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Non-melanoma skin cancers (NMSCs) are among the most common human malignancies. Current methods for their prevention include avoidance of natural and artificial sources of UV radiation and using photoprotective clothing and sunscreens. However, these methods have proven to be inadequate in stemming the rise in skin cancer incidence over the past several years. There is accumulating evidence that cyclooxygenase-2 (COX-2), an enzyme involved in prostaglandin synthesis, may be involved in the pathogenesis of NMSC. In preclinical studies, animals genetically deficient in the COX-2 enzyme or that have been treated with pharmacological inhibitors of COX-2 develop significantly fewer tumors when subjected to a UV-induced skin carcinogenesis protocol compared with control mice. Several epidemiological studies in humans support the concept that this enzyme is intimately involved in UV-induced skin cancer development, and UV radiation is known to augment COX-2 expression in human skin. Recent studies suggest that drugs that block COX-2 expression may prevent the development of NMSCs. Thus, pharmacologic agents that inhibit the enzyme COX-2 may be effective chemopreventive agents for NMSCs.
Several reports have demonstrated the inhibitory effect of metformin, a widely used drug in the treatment of type 2 diabetes, on the proliferation of many cancers including melanoma. Recently, it has been shown that metformin is able to modulate the cAMP level in the liver. As cAMP has a crucial role in melanin synthesis and skin pigmentation, we investigated the effect of metformin on melanogenesis both in vitro and in vivo. We showed that metformin led to reduced melanin content in melanoma cells and in normal human melanocytes by decreasing cAMP accumulation and cAMP-responsive element–binding protein phosphorylation. This inhibitory effect is correlated with decreased expression of master genes of melanogenesis, microphthalmia-associated transcription factor, tyrosinase, dopachrome tautomerase, and tyrosinase-related protein 1. Furthermore, we demonstrated that the antimelanogenic effect of metformin is independent of the AMPK pathway. Interestingly, topical application of metformin induced tail whitening in mice. Finally, we confirmed the antimelanogenic effect of metformin on reconstituted human epidermis and on human skin biopsies. These data emphasize the depigmenting effect of metformin and suggest a clinical strategy for using metformin in the topical treatment of hyperpigmentation disorders.

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The major barrier to effective cancer therapy is the presence of genetic and phenotypic heterogeneity within cancer cell populations that provides a reservoir of therapeutically resistant cells. As the degree of heterogeneity present within tumours will be proportional to tumour burden, the development of rapid, robust, accurate and sensitive biomarkers for cancer progression that could detect clinically occult disease before substantial heterogeneity develops would provide a major therapeutic benefit. Here, we explore the application of chromatin conformation capture technology to generate a diagnostic epigenetic barcode for melanoma. The results indicate that binary states from chromatin conformations at 15 loci within five genes can be used to provide rapid, non-invasive multivariate test for the presence of melanoma using as little as 200 μl of patient blood.

While most cancers have shown both decreased incidence and mortality over the past several decades, the incidence of melanoma has continued to grow, and mortality has only recently stabilized in the United States and in many other countries. Certain populations, such as men >60 years of age and lower socioeconomic status groups, face a greater burden from disease. For any given stage and across all ages, men have shown worse melanoma survival than women, and low socioeconomic status groups have increased levels of mortality. Novel
risk factors can help identify populations at greatest risk for melanoma and can aid in targeted early detection. Risk assessment tools have been created to identify high-risk patients based on various factors, and these tools can reduce the number of patients needed to screen for melanoma detection. Diagnostic techniques, such as dermatoscopy and total body photography, and new technologies, such as multispectral imaging, may increase the accuracy and reliability of early melanoma detection.

5. Classifying distinct basal cell carcinoma subtype by means of dermatoscopy and reflectance confocal microscopy

Background

The current guidelines for the management of basal cell carcinoma (BCC) suggest a different therapeutic approach according to histopathologic subtype. Although dermatoscopic and confocal criteria of BCC have been investigated, no specific studies were performed to evaluate the distinct reflectance confocal microscopy (RCM) aspects of BCC subtypes.

Objectives

To define the specific dermatoscopic and confocal criteria for delineating different BCC subtypes.

