Role of UV and Interferon-γ in Melanoma: The Value of Mouse Models

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I have the following relevant financial relationships to disclose:

None
Prasun Mishra

Session III: Oral Abstract Session I
1:00pm - Dissection of RAS downstream pathways in melanomagenesis

Prasun Mishra

Session III: Oral Abstract Session I
1:30pm - Using embryonic melanoblast transcriptome analysis to identify novel mechanisms promoting metastatic melanoma

UVB
UVA

Cutaneous malignant melanoma development

• Zaidi et al., J Investigative Dermatology 2008
• David Elder
Building a UV-Responsive Mouse Melanoma Model
The hepatocyte growth factor/scatter factor transgenic mouse

Environmental Agent
Neonatal UV:
DNA damage & Systemic effects

Genetic Engineering
HGF/SF Transgene:
Deregulated autocrine MET signaling

Human-like histopathology

Cutaneous Malignant Melanoma in the Mouse

Epidermal melanocytes

UVB induces melanoma in neonatal HGF/SF-Tg mice

Only neonatal UV induces melanoma in HGF/SF mice

Noonan et al., Nature 2001
De Fabo et al., Cancer Research 2004

Only UVB induces melanoma in albino HGF/SF mice

UVB

UVA

Survival

Age (days)

Cumulative melanoma-free survival

No UV or 6 wk

3.5 day

3.5 day + 6 wk

Survival

Age (days)

Cumulative melanoma-free survival
How does UV radiation incite melanomagenesis?

**Melanocytic (Intrinsic)**
- Direct (UVB) & indirect (UVA)
- DNA damage
- Epigenetic modulations
- Proliferation & differentiation

**Extra-melanocytic (Extrinsic)**
- Inflammation & release of mediators
- Immunosuppression / Tolerance

Isolation and analysis of melanocytes *in situ*
Targeting inducible GFP expression in mouse melanocytes

**Dct Promoter**
- **TRE Promoter**

**Dct-rtTA transgenic mouse**
(Dct = dopachrome tautomerase/Trp2)

**TRE-H2BGFP transgenic mouse**
(TRE = tetracycline response element)

**Dct-rtTA+/TRE-GFP+ bi-transgenic mouse**

- No Doxycycline
- Plus Doxycycline

- Normal melanocytes
- Green melanocytes
Melanocyte-specific, doxycycline-inducible GFP label

- **GFP**
- **GFP**
- Melanocyte co-localization of GFP and DCT

E11.5 day

P7 skin

Zaidi et al., *Nature* 2011

What can we do with this mouse?

- **Melanoma**
- **Nevi**
**Therapeutic Opportunities**
- Evaluate drug combinations to facilitate development of better treatment of recurrent BRAF-driven metastatic melanoma
- Identify novel molecular targets and biomarkers of recurrent metastases
- Determine the predictive value of this model for future preclinical testing

**Improved preclinical modeling of metastatic melanoma patients harboring residual metastatic disease**

**Required Features for Preclinical Model**
- No cell lines (in vivo serial transplants)
- Fully immunocompetent mice
- GEM-derived allograft (GDA) approach
- Stable cell labeling (Luciferase/GFP)
- Host mice pre-tolerized to Luc/GFP
- Efficient spontaneous metastasis
- Industry-friendly turnaround time

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**Perspectives in Melanoma XV**
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