Category: Early experiments with well defined objectives/ hypotheses

Poster 26

PUBIC HAIR REMOVAL: STUDY OF ADVERSE EVENTS AND DISEASE TRANSMISSION

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Hair grooming trends have changed throughout the ages. Increasing numbers of people have had permanent or transient removal of some or all of their body hair. Recent studies suggest that at least 30 % of women and 10 % of men have complete removal of their pubic hair, while up to 65 % of women and men engage in some degree of pubic hair removal. The health impact of this trend is unknown. We aim to understand the adverse effects of different modalities of pubic hair removal and the associated risks of disease transmission. A case from St. Paul's Hospital will serve as an example. In this case, the patient having undergone pubic hair removal using hot wax developed epidermodysplasia verruciformis (EDV), known to be associated with Human Papilloma Virus (HPV). Pubic hair is a reservoir of HPV which is also responsible for genital warts and the development of cervical cancer. Other studies have shown that as the rate of pubic hair removal increases the rate of pubic lice transmission goes down. A case report has linked pubic hair removal and herpes infection. Overall, there are few studies investigating the health impact of pubic hair removal. We will employ an online and paper-based survey with questions directed at correlating pubic hair status and hair removal methods with adverse events and disease transmission. The results from this study will provide insight into the risks associated with pubic hair removal allowing consumers to make better choices about their personal grooming habits.
Category of this study: Pilot/exploratory experiments

Poster 27

NUCLEAR LOCALIZATION OF ING3 AND ITS ROLE IN MELANOMA CELL MIGRATION AND INVASION

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Inhibitor of growth family member 3 (ING3) is tumour suppressor protein which plays a crucial role in cell cycle regulation, apoptosis and transcription. We previously showed that nuclear expression of ING3 is reduced in metastatic melanoma suggesting functional attribute of nuclear localization of ING3. In addition, we have observed reduced nuclear ING3 expression in melanoma cells when compared to melanocyte. However, the nuclear translocation mechanisms have never been addressed so far. In the present study we show that ING3 is imported into the nucleus by the classical nuclear transport mechanism where in ING3 binds to the adaptor protein importin-α which in turn binds to importin-β forming a ternary complex and passes through the nuclear pore complex. We also identified that the nuclear localization signal (NLS) of ING3 is of classical monopartite type containing basic amino acid consensus. Replacement of Lys164 residue of ING3 with alanine resulted in retention of ING3 in the cytoplasm and loss of importin-α binding. Furthermore, we examined if this NLS is essential for the tumour suppressive function of ING3. ING3 overexpression significantly inhibited migration and invasion of melanoma cells, and these effects were abrogated when K164A mutant of ING3 was expressed in the cells. Our data show that mutation in the NLS of ING3 decreases its tumour suppressive function, suggesting that overexpression of importin-α and nuclear ING3 as a potential treatment strategy for melanoma patients.
Category: Early experiments with well defined objectives and hypothesis

Poster 28

ANALYSIS OF THE POTENTIAL FOR SKIN-LOCALIZED TREGS TO TRANSDIFFERENTIATE INTO CYTOKINE PRODUCING CELLS

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T regulatory cells (Tregs) are critical for maintaining self-tolerance. They express constitutively high levels FOXP3 but typically do not express inflammatory cytokines. Recently Tregs have been observed producing inflammatory cytokines in autoimmune diseases, such as multiple sclerosis, implying that Treg plasticity may underlie the breakdown of tolerance in autoimmunity. There is accumulating evidence that deficiencies or dysfunction in Tregs underlie the pathogenesis of a number of inflammatory skin diseases such as scleroderma (SSc) and chronic graft versus host disease (cGVHD) however these studies have not evaluated the potential of plasticity. In this work, skin biopsies from cGVHD and SSc patients were minced, placed on Statamatrix®, and after a 3 week culture analyzed by intracellular cytokine staining. We found no difference in the number of FOXP3+ T cells in patients compared with healthy controls, but interestingly, found that a significant proportion of FOXP3+ T cells in SSc produce IL-4 and IL-13. In contrast, Tregs from patients with cGVHD produced IFN-g. Studies are underway to analyze Tregs from the blood of patients and healthy controls to determine whether the changes in Tregs are systemic or localized to inflamed tissue. Preliminary results show that normal donor peripheral blood Tregs can begin producing IFN-g and lose their suppressive capacity. This research will better define the immune mechanisms which underlie chronic skin inflammation and potentially lead to more targeted treatment of skin inflammation.
Early experiments with well defined objectives/hypotheses

Poster 29

A SINGLE CENTRE CONTROLLED COMPARISON STUDY TO EVALUATE THE SAFETY OF LIDOCAINE 30% IN PLASTICIZED BASE USED AS LOCAL ANAESTHESIA FOR INTENSE PULSED LIGHT TREATMENTS