Methods

Dermatoscopic and confocal images of histopathologically confirmed BCCs were retrospectively evaluated for the presence of predefined criteria. Frequencies of
dermatoscopic and confocal parameters are provided. Univariate and adjusted odds ratios were calculated. Discriminant analyses were performed to define the independent confocal criteria for distinct BCC subtypes.

Results

Eighty-eight BCCs were included. Dermatoscopically, superficial BCCs \((n = 44)\) were primarily typified by the presence of fine telangiectasia, multiple erosions, leaf-like structures, and revealed cords connected to the epidermis and epidermal streaming upon RCM. Nodular BCCs \((n = 22)\) featured the classic dermatoscopic features and well outlined large basaloid islands upon RCM. Infiltrative BCCs \((n = 22)\) featured structureless, shiny red areas, fine telangiectasia, and arborizing vessels on dermatoscopy and dark silhouettes upon RCM.

Conclusion

Dermatoscopy and confocal microscopy can reliably classify different BCC subtypes.

Background

Oral hedgehog inhibitors (HHIs) have shown significant efficacy in the treatment of basal cell carcinoma (BCC). The evaluation of tumor regression has been performed using clinical photography and radiographic scans. Noninvasive imaging techniques, such as reflectance confocal microscopy (RCM) and high-
definition optical coherence tomography (HD-OCT), have been shown to be valuable in detecting BCC in the skin.

Objective

We monitored HHI-treated BCC using RCM and HD-OCT in vivo and correlated morphologic changes seen on imaging to changes in traditional histopathology.

Methods

Six BCCs in 5 patients receiving HHIs (vismodegib or sonidegib) were examined by RCM and HD-OCT before and during treatment. Characteristic features were compared to histopathologic findings, including immunohistochemical analysis.

Results

Characteristic features of BCC in RCM and HD-OCT decreased or disappeared completely during HHI treatment. Half of the clinically complete responding tumors still featured tumor residue. Pseudocystic structures (“empty” tumor nests in imaging) and widespread fibrosis (coarse bright fibers) were new findings and could be confirmed by histopathology.

Limitations

Our study was limited by the number of tumor samples and imaging timepoints.

Conclusion

Using RCM and HD-OCT, HHI-induced regression of BCC can be visualized noninvasively in the skin. The formation of pseudocysts and fibrosis were characteristic signs of BCC response to HHIs.
Fibronectin and vitronectin are the important components of the extracellular matrix proteins. The aim of this study was to determine the clinical significance of these protein serum levels in patients with melanoma. A total of 60 patients with a pathologically confirmed diagnosis of melanoma were enrolled in this study. Serum fibronectin and vitronectin concentrations were determined using the solid-phase sandwich ELISA method. Thirty age-matched and sex-matched healthy controls were included in the analysis. The baseline serum fibronectin and vitronectin levels were significantly higher in patients with melanoma than those in the healthy control group (\( P < 0.001 \) and \( P = 0.04 \), respectively). However, known clinical variables including age of the patient, sex, site of lesion, histology, stage of disease, serum lactate dehydrogenase levels, and response to chemotherapy were not found to be correlated with either serum fibronectin or vitronectin concentrations (\( P > 0.05 \)). Moreover, neither serum fibronectin nor vitronectin levels played a prognostic role in outcome in melanoma patients (\( P = 0.47 \) and 0.24, respectively). In conclusion, serum levels of both fibronectin and vitronectin may be diagnostic markers in melanoma patients. However, their predictive and prognostic values were not determined.
The combination of dabrafenib and trametinib (CombiDT) is an effective treatment for BRAF-mutant metastatic melanoma; however, over 70% of patients develop drug-related pyrexia, and little is known about this toxicity. We sought to examine the features and management of CombiDT pyrexia. The association between pyrexia and patient demographics, disease characteristics and outcome variables was assessed in patients treated with CombiDT at a single institution. The clinicopathological features of pyrexic events were analysed. Fourteen of 32 (44%) patients developed pyrexia (temperature ≥ 38.5°C). Pyrexia was recurrent in 11/14 (79%). The median time to pyrexia was 38 days. Pyrexia was not associated with age, sex nor disease burden, and did not correlate with RECIST response, progression-free nor overall survival. Paracetamol, NSAIDs and/or dose reduction (DR) were ineffective secondary prophylaxis for pyrexia, whereas corticosteroids were effective in all patients (n=8), including two with multiple previous pyrexic events despite several DRs. In patients with previous DRs who commenced steroids (n=3), CombiDT doses were re-escalated without pyrexia. Pyrexia is a frequent and recurrent toxicity with CombiDT, with no predictive clinical characteristics. Pyrexia does not correlate with clinical outcome. Neither DR nor antipyretics are effective secondary prophylaxis, whereas corticosteroids are effective, prevent DR and enable re-escalation of CombiDT dosing.

