Temporal-weight Estimation Of The Copy Number Alterations Of 1384 Multiple Myeloma Patients Defines An Ancestrality Index Impacting Patients Survival

Andrea Poletti

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The Multiple Myeloma CNAs heterogeneity

Primary genetic events:
- IGH translocations
- Hyperdiploidy

Secondary genetic events:
- Copy number abnormalities
- DNA hypomethylation
- Acquired mutations

Kumar, S. et al. (2017) Nature Reviews

Davis, A. et al. (2017) Reviews on Cancer
The Multiple Myeloma clinical and genetic onset

- Active MM is defined by the onset of clinical symptoms, but there is no clear connection between the MM diagnosis and the genomic lesions in the tumor cells.

- However, genetic alterations are widely recognized to have a driving role for tumors onset as they can cause all the biological “hallmarks of cancer”

- Alterations present in the MM tumors at diagnosis are often found in MGUS and SMM, so if precisely characterized, they could support a correct MM diagnosis in “ambiguous” SMM patients
The importance of **timing** the genetic cancer alterations

- The recognition of *ancestral alterations* can help identify true «driver» lesions, relevant for the onset of the MM and clinical symptoms.

- Using statistical algorithms, it's possible to create a **time-map** of the acquired **CNAs** during **MM oncogenesis** and rank them as “late” or “early”.

- The correct CNAs’ timing in previous works is biased by the low number of patients analysed (< 100).

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Maura *et al.* Nat Comm (2019)

Harmonizing datasets – the importance of statistical power

High statistical power is required to precisely time CNAs, especially rare ones.

We combined two huge (but different) different datasets:
- MM-BO: 512 samples profiled with SNP-arrays
- CoMMpass cohort: 871 samples profiled with WGS

**BUT**
- Need for data-harmonization to compare CN profiles, since clonal and subclonal CN events can be biased by multiple methodological aspects:
  - different assays methods
  - different tools/pipelines
  - different analysis algorithm parameters
Bradley-Terry algorithm to date MM CNAs – a precise time map

- **SPORT classification algorithm**
  - PLAYERS = any secondary (non-HD) CNAs
  - MATCHES = clonality contest
    
    => any clonal and subclonal CNAs «competed», according to 10% clonality difference threshold
    
    => only secondary CN events do participate to the competition since IgH traslocations and Hyperdiploidy are primary ancestral events (they are always clonal)

![Reconstructing events during the life history of each tumor](image1.png)

**Jolly C. and Van Loo P. Genome Biology (2018)**

- **Chr 1q amp (CKS1B)**
- **Chr 13q del (RB1)**
- **Chr 17p del (TP53)**
- **Chr 6p amp (CCND3)**
Implementatation of CNAs timing information to date MM patients’ *ancestrality*

• We developed a **combinatorial scoring model** to produce an **ANCESTRALITY INDEX (AI)** that weights each CNA in any given sample for its relative Timing Estimate (TE).

For each patient (p):

\[
AI_p = \sum_{i=1}^{n} (CNA_i \times TE_i) = (CNA_1 \times TE_1) + (CNA_2 \times TE_2) + (CNA_3 \times TE_3) \ldots
\]

• Statistical categorization of patients according to the **AI quartiles**:  
  – «*ancestral*» (high AI) patients  
  – «*young*» (low AI) patients
"ancestral" and "young" MM patients => survival analysis

- Patients included in the «ancestral» time-weighted category present worse prognosis, as compared to patients included in the «young» time-weighted category, in terms of both OS and PFS.

- At the time of MM diagnosis, the timing characterization of the whole CNAs landscape significantly impact patients’ survival.
• CNAs can be dated during MM oncogenesis and evolution
• OLD CNAs are probably driver alterations => patients with high AI have bad prognosis;
• The timing analysis of molecular lesions (particularly CNAs) help in defining newly diagnosed patients’ clinical characteristics and might identify driver lesions
• The use of AI score in SMM patients might help in defining their evolutive status by distinguish either MGUS-like or high-risk SMM subtypes

the whole CNAs landscape carries information concerning the MM evolution ancestrality state and this impacts patients’ survival
By this approach, it has been possible to define **genomically distinct states at the onset of MM**, i.e.

- **“young/simple” MM tumors** with **low** temporal-genomic heterogeneity
- **“ancestral/evolved” tumors** with **multiple** different driver ancestral alterations distributed across the genomic profile

Clinical correlations highlighted that:

- novel biomarkers can be defined, based on the **genome ancestrality**, useful for the clinical management of MM patients
- MM evolution in **pre-clinical phases** can be elucidated, thus possibly improving knowledges on high-risk SMM patients
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Paola Tacchetti
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Giada Giulia Riso
Simona Barbato
Federica Pedali

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Andrea Poletti
Vincenza Solli
Gaia Mazzocchetti