Definition of consensus melanoma subtypes with distinct phenotypes and clinical implications

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Topics

1. Precision medicine
2. Large scale cancer genomic projects: the raise of big data
3. The Cancer Genome Atlas (TCGA)
4. Focus on a big killer: melanoma
5. Consensus subtypes of melanoma (publicly available data)
6. Gene expression analysis of a clinical cohort for melanoma therapy
"Precision medicine" is a rapidly evolving approach of tailoring therapeutic interventions to the individual molecular features of a patient and/or their disease that moves beyond the conventional approach of stratifying patients into treatment groups based on phenotypic biomarkers.

In oncology, central to precision medicine is the ability to characterise precisely the molecular and cellular features of a tumour, and its microenvironment, in addition to taking into account genetic markers, the lifestyle and environmental factors of the individual, to determine which treatments are likely to confer the greatest benefit.

The European Society for Medical Oncology (ESMO)
Precision Medicine Glossary Annals of Oncology 29: 30–35, 2018
Cancer Genomics Projects

2006-The Cancer Genome Atlas (TCGA)

2011-International Cancer Genome Consortium (ICGC)
TCGA: a decade of discovery
2006-2015 (end of the beginning of cancer genomics)
April 2018: The Pan-Cancer Atlas

Tumor aggregation based on a biological system approach or histological subtypes

Patterns of vulnerabilities that will aid in the development of personalized treatments and new combination therapies

Oncogenic processes across all the tumor types characterized (immunity, mutation, aneuploidy)

Ancillary results

**Team Science.** Integrative, cross-platform interdisciplinary investigation is an extremely valuable and valid model of research.

**Genomic pipelines.** Establish infrastructure for effective team science. Pipelines, standards and best practices become invaluable resources for the research community.

**Sample acquisition and study design.** TCGA has been instrumental in highlighting the need for thoroughly annotated, high quality tumor samples with matched normal controls and informed consent.

**Data accessibility.** Make the data publicly and broadly available to the cancer community while protecting patient privacy.
Moving the field closer the goal of improving the ability to diagnose, treat and prevent cancer

Cutaneous malignant melanoma is the most aggressive and deadly form of skin cancer. Whilst cutaneous melanoma accounts for only 5% of all skin cancers, it is responsible for 75% of all skin cancer-related deaths. Since the mid-1960s, melanoma incidence has increased by 3–8% per year in western countries reaching approximately 10–50 cases per 100,000 individuals. Increase in the incidence and resistance to conventional therapies makes melanoma one of the major challenges in cancer research.
Melanoma — An Unlikely Poster Child for Personalized Cancer Therapy

Keiran S.M. Smalley, Ph.D., and Vernon K. Sondak, M.D.
Mutation of the BRAF gene in human cancer

Cancers arise owing to the accumulation of mutations in critical genes that alter normal programmes of cell proliferation, differentiation and death. As the first stage of a systematic genomic-wide screen for these genes, we have prioritized for analysis signalling pathways in which at least one gene is mutated in human cancer. The RAS–RAF–MEK–ERK–MAP kinase pathway mediates cellular responses to growth signals. RAS is mutated to an oncogenic form in about 15% of human cancer. The three RAF genes code for cytoplasmic serine/threonine kinases that are regulated by binding RAS. Here we report BRAF somatic missense mutations in 66% of malignant melanomas and at lower frequency in a wide range of human cancers. All mutations are within the kinase domain, with a single substitution (V599E) accounting for 80%. Mutated BRAF proteins have elevated kinase activity and are transforming in NIH3T3 cells. Furthermore, RAS function is not required for the growth of cancer cell lines with the V599E mutation. As BRAF is a serine/threonine kinase that is commonly activated by somatic point mutation in human cancer, it may provide new therapeutic opportunities in malignant melanoma.
From BRAF oncogene discovery to the clinic

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D.,
John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D.,
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and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group*

Targeted agents and immunotherapies for advanced-stage SKCM

Targeted therapies
- Vemurafenib/Dabrafenib: BRAF inhibitors (BRAF<sup>V600E</sup> tumors)
- Cobimetinib/Trametinib: MEK inhibitor (in combo with BRAFi for BRAF<sup>V600E</sup> tumors)

Gene expression-based molecular subtypes

The phenotypic state of melanoma cells predicts MAPKi resistance

Hoek et al. Pigment Cell Res. 2006

Published gene expression signatures have poor overlap
Analytical workflow

Public repositories

Melanoma Cell Lines (MCL) (15 datasets, n = 504)

TCGA SKCM (n = 473)

- i. Subtype assignments
- ii. Consensus subtype identification
- iii. Subtypes characterization

Association to drug sensitivity data (CCLE and GDSC)

Survival analysis

6 in-vitro signatures (Widmer, Sensi, Dugo, Verfaillie, Rambow, Tirosh*)

1 clinical signatures (TCGA)
Identification of consensus melanoma subtypes

Melanoma cell lines datasets (A)

TCGA dataset (B)
Impact of consensus melanoma subtypes for prognosis and response to BRAF-inhibitors

Subtypes has a prognostic value

Subtypes predict sensitivity to BRAFi \textit{in-vitro}

![Graph showing survival probability over years with log-rank p = 0.003]

![Graphs showing IC50 values for different subtypes in CCLE and GDSC datasets]
Transcriptomic analysis of pre-treatment lesions from stage III-IV BRAF^{V600E} mutant melanoma patients treated vemurafenib

The expected enrichment of invasive samples in pre-therapy/non-responder lesions and of proliferative samples in long responder lesions is not observed. Subtypes are randomly distributed between the two response groups.
Meta-analysis of gene expression data leads to the identification of three transcriptional consensus subtypes into which the majority of melanoma cell lines and clinical samples can be categorized.

Subtypes are driven by epigenomic and transcriptional differences not by genomic alterations.

Molecular subtypes predict resistance to the BRAFi PLX4720 \textit{in vitro}.

Molecular subtypes has prognostic value in untreated patients but so far do not appear to play a significant role in governing clinical response to BRAFi based therapy.