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Cetuximab and panitumumab are epidermal growth factor receptor (EGFR) inhibitors used in metastatic colorectal cancer (mCRC). Most patients develop a papulopustular rash that may predict tumor response to treatment. EGFR gene polymorphisms may also determine tumor response and appearance of skin rash. We hypothesized an association between EGFR gene polymorphisms, papulopustular rash and response to anticancer treatment. Four EGFR polymorphisms (−216, −191, CA-SSR, R521K) were analysed in 51 patients with mCRC receiving anti-EGFR. Severity of cutaneous rash and tumor response was measured following standard scales. We report an association between SNP-216 and tumor response (\(P = 0.003\)): no tumor progression occurred in TT genotype. Moreover, 92.3% of the responder patients developed skin rash, 62.9% of them presenting a grade \(\geq 2\) (\(P = 0.015\)). Thus, although underpowered, our preliminary data suggest that SNP-216 polymorphism of the EGFR gene could be useful in predicting tumor response and the appearance of severe skin rash might also be associated.

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Vitamin D is formed mainly in the skin upon exposure to sunlight and can as well be taken orally with food or through supplements. While sun exposure is a known risk factor for skin cancer development, vitamin D exerts anti-proliferative and pro-apoptotic effects on melanocytes and keratinocytes in vitro. To clarify the role of vitamin D in skin carcinogenesis, we performed a review of the literature and meta-analysis to evaluate the association of vitamin D serum levels and dietary intake with cutaneous melanoma (CM) and non-melanoma skin cancer (NMSC) risk and melanoma prognostic factors. Twenty papers were included for an overall 1420 CM and 2317 NMSC. The summary relative risks (SRRs) from random effects models for the association of highest versus lowest vitamin D serum levels was 1.46 (95% confidence interval (CI) 0.60–3.53) and 1.64 (95% CI 1.02–2.65) for CM and NMSC, respectively. The SRR for the highest versus lowest quintile of vitamin D intake was 0.86 (95% CI 0.63–1.13) for CM and 1.03 (95% CI 0.95–1.13) for NMSC. Data were suggestive of an inverse association between vitamin D blood levels and CM thickness at diagnosis. Further research is needed to investigate the effect of vitamin D on skin cancer risk in populations with different exposure to sunlight and dietary habits, and to evaluate whether vitamin D supplementation is effective in improving CM survival.
To improve the diagnosis of skin tumours, extensive research on new technologies has been carried out introducing real-time imaging methods as multiphoton laser tomography (MPT) associated to fluorescence lifetime imaging (FLIM). Multiphoton microscopy relies on the simultaneous absorption of two or more photons of low energy in the near-infrared spectrum, avoiding biological tissue damage that occurs with higher laser powers.

With multiphoton microscopy, endogenous fluorophores, including NADH, NADPH and many others, can be efficiently excited. Since the technique is non-invasive and the laser illumination is harmless, in vivo examination by MPT/FLIM can be repeated on the same site without restrictions, enabling long-term studies of skin diseases. Horizontal and vertical optical sections give the possibility to study the tissue sample three-dimensionally with a subcellular spatial resolution. The MPT/FLIM technique has numerous applications in dermatology, being suitable for the study of many physiological and pathological conditions of the skin in vivo, on ex vivo samples and on cell cultures. The application of MPT/FLIM to the field of skin tumours provides imaging at a cellular and at an architectural level, although the field of view is at present limited to the exploration of a square area of 358 × 358 μm.
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