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P09

IN-SILICO PROTEIN-PROTEIN INTERACTION NETWORKS IN CO-CULTURED MELANOCYTES AND KERATINOCYTES: EVIDENCES OF AUTOPHAGY GENES INVOLVED IN MELANOGENESIS

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Individuals carrying germinal mutations in CDKN2A gene and/or non functional variants (RHC) in MC1R gene show an increased susceptibility to develop melanoma. To date, the effect of germinal CDKN2A mutation and RHC MC1R variants in skin cells has been poorly studied. Melanocyte growth and behaviour is controlled by keratinocytes control through a complex system of paracrine growth factors and cell–cell adhesion molecules which regulate the epidermal homeostasis. Thus, in-vitro studies focused exclusively on melanocytes not reflect the in-vivo conditions.

The aim of the study was to identify molecular networks associated to presence of either germline mutations in CDKN2A or RHC variants in MC1R genes which may be related with the biological impact of both genes into melanoma susceptibility.

Keratinocytes and melanocytes were obtained from two pair of siblings belonging from two familial melanoma pedigrees regarding their germinal status of both genes. After enzymatic digestions cells were co-cultured and the global RNA was analyzed by expression arrays.

Differential gene expression data (1535 transcripts deregulated in CDKN2A mutated cells and 3570 in MC1R variants carriers) was analyzed by the web-based tool SNOW.

Statistically significant networks were identified among down regulated transcripts. Overall, 24.7% of genes in CDKN2A mutants and 27.8% in MC1R variants carriers were connected in molecular networks. The network cores were genes involved in autophagyc vacuole formation (GABARAPL2, MAP1LC3A, ULK1) or co-regulators of autophagy and/or apoptosis (SMAD3, NFKB1, SQSTM1, PRKAA1, CLN3).

28.5% of upregulated transcripts in RHC MC1R cells carrying variants were in a network in which the core was composed by genes playing a role in oxidative phosphorylation and mithocondrial ribosome (GBAS, ICT1 and PRKAA1).

Our **results** suggest that variants in both genes promote autophagy deregulation in skin cell types. Also, we have identified genes involved in the cellular levels of reactive oxygen species in MC1R variant carriers.

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CAPTURING THE BIOLOGICAL IMPACT OF THE STATUS OF CDKN2A AND MC1R GENES IN COCULTURED HUMAN KERATINOCYTES AND MELANOCYTES: IDENTIFICATION OF DEREGULATED PATHWAYS

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Individuals carrying germline mutations in CDKN2A and/or red hair colour variants (RHC) MC1R genes show an increased risk to develop melanoma. So far, the global biological impact of germinal p.G101W CDKN2A mutation or nonfunctional MC1R variants has been poorly studied in skin cells, in addition there is no information combining genotype status of both genes.

The aim of this study was to evaluate the global effect of germinal CDKN2A mutations (p.G101W) and MC1R RHC variants in the transcriptome of primary skin cells.

Human keratinocytes and melanocytes from two pairs of siblings from two familial melanoma pedigrees were obtained. Transcriptome variation within primary keratinocytes and melanocytes cocultures was analyzed by expression array methodology. The results from the differential gene expression analysis were evaluated by functional analysis to identify biological processes and signaling pathways significantly overrepresented in the set of desregulated genes.

Overall, 1536 transcripts were deregulated in CDKN2A mutated cells, finding a downregulation of genes playing a role in Notch signaling pathway and 5 biological processes related with gene expression regulation.

Cocultures carrying MC1R variants showed 3570 transcripts deregulated. In the set of upregulated genes was found an overrepresentation of transcripts involved in oxidative stress pathways, DNA repair pathways (Mismatch repair, Nucleotide excision repair, Base excision repair and Homologous recombination) and in signaling pathways associated to neurodegenerative diseases such as Parkinson's, Alzheimer and Huntington. In contrast, downregulated genes were associated to lysosome and endocytosis pathways which are directly related with melanosome transfer from melanocytes to surrounding keratinocytes or with biological functions linked to melanin synthesis and angiogenesis.

In summary, key molecular functions and/or pathways that are deregulated due to alterations in melanoma susceptibility gene have been elucidated using a coculture system which in turn, could be involved in initiation/progression of the disease.

P11

DISTRIBUTION OF MC1R VARIANTS AMONG MELANOMA SUBTYPES: P.R163Q IS ASSOCIATED WITH LENTIGO MALIGNA MELANOMA IN A MEDITERRANEAN POPULATION

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Melanoma tumour is classified into clinico-histopathological subtypes which may be associated with different genetic and host factors. Few studies have focused on the role of MC1R gene beyond the study of melanoma risk in individuals.

