Update on Melanoma

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Disclosures

• Galileo Group (Consulting)
• Canfield Scientific (Consulting)
• DigitalDerm (Founder, Major Shareholder)
• 12/2015 CaliberID (Equipment and meeting support)

Outline

• Immune Regulation - Microbiome
• Targeted RX - Phenotype Switching
• UV – not trivial
• Genetics: Melanoma Patterns
• Melanoma - Radial Disparity
• Technology – Confocal
• What hasn’t significantly changed
  - Dysplastic nevi vs Melanoma progression
  - Sentinel node

Immune Regulation
Checkpoint Inhibitors


Microbiome Fecal Diversity

Gopalakrishnan et al., Science 359, 97–103 (2018)

Bacterial Types

CD8+ density

Gopalakrishnan et al., Science 359, 97–103 (2018)

Transplantable

Bacteriophages


Opportunities

- Stool
- Blood
- Oral
- Weight
- Gender

#1

- Mom was right - eat your vegetables

Targeted RX


https://www.embopress.org/dof/full/10.15252/embr.201505971

BRAF > Mesenchymal

Melanoma Heterogeneity

DM1N  DM2N  DM3N

Nestin (red) / gp100 (green)

PANX1 inhibition with probenecid down regulates MITF/gp100
Dominant role of the niche in melanocyte stem-cell fate determination


Low MITF/AXL ratio predicts early resistance to multiple targeted drugs in melanoma


AXL Inhibitor

- TP-0903 is a novel oral inhibitor that targets AXL kinase and reverses the mesenchymal phenotype associated with advanced cancers.
- Preclinical studies have shown promising antitumor activity of TP-0903 as a single agent against a variety of tumor types in both in vitro and in vivo studies.
- Have BRAF-mutated melanoma that has not responded to immunotherapy or a combination BRAF/MEK inhibitor.

#2

- To ensure elimination of a problem is to block the escape route
- Eliminate both E (TA) and M (stem) – then there maybe nowhere to hide

UV
• Sun-exposed eyelid skin
• 2-6 mutations/MB/cell
• Positively selected 'driver' mutations were found in 18-32% of normal skin cells at a density of ~140/cm2


http://www.weather.com/health/sun-damage-20130516

P53, NOTCH1/2/HRAS

K15, PTCH1 / p53

61.2/MB

13.2/MB

75.8/MB
Frequent clones of p53-mutated keratinocytes in normal human skin

- Patients w/o h/o skin cancer
- Tissue from cosmetic procedures
- P53 mutated clones, arising from DEJ, 60-3,000 cells in size
- Present at frequencies exceeding 40 cells per cm²
- Together involve as much as 4% of the epidermis
- More frequent in sun exposed areas

#3

- You really are getting toasted
- UV is rewriting your skin’s genetic code – not trivially but extensively
- It’s the combination of mutations that matter
- Of course need the right cell type and in correct state as well.
#4

- Declining death rate

#5

- It is the old white guys that are the biggest problem.
Melanoma Dermoscopic Patterns

Rhomboidal – Wild type

Dark Homogenous Streak Pattern

#6

- Germline may define mutations that develop
- Mutations drive growth pattern
- Paucity of genetic data for thin low risk tumors
#7

- Melanoma is racially biased
- Prevention approaches may need to be modified on germline as well as environment.
Challenges with Melanoma Diagnosis
Visualizing Melanoma Cells and Image Stacks in 3D

- Cell is segmented
- Dendritic Melanoma Cell identified
- Reconstruction
- Registration
- 3D reconstructions

#8
- Confocal helps with those difficult dermoscopic diagnoses
- May help studying melanocyte/melanoma biology

Meiomitosis
- Hallmark is genomic instability
- CT antigens…meiosis proteins
Meiotic protein expression can’t be good during mitosis.

What hasn’t changed
- Dysplastic nevi
- Sentinel node / Staging
Melanomas do not require pre-existing nevi

Melanomas are **growing**, **unusual** and progressively more **non-uniform**

**Summary**

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