Making Education Easy 28 October 2020

In this review:

Abbreviations used in this review:

CI = confidence interval
CNM = congenital melanocytic nevi
ddPCR = droplet digital polymerase chain reaction
DTC = disseminated tumour cells
GWAS = genome-wide association study
ICI = immune checkpoint inhibition
IFN = interferon
PD = Parkinson's disease
PD-1 = programmed cell death protein 1
RECIST = response evaluation criteria in solid tumours
TNF = tumour necrosis factor

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Welcome to this review of the 17th International Congress of the Society for Melanoma Research (SMR) which was held online on the 28th October, 2020.

The SMR Congress was moved from the planned in-person event scheduled for New Orleans and held as an online virtual event for the first time this year in deference to the global coronavirus 2019 pandemic. The Congress provided a forum for the presentation of both clinical and preclinical research and promotes collaboration between researchers. This review provides a snapshot of the latest research presented at the virtual Congress. Of particular interest were the number of ongoing studies investigating the proangiogenic factor midkine which has been shown to induce melanoma tumour cell proliferation, be involved in immune evasion and immunotherapy resistance and metastasis. Several groups are investigating ways to target midkine, alone or in conjunction with other novel targets that may extend the dormancy period of disseminated tumour cells and provide hope for patients with metastatic melanoma. The protocol for the phase 2 SUMMIST trial, planned to commence this month, was also presented and will evaluate the efficacy of metastasectomy following front-line anti-programmed cell death protein 1 (PD-1) therapy for metastatic melanoma. We eagerly await results from this trial. Selection and review of the research has been carried out independently by Dr Katy Harvey, who virtually attended the meeting. Next year's Congress will be held in New Orleans, USA from the 28th – 31st October, 2021.

Abstracts from the 2020 Congress will be available on the SMR website in due course: https://smrcongress.org/.

We hope you find these and the other selected studies interesting, that they help you improve the lives of your patients and look forward to receiving any feedback you may have.

Kind Regards,

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Overlapping genetic architecture between Parkinson's disease and melanoma

Presenter: Umber Dube

Summary: Dube et al add to the numerous epidemiological studies reporting links between cutaneous melanoma and Parkinson's disease (PD) by revealing a positive genetic correlation between the two (correlation: 0.17; 95% confidence interval [CI] 0.10–0.24; $p = 4.09 \times 10^{-06}$). The study used polygenic, linkage disequilibrium-informed methods and inverse-variance weighted meta-analysis to analyse statistic data from the largest available case–control, genome-wide association study (GWAS) for melanoma and PD (using meta-analysis melanoma risk summary statistic data the Melanoma meta-analysis consortium and PD risk summary statistic data from PDGENE, 23andMe, Inc and the IPDGC) with Alzheimer disease and frontotemporal dementia used as negative comparator neurodegenerative diseases (risk summaries from the National Institute on Aging Genetics of Alzheimer Disease Data Storage Site and the International Frontotemporal Dementia Genomics Consortium, respectively). The study also shows shared gene expression profiles (correlation: 0.14; 95% CI, 0.06 to 0.22; $p = 7.87 \times 10^{-04}$) involving the *PIEZO1*, *TRAPPC2L* and *SOX6* genes that argues for a common genetic architecture. This research has also been published in *Acta Neuropathologica*.

Comment: This study investigated the genetic linkage between PD and cutaneous melanoma. The risk of cutaneous melanoma is higher for those with PD, which has been demonstrated to extend to family members, suggesting a genetic aetiology. PD is characterized by the degeneration of pigmented, neuromelanin-containing neurons. Utilising GWAS the correlation of PD with cutaneous melanoma risk was investigated in addition to Alzheimer's disease and frontotemporal dementia, for negative comparison analyses. A significant correlation (0.17) was reported between PD and cutaneous melanoma. No significant genetic correlation was demonstrated between melanoma and Alzheimer's disease or frontotemporal dementia. Seven genes were highlighted: *GPATCH8, MYO9A, PIEZO1, SOX6, TRAPPC2L, ZNF341* and *ZNF778* as potential mediators of the genetic correlation between melanoma and PD. These may offer future potential for therapeutic targets.

