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Genomic heterogeneity in multiple myeloma

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Multiple myeloma (MM) is an incurable malignancy in majority of patients characterized by clonal proliferation of plasma cells. To date, treatment is established based on general conditions and age of patients. However, MM is a heterogeneous disease, featured by various subtypes and different outcomes. Thus, the understanding of MM biology is currently a major challenge to eventually cure the disease. During the last decade, karyotype studies and gene expression profiling have identified robust prognostic markers as well as a widespread genomic landscape. More recently, studies of epigenetic, transcriptional modifications and next generation sequencing have allowed characterization of critical genes and pathways, clonal heterogeneity and mutational profiles involved in myelomagenesis. Altogether, these findings constitute important tools to develop new targeted and personalized therapies in MM.

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Introduction

Multiple myeloma (MM) is featured by a multi-step transformation from normal plasma cell to monoclonal gammopathy of undetermined significance (MGUS), Smoldering MM, symptomatic MM and extramedullary disease (including plasma cell leukemia).

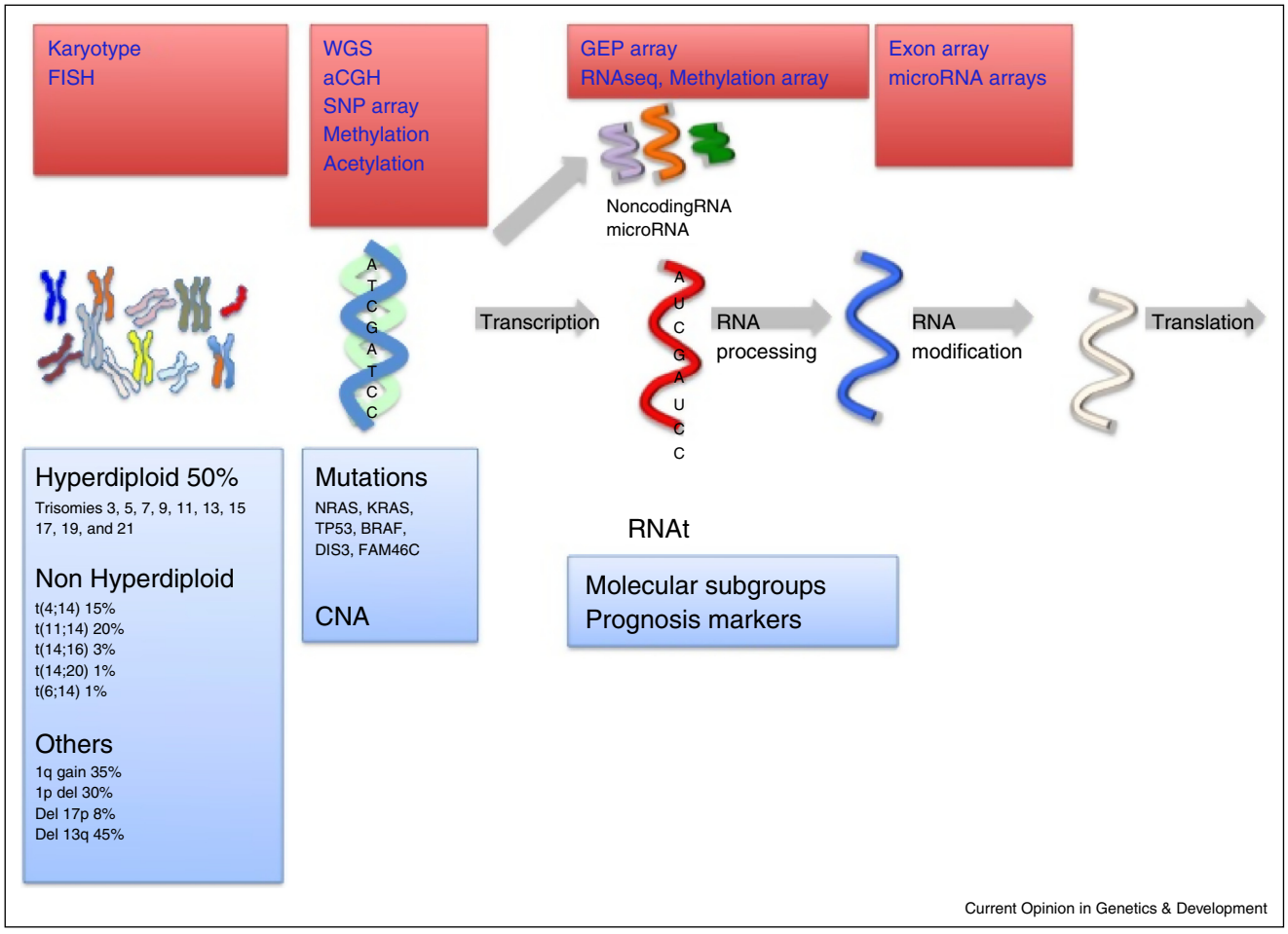
Based on karyotype studies, MM can be divided in 2 groups: Hyperdiploid MM (HDMM) harboring 48–75 chromosomes and non-hyperdiploid MM (NHDMM) usually featured with less than 48 or more than 75 chromosomes. NHDMM harbors rearrangements involving the immunoglobulin heavy chain (IGH) locus with different partners (CCND1, CCND3, cMAF, MAFB, MMSET and FGFR3) in 70% of cases. In HDMM, extra-copies of specific chromosomes (3, 5, 7, 9, 11, 15, 19 or 21) are present [1]. Mechanisms of chromosome abnormalities have not been clearly identified so far however, it may be due to uncontrolled recombination, specific translocation mechanisms such as jumping translocation [2,3] and abnormal somatic hypermutation. The latter mechanism is suggested by frequent involvement of both IGH and IG light chain locus [4]. Other recurrent chromosome abnormalities described are deletions (del(1p), del(6q), del(8p), del(12p), del(14q), del(13q) and del(17p) and gains (amp(5q) and amp(1q)) [5••]. Of note, the del(17p) leads to TP53 deletion. 1q gain, *t*(4;14) and del 17p are to date the cytogenetic markers of poor prognosis [6]. Gene expression profile (GEP) studies have allowed distinguishing different subgroups of patients with different clinical and biological patterns. It has also led of identification pathways and genes critically involved in MM biology [7,8•,9].

