MultipleMyelomaHub

General MM

Genomics of smoldering multiple myeloma (SMM)

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This month, the Multiple Myeloma (MM) Hub are focusing on the educational topic of smoldering MM (SMM). SMM has attracted a lot of interest at recent congresses such as the Clinical Advances in Myeloma (CAM) meeting and the 5th World Congress on Controversies in Multiple Myeloma (COMy). This article will focus on the topic of genomics in SMM, including coverage of two key talks presented during these congresses. The first was presented by Doctor Charlotte Pawyln, Institute of Cancer Research, London, UK, at the CAM meeting in London, UK, on the topic of outcome prediction in MM.[1] The second was given by Professor Nikhil Munshi, Dana-Farber Cancer Institute, Boston, US, at COMy, on the topic of genomics of SMM.[2]

Development of MM from precursor conditions

MM develops from precursor conditions; monoclonal gammopathy of undetermined significance (MGUS) and subsequently, SMM. There are distinct genetic changes associated with the progression from MGUS to SMM to active MM; some of these are spontaneous and some are triggered by immune and/or other factors in the cellular microenvironment.[1,2]

Dr Pawlyn explained that there is often a genetic predisposition to developing myeloma, which is followed by myeloma-initiating events. Subsequently, secondary events occur which, combined with the initiating events, drive disease progression. Examples of secondary events include; translocations of genes such as Myc, copy number alterations (CNAs) such as 17p deletion (del[17p]), epigenetic aberrations including DNA methylation alterations, and somatic mutations, for example in the *KRAS* gene.[1]

MM can also develop into extramedullary myeloma (EM), which is defined as the presence of plasma cells outside the bone marrow and occurs in approximately 30% of MM patients over the course of the disease. Progression to EM can be affected by the aforementioned spontaneous evolutionary factors, as well as therapeutic effects which may induce clonal selection and promote mutations. The molecular mechanisms promoting this progression include hypoxia and an altered expression of adhesion molecules. EM is associated with adverse prognostic factors such as del(17p) and high lactate dehydrogenase levels.[3]

CNAs

During his presentation at COMy, Professor Munshi described two distinct subgroups of MM, based on an analysis of CNAs in 336 patients, submitted for publication by Samur *et al.*,[4]

1. Hyperdiploid MM (HMM): 54.5%

- Associated with trisomies 3, 5, 7, 9, 11, 15, 19, 21 and, at a lower frequency, 6 and 18
- Associated with a higher age (<60 *vs* >60): 46% *vs* 62%, p= 0.004

2. Non-hyperdiploid MM (NHMM): 45.5%

- Including 11q gain, 13q deletion (del), 1q gain and 9 gain

With a knowledge of CNAs of HMM and NHMM, Samur *et al.*, then questioned the order of occurrence of CNAs in HMM and NHMM that triggered the clonal expansion, causing the clone to become dominant. Further evaluation of genetic alterations led the authors to the hypothesis that widespread clonal changes (CNAs present in the majority of clones) occurred early in development, whilst specific subclonal changes (present only in specific subsets of clones) would be later events.[4]

- In HMM: trisomies 9, 15, 19 and 21
- In NHMM: 1q gain, 11q gain and del(13q)
    - Compared to HMM, less CNAs were found to be clonal

Samur *et al.* then attempted to determine if these CNAs were also present at the MGUS and SMM stages. Samples were compared from patients with MGUS or SMM, to MM. The CNAs of SMM were similar to MM, in both HMM and NHMM subgroups, however, the patterns between MGUS and SMM were different:[4]

- In HMM: gain of 9, 15 and 19 were very early events, followed by gain 21, gain 18, del(13) and gain 1q and gain 6
- In NHMM: translocations were early events, followed by gain 9, 11, del(13) and 1q gain

Progression from SMM to MM

Based on the findings that these CNAs occurred early, Professor Munshi questioned what could cause progression from SMM to active MM. To answer this, Professor Munshi used data from a 2018 paper published by Niccolò Bolli and colleagues in *Nature Communications*.[5] In this analysis, Bolli *et al.,* conducted whole exome sequencing (WES) on matched paired myeloma samples.

WES was conducted on samples from 11 patients with SMM. Ten of these subsequently had a paired tumor sample available for analysis following progression to MM; this occurred in all patients, with a median time to progression (TTP) of eight months.

On average there were 500 events per patient, including a high frequency and variety of rearrangements such as deletions (average 30 per sample) and gains (average 50 per sample), indicating that complex genomic changes happen even in early stage disease. Commonly occurring aberrations included gain 1q, del(13q), hyperdiploidy and immunoglobulin heavy (IGH) chain translocations, which were all clonal events maintained in MM.

In serial samples, it was possible to see the timing of these mutations, with distinct clones attributable to different stages. This led to the proposal of two different models:

- **Static progression model**: subclonal structure maintained over progression, with TTP reflecting the time to accumulate a substantial disease burden to display clinical symptoms
    - Since the genomic features of myeloma are present here, these patients should be treated as MM, and this highlights the need to redefine SMM genomically

    - TTP: <1 year
- **Spontaneous evolution model**: subclonal structure changed over time, without selection pressure from treatments. In this model, additional mutations occurred, with one subclone obtaining a proliferative advantage.
    - TTP: longer than in static progression model

The authors found:[5,6]

- Early mutations were driven by activation-induced cytidine deaminase (AID), responsible for more than 70% of all substitutions in hypermutable regions
- AID is known to induce genomic instability in the tumor microenvironment
- The activation of AID is mediated by dendritic cells
- Later mutations were driven by apolipoprotein B mRNA editing enzyme (APOBEC), a DNA deaminase responsible for 27% (range: 3–58) of substitutions
- APOBEC has a prognostic significance in myeloma

Conclusion

Professor Munshi stated this information could be used to inhibit, augment or change specific mutation signatures in order to make the disease more stable, and delay progression. This could be seen as an example of personalizing medicine and may offer future scope for druggable targets to impede the evolution of MM.

It was Professor Munshi's belief that we should redefine SMM from a clinically-defined disease, to a genomically-defined disease.

References

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