Genomic Evolution – germinal B cell to MGUS/SMM/MM

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When does MGUS start?
Examine mutation rates

Clock-like mutations correlate with age
Myeloma initiation at 20-30 years of age

Rustad et al. *Nat Commun* 2020
Kyle et al. *NEJM* 2007
IGH translocations are present

97% of patients have mutations

Mutations happen first, followed by CNAs

Common mutations can be present
KRAS, NRAS, DIS3, etc.

No biallelic deletions in TSGs.
CDKN2C, TP53, CYLD, BIRC2/3

No TP53 mutations or MYC abnormalities

Mikulasova et al. Haematologica 2017
NRAS and FAM46C mutations detected at significantly lower frequencies in SMM

Mutations in FAM46C completely absent in SMM
• Total of 103 (64/223 pts) biallelic events identified in MM, compared to 8 (8/82 pts) in SMM, $\chi^2=10.9$, $p=0.001$

• 1.2% SMM patients with Biallelic TP53, compared to 8.1% in MM

• 2% SMM with Biallelic DIS3, compared to 5% in MM

• Biallelic inactivation may be a hallmark mechanism in the transition to MM
Are there any genomic risk factors predicting progression to active disease?
Markers associated with a short time to progression to MM

<table>
<thead>
<tr>
<th>Mutations</th>
<th>CNAs</th>
<th>MYC</th>
<th>IMWG</th>
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<tbody>
<tr>
<td>Boyle et al.</td>
<td>KRAS</td>
<td>del6q</td>
<td>+</td>
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<tr>
<td>Bustoros et al.</td>
<td>KRAS/NRAS</td>
<td>Biallelic deletion</td>
<td>+</td>
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<tr>
<td>Misund et al.</td>
<td>DIS3</td>
<td>+</td>
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</tbody>
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N.B. 1q+, del(1p), del(13q), etc. not associated with TTP
Detected at t(MYC) in one patient, >70 months after SMM diagnosis

Used digital PCR to determine the evolution of the t(MYC), compared to the V(D)J rearrangement

t(MYC) was undetectable at SMM diagnosis and appeared in a subclone (1%) 3 years later, has increased steadily over time and reached 45% of the tumor cells 8.2 years from diagnosis

Increase in t(MYC) clone coincided with an increase in bone marrow plasma cells
Serial analysis of samples from patients progressing from SMM to MM

Clonal dominance over time shows changes in copy number

SMM patients are not static and require regular monitoring for high-risk genomic markers.