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Background: Intense Pulsed Light (IPL) is used for photorejuventation of photoaged skin on the face, neck, and chest. This procedure induces thermal pain and requires topical anaesthetic prior to treatment. Lidocaine 30% in a plasticized base is an effective topical anaesthetic that, unlike the lidocaine/prilocaine product (EMLA, 2.5% lidocaine/2.5% prilocaine, AstraZeneca Wayne, PA), does not require occlusion. Lidocaine is an amide anaesthetic with rapid onset and intermediate duration (30-60min). Systemic toxicity is a concern whenever using topical anaesthetics. Despite this, no study currently provides blood levels of lidocaine when used in a 30% plasticized base for local anaesthesia. Proposal: We propose a single centre, controlled, open-label comparison study of lidocaine 30% in a plasticized base. Two groups will be recruited: 10 patients scheduled for IPL of the face only and 10 patients scheduled for IPL treatment of the face, neck, and chest. Lidocaine 30% in a plasticized base will be applied to the subject's area of treatment for 30 (+/-15) minutes prior to the treatment. Each subject will have serum lidocaine levels drawn 30 (+/-15) minutes post IPL treatment. Patients will be monitored for any adverse effects during the treatment. Immediately following the IPL treatment each subject will complete a safety questionnaire. A telephone assessment regarding adverse events will be completed 24 hours following the treatment. We hypothesize that post IPL serum lidocaine levels will remain within safe limits in both groups and that lidocaine 30% in a plasticized base is a safe alternative option for application prior to IPL.

Poster 30

ASSESSMENT OF SUN EXPOSURE AND CORRELATION WITH OTHER CANCER RISK BEHAVIOURS AND SERUM VITAMIN D LEVELS

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The incidence of skin cancer is on the rise, non-melanoma skin cancer in particular, was the most common cancer diagnosed in Canadians, representing 43% of all cancers diagnosed in 2010. Even though the dangers of sun exposure are widely publicized and there have been numerous campaigns educating the public about the importance of sun safety, many people are still engaging in behaviours that increase their malignancy risk. Canadian Health Measures Survey (CHMS) conducted by Statistics Canada collects vital information on the health status and practices of Canadians representing over 97% of the population. The CHMS evaluated different sun practices including time out in the sun and use of sunscreen. Using the available data, this study aims to identify whether individual sun practices are associated with other behaviour patterns. In particular correlation between safe sun practices and other cancer prevention strategies such as regular pap, mammography, colorectal, prostate cancer screening, regular exercise, healthy eating habits, proper immunization, smoking cessation and reduced alcohol intake are evaluated. In addition, we would like to use the data to see whether sun exposure correlates with measured serum Vitamin D levels. Collected data will be analyzed using SAS software and statistically significant variables will be included in a multiple logistic regression analysis. Results of this study will help to identify areas where more public education may be beneficial. In addition, these results can be used to identify patients who may not only be at risk for skin cancer but other types of malignancies as well.
Abstract Category: Exploratory Study

Poster 31

ASSESSING PATIENT ADHERENCE ON PHOTOTHERAPY

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Background: Phototherapy is provided as an effective and relatively safe treatment option for skin disorders. In this study, the compliance with phototherapy is assessed in a hospital phototherapy clinic. Patients are referred for phototherapy directly by local community dermatologists as well as dermatologists within the hospital phototherapy clinic.
Objective: To characterize the degree of compliance with phototherapy by patients, and to assess the number of treatments sessions patients receive before discontinuing phototherapy. Methods: A database of all patients that received UVB phototherapy at the Vancouver Skin Care Centre Psoriasis Clinic between 2004 and 2011 was generated. The primary outcome assessed was the number of visits for phototherapy per patient. In addition, patient demographic variables were recorded. Results: Of the 880 patients evaluated thus far, 432 (49%) received fewer than 30 treatments, 304 (35%) received under 20 treatments, 176 (20%) received less than 10 treatments, and 100 (11%) received even fewer than 5 treatments.
Conclusion: Evaluation of phototherapy treatment sessions in this study demonstrated that approximately one third of patients received less than ten treatment sessions. Our results indicate that a large number of patients do not adhere to the full course of recommended phototherapy sessions. This may account for some patient's skin diseases not improving after a course of phototherapy. Currently further studies are being evaluated to determine the barriers that may impede patients from receiving phototherapy.
Exploratory Study

Poster 32

PREVALENCES OF PHYSICIAN-DIAGNOSED DEPRESSION AND RELATED MOOD DISORDERS AMONG PATIENTS WITH PSORIATIC ARTHRITIS: A POPULATION-BASED STUDY.

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Background: Emerging evidence suggests that psoriatic arthritis (PsA) is linked to substantial psychiatric comorbidities, although the extent of this burden on a population level is unknown. Methods: Data from the entire province of British Columbia, Canada were used to estimate the prevalence of depressive disorders in PsA between 1991 and 2006. PsA was ascertained in two ways: 1) Primary definition: at least 2 ICD9 codes of 696.0 between 30 days and 2 years apart, or one hospital code of 696.0; 2) Secondary definition: any ICD9 code of 696.0. Age- and sex-adjusted logistic regression was used to compare the odds of depressive disorders between cases and controls. Depressive disorders identified by ICD9 codes included: episodic mood disorders; major depressive disorder (single or recurrent episode); neurotic depression; adjustment reaction disorder; adjustment reaction, depressive; prolonged depressive reaction; depressive disorder, NOS. Results: Over 15 years of follow-up, we identified 6,096 cases of PsA (mean age=54.3, 51.2% male) according to our primary and 14,296 cases (mean age=52.8, 48.8% male) according to our secondary definition. Overall, the prevalence of depressive disorders was high in PsA, corresponding to an increased odds compared to age- and sex-matched controls. Results were similar using our primary and secondary definition of PsA. Conclusion: There is a high prevalence and increased odds of depressive disorders in PsA compared to age- and sex-matched controls. Given that depressive disorders contribute to pain, fatigue, poor treatment adherence, reduced quality of life, and premature mortality, these data call for increased screening for depressive disorders in PsA.
Category: Early experiments with well-defined objectives/hypotheses