Room 122
Monday 10:45 AM — 12:30 PM

Anatomy & Pathology
Pathobiology of Uveal Melanoma

MODERATORS: Kathryn S Pokorny
Miguel N Burnier

PGM#	TIME	AUTHORS
954	10:45	Pe'er, Mehaffey, Fleck, Meyer, Bentler, Woolson, Folberg
955	11:00	Grossniklaus, Wilson, Barron, Lynn
956	11:15	Foss, Alexander, Jefferies, Hungerford, Harris, Lightman
957	11:30	Daniels, Boldt, Folberg
958	11:45	Tabesh, Duclos, Corriveau, Antecka, Halwani, Baines, Burnier, Deschenes
959	12:00	Brand, Sisley, Rennie, Parsons, Rees
960	12:15	Tran, Murray, Uno, Valore, Ksander

NOTE: Potential conflicts of interest of presenters and authors are noted at the end of the Abstract either by "None" or with codes (see code definitions under the section "Abstract Content/Commercial Relationships/Disclosure Codes" in the front matter).

954 — 10:45

SIGNIFICANCE OF QUANTIFYING AND LOCALIZING VASCULAR NETWORKS IN CHOROIDAL AND CILIARY BODY MELANOMAS ((J. Pe'er[1], M.G. Mehaffey[2], M. Fleck[2], M. Meyer[2], S.E. Bentler[2], R. Woolson[2], R. Folberg[2])) Hadassah-Hebrew University, Israel[1] and University of Iowa[2]

Purpose: To determine the significance of quantifying the area occupied by vascular networks and parallel with cross-linking patterns in choroidal and ciliary body melanomas and to determine the most likely location of these prognostically significant stromal-vascular formations. **Methods:** From a previously studied group of 234 eyes removed for ciliary body or choroidal melanoma, 152 cases were identified that contained networks or parallel with cross-linking. The total cross-sectional area occupied by tumor and the total area occupied by each of the two vascular patterns were calculated from digitized images of histologic sections. The location of these patterns was mapped within the tumor. **Results:** A revised Cox regression model was generated: (1) the presence of networks, (2) total cross-sectional area, (3) percentage area occupied by networks and parallel with cross-linking, (4) mitoses, (5) tumor infiltrating lymphocytes, (6) the presence of parallel with cross-linking and (7) arcs (model X^2=108.962, df=11, P=0.0001). Networks and parallel with cross linking tend to appear at the tumor periphery, defined by the zone encompassed by 1/8 of the diameter of the largest circle that fits within a tumor (P<0.0001). **Conclusions:** The variable of cross-sectional tumor area replaces largest tumor dimension in the Cox model. The combined percent areas of networks and parallel with cross-linking adds prognostic information to the model. These patterns tend to appear in the tumor periphery. These observations may be useful in developing clinical imaging techniques to assess clinically the biological behavior of ciliochoroidal melanomas.
NIH Grant EY10457 None

955 — 11:00

ANTERIOR VERSUS POSTERIOR INTRAOCULAR MELANOMA METASTATIC DIFFERENCES IN A MURINE MODEL ((H.E. Grossniklaus, M.W. Wilson, B.C. Barron, M.J. Lynn)) Department of Ophthalmology, Emory University School of Medicine, Atlanta, GA

Purpose. We evaluated the utility of a murine model to study differences in metastatic rate of anterior versus posterior ocular melanoma. **Methods.** Twenty-nine 12-week old C57BL6 mice were inoculated into the anterior chamber (AC) or posterior compartment (PC) of the right eye with $5X10^5/5\mu l$ tissue culture Queens melanoma cells. The right eye was enucleated at 14 days post-inoculation with a necropsy performed. The eye was evaluated for presence of melanoma and the mean of the ten largest nucleoli (MLN) in tumor cells was measured with a digital Filar micrometer. The number of metastases was determined at necropsy. **Results.** Melanoma grew in 12 of 18 AC mice (66%) and 9 of 11 PC mice (82%). The metastatic rate was significantly smaller for AC tumors (33%) versus PC tumors (89%) (p=.02). All AC and no PC melanomas that metastasized to the lungs metastasized to ipsilateral cervical lymph nodes. The median number of metastases per tumor was significantly smaller for AC tumors compared to PC tumors (p=.01). There was a median of 0 metastases (range 0 to 14) per AC tumor and 4 metastases (range 0 to 38) per PC tumor. There was no significant difference of the MLN for AC versus PC melanoma (p=.215). The mean MLN of melanomas that did and did not metastasize was 3.12 μm for each. **Conclusions.** Posterior ocular melanoma metastasizes more often than anterior ocular melanoma in this murine model, similar to human ocular melanoma.