Reference: Acta Neuropathol 2020;139(2):347-64
Abstract

Surgery of metastatic melanoma after systemic therapy – The SUMMIST TRIAL

Authors: Holmberg, C et al.

Summary: This poster presentation detailed the protocol for the open-label, phase 2, randomised controlled SUMMIST trial (ClinicalTrials.gov Identifier: NCT04242329) that aims to assess the efficacy of metastasectomy following front-line anti-programmed cell death protein 1 (PD-1) therapy for metastatic melanoma. The trial is sponsored by Sahlgrenska University Hospital, Sweden and plans to enrol 26 patients with biopsy or cytology proven metastatic stage 4 M1a-c melanoma who have achieved stable disease or a partial response according to response evaluation criteria in solid tumours (RECIST 1.1) following nine months of PD-1 inhibition (as a monotherapy or in combination). Patients with metastases suitable for radical surgical resection will be randomised to surgery plus immunotherapy or prolonged PD-1 inhibition alone. Efficacy will be determined by disease-free survival at 12 months, R0 surgical resection rate, progression-free survival, melanoma-specific and overall survival. The trial is due to commence in November 2020 and has an estimated study completion date of December 2022.

Comment: The SUMMIST trial is a Swedish multicentre phase 2 randomised control trial involving patients with stage 4 melanoma (M1a-c). Patients are treated for a minimum of nine months with immunotherapy, and then randomised to either surgery and continued immunotherapy (interventional arm), or to continued immunotherapy (control arm). Patients are only included if metastasectomy with full surgical (R0) radicality was deemed feasible. The primary endpoint is disease free survival at 12 months. Patient inclusion is due to start in the last quarter of 2020 and is anticipated to run for two years. This important prospective study aims to provide data to guide the treatment of stage 4 melanoma, and crucially highlight the relative benefit of additional surgical intervention to this cohort of patients.

Use of droplet digital PCR for *NRAS* characterization in minimally invasive microbiopsies and plasma cell-free DNA from congenital melanocytic naevi patients

Presenter: Neus Calbert-Llopart

Summary: This Spanish group concluded that droplet digital polymerase chain reaction (ddPCR) technology provided a minimally invasive way to monitor *NRAS* mutations in patients with congenital melanocytic nevi (CMN). The group analysed somatic DNA from microbiopsies of CMN and found *NRAS* p.Q61 mutations in almost 60% (10/19; 58.8%). Examination of plasma cell-free DNA from seven patients with confirmed *NRAS* mutations in the CMN revealed the presence of plasma mutated *NRAS* copies only in patients with comorbidities at the time of sample collection (two patients: one with neurocutaneous melanosis and one with disseminated metastases). This research allows low-frequency alleles such as oncogenic *NRAS* to be quantified and may serve as a biomarker for early diagnosis of cancer.

Comment: This small study (19 patients) explored the potential benefit of the *NRAS* characterization in somatic DNA isolated from CMN. CMN are benign tumours of which 60-80% have a mutation predominantly in the *NRAS* gene. Those patients with large CMN have a higher risk of developing melanoma or neurological abnormalities. Minimally invasive techniques to acquire tissue for genetic analysis holds promise with potential use for monitoring high-risk patients and children, as it is a practically painless procedure with a 0.5 x 0.2 mm lancet. The CMN microbiopsies were analysed for the presence of the *NRAS* gene by ddPCR and in plasma cell-free DNA from CMN patients. Data was obtained from all samples but two (total 17 of 19 patients), where there was not enough DNA collected. This study highlights how ddPCR is a potentially useful tool to rapidly classify CMN from both minimally invasive skin microbiopsies and plasma samples for monitoring CMN patients.