The aim was to analyze whether certain MC1R variants are associated to particular melanoma subtypes with specific clinico-histopathological features.

Clinic-pathological data of primary melanoma tumours derived from 1679 patients and the germinal status of MC1R gene were included in the study.

We detected 53 MC1R variants (11 synonymous and 43 non-synonymous). Recurrent non-synonymous variants were p.V60L (29.9%), p.V92M (11.7%), p.D294H (9.4%), p.R151C (8.8%), p.R160W (6.2%), p.R163Q (4.2%) p.R142H (3.3%), p.I155T (3.8%), p.V122M (1.5%) and p.D84E (1%). Melanoma subtypes showed differences in number of total MC1R variants (P-value=0.028) and number of Red hair colour variants (P-value=0.035). Furthermore, an association between the p.R163Q variant and lentigo maligna melanoma subtype was detected under a dominant model of heritance (OR: 2.16 95%IC: 1.07-4.37; P-value=0.044). No association was found between p.R163Q and skin phototype, eye colour or skin colour indicating that the association was independently of the role of MC1R in pigmentation. No association was observed between MC1R polymorphisms and the other melanoma subtypes.

Our findings suggest that certain MC1R variants could increase the melanoma risk by means of their impact in pathways other than pigmentation and therefore be linked to specific etiopathological melanoma subtypes.

P12

PROLIFERATING PERINEAL ULCERATIONS

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Background: Rapidly proliferating squamous cell carcinoma (SCC) is a rare, but the most feared complication of hidradenitis suppurativa (HS) of the anogenital region.

Case report: A 43-year-old man presented painful proliferations on his buttocks, progressively increasing in size. The lesions affected particularly the borders of the ulcerations of the longstanding HS. Besides multiple cutaneous cysts, recurring perianal abscesses, multiple perineal sinuses, extensive scar tissue and facial acne scars, his prior medical history was unremarkable. Clinical examination revealed multiple and easily bleeding tumors. Bilateral inguinal painful lymphadenopathies were evidenced. A PET SCAN showed hyperfixation of both inguinal lymph node areas. MRI revealed subcutaneous extension of the tumors. A skin biopsy revealed medium grade squamous cell carcinoma. Despite multiple surgical interventions, the patient rapidly died of disseminated SCC carcinomatosis.

Conclusion: Rapid recognition of HS-associated SCC is crucial as the survival rate is approximately 50% at 2 years. Wide surgical resection with grafting is the only curative therapeutic option as HS-associated SCC does not respond to chemotherapy. Radiotherapy is only considered as palliative option.

P13

ATYPICAL SPITZ TUMOR AND METASTATIC MALIGNANT MELANOMAS ARISING IN GIANT CONGENITAL MELANOCYTIC NEVUS: A CASE REPORT

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Purpose: A variety of malignancies have been reported to arise within congenital melanocytic nevus(CMN), but rarely atypical spitz tumor with metastatic malignant melanoma. We report a very unusual case of atypical spitz tumor with metastatic malignant melanoma arising in giant CMN.

Methods: A 25-year-old female presented with a protruding nodule (3 cm x 2 cm x 1.5 cm) that developed within a giant CMN on her left gluteal region and flank region. After excision, histopatholgic evaluation showed atypical spitz tumor with spitzoid features distinguished from malignant melanoma. We recommended further evaluation and proper management but, she refused following our counsel.

Results: 9 months later, multiple palpable masses were found on the left shoulder and both thighs, and diagnosed as metastatic malignant melanomas. We thought that giant CMN was the origin of metastatic malignant melanoma, so wide excision on left gluteal and flank region and reconstruction were performed with palliative chemotherapies.

Despite 5 years of therapies, metastatic malignant melanomas were found continuously and patient died.

Conclusion: We experienced 25-year-old female who had atypical spitz tumor and metastatic malignant melanoma arising in giant CMN, which is very uncommon. So, we report an very uncommon case of atypical spitz tumor and metastatic malignant melanomas arising in giant CMN to discuss about our experience with relevant journal discussion.

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Case Reports

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MERKEL CELL CARCINOMA OF UNKNOWN PRIMARY ORIGIN. CASE REPORT AND REVIEW OF PATHOLOGICAL FEATURES

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Introduction: Merkel cell carcinoma (MCC) is a rare neuroendocrine tumor of the skin. MCC from an unknown primary origin (MCCUP) can present a diagnostic and therapeutic challenge. When it happens within the lymph nodes in the absence of a primary site, it is even more rare and has only been reported sporadically.

