MGUS predispositions

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Monoclonal gammopathy of undetermined significance (MGUS) is associated with a 0.5-1% annual risk of developing multiple myeloma, Waldenström's macroglobulinemia, and other lymphoproliferative disorders. Prior investigations show that multiple myeloma (Landgren et al. Blood 2009) and AL amyloidosis (Weiss et al. J Clin Oncol 2014) are consistently preceded by a precursor state.

Comparisons of plasma cells in cohorts of multiple myeloma versus MGUS/smoldering myeloma show a higher proportion of cytogenetically abnormal plasma cells in multiple myeloma, suggesting the expansion of pre-existing and more proliferative clones during transition to multiple myeloma. However, nearly all of the cytogenetic changes described in myeloma cells have also been observed in MGUS/smoldering myeloma.

Lohr et al. (Cancer Cell 2014) recently showed that multiple myeloma patient at diagnosis have evidence of massive genetic heterogeneity, including frequent mutations in KRAS, NRAS, BRAF, FAM46C, TP53, and DIS3. Importantly, certain mutations have been found to be present in subclonal populations, and, perhaps unexpectedly, multiple mutations within the same pathway (e.g., KRAS, NRAS, and BRAF) have been found to exist in the same patient.

Zhao et al. (Leukemia 2014) recently studied somatic non-synonymous variants (SNVs) in a small series of paired samples (3 MGUS and 7 smoldering myeloma patients; four progressed to multiple myeloma). Overall 261 SNVs were seen in these 10 patients, with a mean of 26 (range 10–74) variants per patient; numbers were similar for progressors versus non-progressors. Among progressors, sequencing data showed no significant evolution from baseline to progression. Serial samples available from one of the non-progressors showed stable SNV profile. These observations indicate that nearly all of the SNVs found in plasma cells at the diagnosis of clinical multiple myeloma are present at MGUS/smoldering myeloma.

Treon et al. (NEJM 2012) used whole-genome sequencing to identify the highly recurrent somatic mutation, myeloid differentiation factor 88-(MYD88)-L265P in Waldenström's macroglobulinemia. Follow-up work has identified additional targets including CXCR4 and PI3K-delta. Based on small numbers, MYD-88 has been found in a high proportion of IgM MGUS cases with lymphoplasmacytic histology.

This presentation will discuss recent data on MGUS biology and transformation. Also it will discuss major gaps in our understanding of this topic.