Germline genetic variants influence on dermoscopic features of melanoma

Presenter: Gemma Tell-Marti

Summary: This collaborative study from researchers at the Hospital Clinical, The August Pi i Sunyer Biomedical Research Institute (IDIBAPS) and Biomedical Research Networking Centers on Rare Diseases, both in Barcelona, Spain investigated the affect germline genetic variants of melanoma have on dermascopic features. A total of 371 melanomas from 310 patients underwent genotyping of nine single nucleotide polymorphisms in the *MTAP*, *PLA2G6*, *IRF4* and *PAX3* genes. Multivariable logistic regression analysis showed that genetic variants of the *MTAP*, *PLA2G6, PAX3* and *IRF4* genes associated both with low naevus counts and dermascopic features considered prognostic for worse disease such as regression structures and shiny white structures (all $p \leq 0.05$).

Comment: Distinctive dermoscopic features are seen in *de novo* melanomas. In this study 371 melanomas from 310 patients were evaluated for dermoscopic features associated to specific genotypes. The following genetic variants were investigated: *MTAP*, *PLA2G6*, *IRF4* and *PAX3* genes and sequencing of the *MC1R* gene. The results demonstrated that *MTAP* variants were associated with peppering and mixed regression features, blue-white veil, shiny white structures and pigmented network. Moreover, shiny white or mixed regression features were associated with *PLA2G6*, *PAX3* and *IRF4* genes. Red-haired *MC1R* variant carriers showed less blotches than non-carriers. These findings provide further support for genotypes determining the biology and dermoscopic features of melanoma.

Molecular mechanisms of resistance to immunotherapy in human melanoma

Presenter: Christophe Martignier from the University of Lausanne and CHUV, Switzerland

Summary: This preclinical work from a group at the University of Lausanne and CHUV, Switzerland aimed to uncover mechanisms of resistance to immunotherapy in patients with melanoma. They utilised a set of human melanoma cell lines to examine *in vitro* responses to cytokines and whole exome sequencing to identify gene mutations that may be involved in either primary or acquired resistance. This group identified a mutation in the *JAK1* gene that may result in an impaired ability to mount an immune response and offers a possible new therapeutic target.

Comment: Despite the success of immunotherapy, many patients do not respond or experience a relapse during the treatment. Crucially, identifying the underlying mechanism of resistance aims to lead to more successful clinical outcomes. This study explores the response of 21 human melanoma cell lines to different cytokines. Only interferon (IFN)-γ and tumour necrosis factor -alpha (TNF-α) lead to major changes *in vitro*. Notably, one cell line presented genetic defects in the *JAK1* gene which lead to an abrogated IFN signalling. This suggests that subsequent failure of immune gene upregulation may explain the final relapse of the patient. This research highlights that the melanoma tumour cells are able to adapt to immunological cues present in the microenvironment. Future research would be required to identify whether the T672E mutation is responsible for the final relapse of the patient to immunotherapy. This provides a potential target for future therapy.

Independent commentary by Dr Katy Harvey *BMBCh MA (Oxf), DRANZCOG, DCH-SA, FRACGP, Professional Diploma in Skin Cancer Medicine, Professional Diploma in Dermoscopy*

Dr. Katy Harvey graduated from Oxford University with First Class honours (BMBCh, MA) before moving to Melbourne in 2011 to undertake her postgraduate studies. She was awarded the Fellowship of the Royal Australian College of General Practice (FRACGP), Diploma in Obstetrics and Gynaecology (DRANZCOG) and Diploma in Child Health (DCH), and developed a special interest in skin cancer medicine.

Katy holds a Professional Diploma in Skin Cancer Medicine and a Professional Diploma in Dermoscopy, in addition to certificates in Advanced Dermatoscopy and Histopathology and Primary Care Skin Cancer Therapeutics. Since 2015, she has held the position of Senior Lecturer with the University of Queensland School of Medicine, assisting with the Masters of Medicine (Skin Cancer) course. In 2018, she completed the International Short Course in Dermoscopy (ISCD) at the Medical University of Graz, Austria.

