Multiple myeloma (MM) is a human cancer of malignant plasma cells. Recent genomic studies have started to catalog all the genetic alterations in selected panels of MM samples, and, within a short period of time, the large majority of MM-associated genetic and transcriptional alterations will have been identified. These recent insights, on one hand, indicate that MMs can harbor extensive clonal heterogeneity, and, on the other hand, they will help to reconstruct the molecular ontology of the disease’s evolution (i.e., the clonal architecture of each individual MM). However, a pending challenge is to delineate the stages of hematopoietic differentiation at which the individual genetic alterations arise, or, in other words, to elucidate the cellular architecture of MM.

In the classical view of the initiation and progression of MM, an initiating genetic alteration is required to immortalize a plasma cell (Fig. 1A). Such cell is then destined to acquire additional genetics hits over time. The acquisition of additional hits further deregulates the behavior of the plasma cells, thus leading to the clinically recognized features of MM, including the lytic bone lesions. In this classical model, MM is therefore a disease arising from mutations occurring in an already differentiated plasma cell. However, in the last years it has been shown that cellular heterogeneity is also a feature of human MM. Indeed, by studying the engraftment of primary MM specimens in immunodeficient mice, it was found that tumor plasma cells were unable of engraftment following intravenous injection, suggesting that the MM-propagating/maintaining cell was not a tumor plasma cell. Therefore, an essential gap that must be covered in order to define the cellular architecture of MM is the identification of the nature of the MM cell of origin. In fact, in spite of the assumptions of the above-mentioned classical view of MM origin, very little is still known about the cancer cell of origin from which MM arises and about how the initial genetic lesion(s) regulate this essential step. These initial genetic lesions have always been detected in differentiated tumoral plasma cells, although the presence of a human myeloma stem cell was postulated many years ago. It is true that the patient’s hematopoietic progenitor and stem cells (HS/PCs) seem not to show any of the initiating genetic alterations detected in tumor plasma cells; however, it is also true that these alterations would be very difficult to detect if the frequency of these putative stem cells harboring the MM-inducing genetic lesion was low. Therefore, due to this purely statistical reason, experimental results would seem to suggest that the MM cell of origin is not a stem/progenitor cell. However, until now, all the experiments in which the expression of human MM-linked oncogenes is targeted to the mouse differentiated B cell compartment have failed to reproduce the human disease in mice. Therefore, it is potentially possible that in human patients, the occurrence of MM-associated oncogenic alterations might happen in the HS/PCs compartment, and this cell of origin adopts/acquires afterwards a MM cell fate as a consequence of the oncogene activity.

To elucidate if MM is a stem cell-driven disease, we initially focused on the effects of the MafB oncogene, since the MAF family of proteins seems to be implicated in 50% of human MM. In consequence, we have developed mice in which we limited the expression to the mouse HS/PCs Sca1+ cells. In human MM and in most animal models of cancer, the oncogenic alterations are expressed in all the cellular types that compose the tumoral tissue, from the MM stem cell to the terminal differentiated plasma cells. In our stem cell-driven Sca1-MafB model, the expression of MafB is restricted to the HS/PCs compartment, but this restricted expression pattern is nevertheless capable of generating a full-blown MM with all its differentiated cellular components, in such a way that Sca1-MafB mice share both major and minor diagnostic criteria with the human pathology. The demonstration that MM development can be established in mice by expressing MafB only in Sca1+ cells implies that MafB can impose a gene regulatory state in these stem cells that somehow persists during hematopoiesis, and that can program a tumor plasma cell phenotype symptomatic of MM. This is an observation that seems to apply to other cancer-initiating gene defects. In the oncogenic reprogramming model here presented, the reprogrammed Sca1+ population can nevertheless complete a multistage differentiation pathway involving an initial commitment to the B cell lineage and a subsequent differentiation to tumor plasma cells. This model of MM is very informative with respect to the fact that the oncogenic mutations can have different roles in MM stem cells vs. differentiated tumor plasma cells. Thus, genetically distinct MM stem cell subclones may exist on top of each MM tumor mass, revealing an even higher complex cellular architecture.
composition of MM than initially thought (Fig. 1B).

In order to gain even more insight into the mechanism by which MafB can induce the reprogramming of stem cells into tumor plasma cells, we have also generated in vivo genome-scale maps of DNA methylation from both stem cells and mature B cells from Sca1-MafB mice. We found that a substantial number of CpG islands and promoters are specifically hypermethylated or hypomethylated in the stem cells of Sca1-MafB mice, setting a pattern inherited throughout B cell development. Thus, the results presented in our study demonstrate a novel molecular mechanism involved in tumor initiation, by showing that HS/PCs can be epigenetically reprogrammed to give rise to terminally differentiated tumor plasma cells by MafB. To our knowledge, these results represent the most convincing evidence to date that MM development can arise and be driven by a tumor cell fate change within the stem cells. These findings represent a novel paradigm in MM biology and will revolutionize the current modeling of MM tumorigenesis and progression and are likely to have profound therapeutic implications (Fig. 1C).
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