Charles Darwin, cancer evolution and the concept of progression in melanocytic neoplasms

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What reggae has to do with evolution?!

Charles Darwin

Bob Marley
Branched evolution

Cancer starts with one cell mutating.
In some tumours, this then develops into a Darwinian ecosystem of genetic diversity...

Together we will beat cancer

...this branched development echoes Darwin's "Tree of Life", which describes the evolution of species.
This helps explain why:
• tumours are so hard to treat once they've spread
• how they become resistant to cancer drugs.
• and why it’s so hard to find molecular ‘markers’ to predict patients’ outcome.
Cancer’s wish list

- Self-sufficiency in growth signals
- Insensitivity to growth-inhibitory signals
- Evasion of programmed cell death (apoptosis)
- Limitless replicative potential
- Sustained angiogenesis
- Tissue invasion and metastasis
The Genetic Evolution of Melanoma from Precursor Lesions

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Melanocytes
Two distinct subtypes of melanoma
Melanomas often arise from distinctive precursor lesions such as:
  - melanocytic nevi
  - intermediate lesions
  - melanoma in situ
Known oncogenes

- BRAF
- NRAS
- GNAQ, GNA11
- Kinases fusions
Recurrent somatic mutations

- Proliferation (BRAF, NRAS, NF1)
- Growth and metabolism (PTEN and KIT)
- Cell identity (ARID2)
- Resistance to apoptosis (P53)
- Cell Cycle control (CDKN2A)
- Replicative life span (TERT)
Melanocytic nevus

BRAF\textsubscript{V600E} mutations
Melanocyte

Polyclonality

Naevus

Intermediate neoplasm

Melanoma in situ

Invasive melanoma

Metastasis

Proliferative index (by e.g. mitosis, Ki67 or PCNA)

Mutagen

UV radiation

Point mutation burden

Copy number burden
Intermediate lesions/dysplastic nevus
Melanoma in situ
Subtypes

- Non chronically sun-damaged skin
  - Pagetoid growth pattern
  - BRAFV600E
  - Usually in association with nevi
- Chronically sun-damaged skin
  - Lentiginous growth pattern
  - No BRAFV600E
  - Frequently De novo
Lentigo maligna melanoma
Melanocytet Naevust Intermediate neoplasmt Melanomain situt
Polyclonality

Proliferative index (by e.g., mitosis, Ki67 or PCNA)

Mutagen

Point mutation burden UV radiation

Copy number burden
Invasive melanoma
Nodular melanoma
Metastasis

Melanoma cells disseminate from primary tumours in parallel via both vascular and lymphatic routes to regional and distant sites.

Due to their proximity, the regional lymph nodes show metastatic deposits earlier, possibly due to repeated seeding.

Distant metastases arise later; circulating tumour cells can seed different existing metastases, increasing the heterogeneity of individual metastases.

Stage I or II

Stage III

Stage IV
Stage III

Naevus cells can travel to regional lymph nodes and form small metastatic deposits.

In a subset of patients melanoma presents as a metastasis with no apparent primary tumour; these may form from primary melanomas that have regressed or from nodal naevi.
Conclusion

• Improved diagnosis
• Earlier recognition of lesions at increased risk of progression
• Selective intervention at an earlier stage
• Crucial role of UV radiation has become unequivocally clear
Melanoma: from mutations to medicine

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Biologic Progression of Melanoma

International Health Fund

- Established in collaboration with Dartmouth University and Dartmouth-Hitchcock Medical Center, Pathology Department
- Free consultations from abroad
- Includes second opinion, ancillary studies (immunohistochemical, molecular studies) and courier service
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