Katy also enjoys being a part of the GP Registrar education program in Victoria and also teaches skin cancer skills to doctors and heathcare professionals for HealthCert. She works full time in skin cancer clinics based in Carnegie and Wantirna, Melbourne.

References: 1. OPDIVO® (nivolumab) PBS information (http://www.pbs.gov.au). **2.** Larkin *et al. New Engl J Med* 2019;381:1535–46 (including supplementary appendix).

Familial melanoma *CDKN2A* mutation carriers under surveillance: Is it time for lung cancer screening?

Presenter: Miriam Potrony

Summary: This observational prospective study in two centres shows a benefit to lung cancer screening in patients carrying the melanoma *CDKN2A* mutation. A total of 59 patients carrying the melanoma *CDKN2A* mutation seen at the Hospital Clinic of Barcelona or the Oncology Institute of Southern Switzerland underwent thoracic imaging surveillance between 2013 and 2019. In this time period three patients (all over 50 years old) developed lung cancer. All patients were treated with surgical intervention with or without neoadjuvant therapy and no patients had relapsed at three-year follow-up.

Comment: Germline mutations in *CDKN2A* are known to confer an increased risk of pancreatic cancer and lung cancer, in addition to cutaneous melanoma. This multicentre prospective study explores the potential benefits of performing thoracic imaging of *CDKN2A*-mutation carriers. Of the 59 patients who underwent lung imaging, three patients developed lung cancer, one of these was a non-smoker and all were over the age of 50. Reassuringly, surgery was possible in all cases and following three years of follow-up, all are free of disease relapse. *CDKN2A*-mutated families had a higher prevalence of lung cancer and *CDKN2A* carriers had a higher co-occurrence of melanoma and lung cancer. This research supports a lung cancer screening program for early detection of lung cancer in *CDKN2A*-mutant carriers over 50-years old.

A retrospective multicentre study of melanoma in children and adolescents

Presenter: Elena Hawryluk

Summary: Elena Hawryluk from the Massachusetts General Hospital, USA, presented this multicentre retrospective study of paediatric melanoma and found a diverse range of clinical manifestations with no factors correlating to reduced survival. A total of 317 paediatric patients (younger than 20 years) diagnosed over a twenty-year period at 11 academic centers were included in the analysis. Melanoma was fatal in 20 cases (7%). Compared to healthy control patients (seen at the Boston Children's Hospital), paediatric melanoma patients were significantly more likely to have other skin cancers or a family history of melanoma (p=0.006 and p=0.046, respectively). Survival was not influenced by family history of melanoma, sunburn, immunosuppression, radiation or chemotherapy.

Comment: Melanoma in children and adolescents is rare and this study aims to characterize and identify potential risk factors in this population. This multicentre retrospective study looks at patients diagnosed with melanoma under the age of twenty, utilizing data over a 20-year period across 11 academic medical centres in the USA, and included age and gender-matched controls from a five-year period at Boston Children's Hospital. In total, 317 melanomas were diagnosed. Of these, the majority were in children aged 11 or over (72.6%). The most common melanoma subtypes were spitzoid (31%), superficial spreading (26%) and those arising in a congenital naevus (11%). Two main risk factors were identified; the presence of another cutaneous malignancy, or a family history of melanoma. Interestingly, no significant association was found between overall survival and family melanoma history, sunburn history, radiation therapy, chemotherapy or prolonged immunosuppression.

Development of a new molecular predictor for risk of melanoma brain metastases

Presenter: Christopher Stehn

Summary: This group from the Huntsman Cancer Institute developed a gene expression profile capable of identifying melanoma patients at high-risk of brain metastases development who would therefore benefit the most from adjuvant immunotherapy. The researchers used RNA sequencing to identify genes dysregulated in melanoma tumours that metastasise (p<0.05). The technology still needs to be validated, translated to a sequencing platform and evaluated in a clinical trial. This research was also presented at the 2019 Society for Neuro-Oncology Inaugural Conference on Brain Metastases and has been published in *Neuro-Oncology Advances*.