Recently, a new era has been opened thanks to new technologies such as next generation sequencing (NGS) and whole genome epigenetic profiling. Recurrent mutated genes, corresponding to oncogenes and tumor suppressor genes, and critical pathways involved in myelomagenesis have been identified. Furthermore, the clonal architecture of MM and its evolution over time in patients have been characterized. In this review, we present the current knowledge of genomic data in MM and discuss its therapeutically implications (Figure 1).

Gene expression profiles

Gene expression profiling has provided important information defining molecular subgroups and identifying genes and pathways carrying a significant impact on patient's survival in MM. Different methods have been used to characterize GEP: including array-based expression profiling that evaluate whole transcribed genome or RNA-sequencing based studies. All of these studies identified genes that are commonly overexpressed, e.g. cyclin D genes family [10] in malignant plasma cells as compare to normal plasma cells [11] or genes that are only overexpressed in certain subgroups as MMSET in the *t*(4;14) MM. Importantly, some differentially expressed genes that have been identified in malignant plasma cells are present since the earliest stage of the disease (MGUS). These genes includes oncogenes, tumor-suppressor genes, cell signaling genes (RAS family members, B-cell signaling and NF-kB genes), DNA binding and transcription-factor genes, and developmental genes. Importantly, NF-kB pathway is one of the most recurrently affected pathways in the different reported studies [12,13].

Figure 1



Spectrum of genomic studies in multiple myeloma.

GEP studies identified several prognostic factors that significantly influence patient outcome [14–16]. To date, three main studies reported 3 different clusters of genes associated with poor outcome in MM. The Arkansas group identified a 70 genes signature, IFM group a 15 genes signature and the HOVON group a 92 genes signature [8•,17,18]. Interestingly, in those studies there were very few overlapping genes, suggesting redundancy in genes and pathways that lead to cancer progression. GEP is strongly influenced by chromosomal lesions, such as IGH translocations and hyperdiploidy or chromosome duplications and it was recently shown that it does not allow predicting complete response to chemotherapy [19]. For these reasons, important efforts have been made to study alternative mechanisms involved in gene expression, principally, the transcriptome modifiers such as alternative splicing, microRNAs and epigenetic profiles. Our group is currently developing a novel approach to discover genes that show significant isoform switching using high throughput RNA-sequencing. A first study of 328 newly-diagnosed patients with multiple myeloma and 18 normal bone marrow donors has shown significant changes in relative isoform abundances between normal and malignant plasma cells in over 600 genes. Importantly, an alternative splicing profile seems to be associated with different molecular sub-groups and with survival, highlighting the need to better understand the mechanisms involved in post-translational regulation [20].

DNA-based studies

DNA-based methods such as array comparative genomic hybridization (aCGH) and high-density single nucleotide polymorphism (SNP) array have been utilized to assess copy number alterations (CNA) [5••,7,11–13,21–24]. In MM, the conventional cytogenetic studies are relevant only in a limited number of patients due to a lack of proliferative cells. SNP arrays that determine the CNA, represent an important option to molecularly characterize the MM cells. These studies have been crucial to identify