Objectives: To describe a MCC of unknown origin presented as nodal disease, initially diagnosed as melanoma

Case report: We present a 68 years old male patient who developed groin lymphadenopathy. No cutaneous lesions were found. Fine needle aspiration (FNA) biopsy revealed malignant melanoma. No other site of disease was found during staging and we performed groin and iliac lymphadenectomy, in which 5 from 20 lymph nodes had metastatic disease, also reported as melanoma. The patient developed wound-healing problems and during its treatment he presented with a cervical node. FNA was unable to define the etiology so we performed excisional biopsy of the node. The imunohistochemistry (IHQ) revealed MCC, which lead to a review of previous diagnosis and they were all considered MCC. Re-staging revealed metastatic disease in retroperitoneum and in right adrenal gland. The patient was referred to chemotherapy.

Discussion: There's a controversy in literature about MCC form a regressed or unknown primary versus lymph nodal MCC. Nevertheless, it represents a very aggressive disease. In our case, it's important to discuss the importance of IHQ in the differential diagnosis between MCC and melanoma.

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EFFECTIVE CLEARANCE OF ACTINIC KERATOSIS WITH IMIQUIMOD 3.75%: CASE STUDY CONFIRMING THE NEED FOR REPEAT IMMUNE STIMULATION WITH TWO TREATMENT CYCLES

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Aim of the investigation: Imiquimod 3.75% is a new large field treatment for actinic keratosis (AK). Imiquimod stimulates an immune response to destroy clinically visible lesions in the treated area and can also reveal and treat subclinical lesions that were previously not detectable. To fully assess the efficacy of imiquimod 3.75%, novel efficacy parameters such as the reduction in lesion count from Lmax (maximum lesion count during treatment) have been introduced which take into account the clearance of clinical and subclinical lesions. The aim of this case study was to confirm the need for two treatment cycles with imiquimod 3.75% to ensure effective clearance of both clinical and subclinical AK lesions.

Materials, Subjects and Methods: The patient was treated with imiquimod 3.75% as part of a vehicle-controlled, double-blind study. The patient applied ≤2 sachets of treatment to the affected area each day for two weeks. This was followed by a period of two weeks without treatment, and then a second cycle of treatment. The patient was followed-up for a further eight weeks.

Results: This patient was white, male, 78.7 years old and had Latino ethnicity. The patient had 12 lesions at baseline with an increase to an Lmax of 30 during the first treatment cycle. By week 4 the patient had no clinical lesions; however during the second treatment cycle, 12 lesions became detectable which cleared by week 10 with no further lesions developing during the study.

Conclusions: Imiquimod 3.75% is currently the only treatment which can detect and treat both clinical and subclinical AK lesions on the entire face or balding scalp. For complete clearance of all lesions, including all subclinical lesions, two treatment cycles are required. These treatment cycles may lead to a more sustained long-term effect and possibly the best prevention of invasive squamous cell carcinoma.

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AN IMMUNE-RELATED, RARE ADVERSE EFFECT OF IPILIMUMAB: AUTOIMMUNE NEPHRITIS; A CASE REPORT

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Ipilimumab is the first immunotherapeutic agent with survival prolonging effect in metastatic melanoma. Its adverse effects are related to the immune system. We present a patient with autoimmune nephritis that is a rare side effect in the course of ipilimumab therapy.

According to the medical history of the 72-year old male patient a nodular melanoma (Clark V, Breslow 5 mm) was removed from the back in 1999. Five years later, in 2004, a new melanoma (Clark IV, Breslow 1.7 mm) was removed from the right shoulder region. Both lesions were treated with adjuvant low dose interferon-a. Chest CT in December 2009 visualized multiple pulmonary metastases. Chemotherapy was initiated. In spite of DTIC monochemotherapy followed by different combinations of chemotherapeutics the progression of the pulmonary status was associated with adrenal and osseal propagation by June 2011. Since no other relevant diseases had been recorded in his history and the patient was in a good physical condition, 3mg/kg/cycle ipilimumab therapy was started within the frame of the Expanded Access Programme (Bristol-Myers-Squibb). Double cerebral metastases developed having completed the first cycle of therapy, which was treated by stereotactic irradiation. Subsequent to the third ipilimumab treatment cycle, we observed Grade 2 dermatitis, diarrhea and febrile state that responded to oral and local steroids. We omitted the fourth treatment cycle because Grade 3 immune-originated nephritis developed. Blood chemistry resulted creatinine 2007 µmol/L, carbamide 42,8 µmol/L. 250 mg/day methylprednisolon turned to be ineffective so the patient needed continuous haemodialysis. Imaging studies performed in November 2011 did not identify progression, nevertheless multiple cerebral metastases were detected in March 2012.

The most frequent immune-related adverse events of ipilimumab are dermatologic, gastrointestinal or endocrine, however other autoimmune diseases cannot be excluded, either. Our patient suffered from serious, haemodialysis-dependent nephritis while the basic disease was not progressing for 9 months.