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956 — 11:15

MICROVESSEL COUNT PREDICTS SURVIVAL IN UVEAL MELANOMA. ((A.J.E. Foss[1], R. A. Alexander[2], L. W. Jefferies[2], J.L. Hungerford[3], A.L. Harris[4] and S. Lightman[1])) [1]Department of Clinical Science, Institute of Ophthalmology, London. [2]Department of Pathology, Institute of Ophthalmology, London. [3]Oncology Clinic, Moorfields Eye Hospital, London. [4]Department of Oncology, Churchill Hospital, Oxford.

Purpose. Microvessel density has become established as an important prognostic indicator for many tumour types. This study investigates the microvessel density as a prognostic factor for survival in patients with uveal melanoma. **Methods.** Factor VIII related antigen was identified immunohistochemically in bleached sections from 123 tumours. Maximum blood vessel density in an area of $0.25mm^2$ was recorded along with other accepted prognostic information. **Results.** Microvessel density was the single most important prognostic factor. The actuarial 5 year survival for patients divided into quarters on the basis of counts was 42% for the top quarter, 55% for the next, 70% for the next and 90% for the lowest quarter. On univariate testing, cell type, tumour size, presence of extra-ocular extension, ciliary body involvement, mitotic count and five of the Folberg patterns were significant. In a forward selection Cox's proportional hazard model, microvessel density was the most important variable and the only other variable to enter the model was tumour size. **Conclusions.** Microvessel density is an important prognostic factor for survival in patients with uveal melanoma and is the best single measure of tumour grade.

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TYPE VI COLLAGEN IS SYNTHESIZED BY UVEAL MELANOMA AND ASSOCIATES WITH MICROVASCULAR NETWORKS: SIGNIFICANCE FOR CLINICAL DIAGNOSIS AND THERAPY ((K.J. Daniels, H.C. Boldt, R. Folberg)) University of Iowa

Purpose: To determine the composition of the extracellular matrix of choroidal and ciliary body melanomas that accompany prognostically significant vascular patterns. **Methods:** Eight uveal melanoma cell lines, maintained in serum-free media, were established from ciliary body or choroidal melanomas. The invasive properties of these lines were studied in hydrated collagen gels. Expression of type VI collagen was identified in lines by RT-PCR of purified mRNA, and was confirmed in lines and tissue sections by immunocytochemistry. **Results:** Uveal melanoma cells produce Type VI collagen microfibrils which are usually associated with the normal subendothelial matrix, and in normal and pathologic tissue remodeling and scarring. In histologic sections, Type VI collagen was associated predominantly with the tumor microvascular networks but foci of Type VI collagen were also noted separately in the tumor stroma. Expression of Type VI collagen correlated with invasive behavior by cell lines in three-dimensional gels. **Conclusions:** Uveal melanoma cells produce Type VI collagen which forms a component of the prognostically significant stromal-vascular patterns. The association between invasion and pattern formation may explain the correlation between pattern expression and metastasis. Tissue boundaries establishing patterns in uveal melanoma, are likely determined by Type VI collagen deposition These stromal-vascular patterns may be a key element detected clinically by ultrasound tissue characterization, forming the basis of a non-invasive biopsy of this tumor. Known interactions between Type VI collagen and hyaluronan-CD44 signal transduction may form the basis of adjuvant chemotherapy for this tumor.
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