Comment: The prognosis for patients with brain metastases is very poor. Identifying which patients are at high-risk of developing brain metastases is of great clinical importance in improving overall survival. Current methods are limited and this study explores a combination of molecular, clinical and pathologic predictors of brain metastases risk utilizing RNA-sequencing from three international data sets. This research identified a distinct gene expression signature that appears predictive for the risk of brain metastases, and distinguishes patients into high and low-risk profile groups. This work is promising and provides the first step towards a prospective risk assessment model that will facilitate patient decisions whether to undergo adjuvant therapy.

Reference: Neurooncol Adv 2020; 1(1 suppl): i12
Abstract

Midkine rewires the melanoma microenvironment toward a tolerogenic and immune-resistant state

Presenter: Daniela Cerezo-Wallis

Summary: This research from a team at the Spanish National Cancer Research Centre (CNIO) shows that the melanoma-secreted heparin-binding protein midkine promotes immune suppressive activity and contributes to immune checkpoint blockade resistance. *In vitro* studies showed midkine activated nuclear factor-κB and contributed to downregulation of interferon pathways and immune dysfunction. Blockade of midkine in knockdown animal models revealed that sensitivity to anti PD-1/PD-ligand (L)1 therapy was reinstated in the absence of midkine and the relevance to human disease was confirmed with analysis of patients with immune checkpoint inhibition (ICI) resistance from six clinical trials that showed high expression of a group of genes related to midkine expression. The authors suggest that for successful melanoma treatment a dual approach is warranted that combines ICI with midkine inhibition.

Comment: A key question remains; how do malignant cells shift the immune system to favour or block cancer development? This research aims to dissect the impact of midkine, a melanoma-secreted factor, and the extent to which it controls the immune system. The findings reveal that midkine acts as an internal modulator of autocrine and paracrine signals that maintain immune suppression in aggressive melanomas. Midkine rewires melanoma cells to promote an immunosuppressive state and enable macrophages to drive CD8 T cell dysfunction. Moreover, midkine silencing increased sensitivity to ICI and correlated to resistance in patients. Further work to elucidate additional clinical therapeutic targets would be beneficial.

Reference: Nat Med 2020; Oct 19 [Epub ahead of print]
Abstract

Midkine inhibits dormancy of melanoma disseminated tumour cells

Presenter: Alcina Rodrigues

Summary: This preclinical research from the Icahn School of medicine at Mount Sinai investigates the role midkine and the nuclear receptor NR2F1 play in dormancy of disseminated tumour cells (DTC). Using murine animal models infected with melanoma the group show that midkine and NR2F1 play opposing roles in cancer dormancy with midkine knockdown reducing metastasis and increasing NR2F1 induction. They have developed a new agonist of NR2F1 which has been tested in head and neck carcinoma models. They propose that the dormancy of disseminated melanoma tumour cells may be extended by dual induction of NR2F1 activity with midkine inhibition.

Comment: Midkine has an established premetastatic role in melanoma progression due to neo-lymphangiogenesis inducement. This study investigates the correlation between NR2F1 and midkine functions in melanoma dormancy *in vitro* and *in vivo* (mice). Results revealed that midkine expression inversely correlates with NR2F1 and its dormancy signatures, and negatively regulates expression of NR2F1 in DTC. Reactivation of DTCs is believed to cause disease relapse and the formation of deadly metastases. Profiling DTCs will help in understanding the dormancy mechanisms and hopefully lead to preventing DTC reactivation. The author states that a new agonist for NR2F1 has been identified, that specifically induces NR2F1 activity. Future testing of this NR2F1 agonist alone and in combination with midkine blockers is proposed. Extending the dormancy of melanoma DTCs could hold the key to a novel therapeutic strategy to improve melanoma survival rates.

