HEMATOLOGY IN FOCUS

14q32 chromosomal translocations: a hallmark of plasma cell dyscrasias?

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Introduction

Multiple myeloma (MM) is a plasma-cell (PC) malignancy, characterized by the accumulation of PCs within the bone marrow.1 Since PCs are terminally differentiated B cells, 14q32 translocations could be expected in MM as observed in many B-cell malignancies. Analysis of large cytogenetic studies reveals a 14q32 abnormality in 20 to 30% of patients with clonal abnormalities.2,3 Approximately half of these abnormalities are described as an ‘add(14q32)’, reflecting that an abnormality recognized at 14q32 cannot be fully identified. Another one third of patients presents a typical t(11;14)(q13;q32). The other 14q32 abnormalities are translocations with various partners, the most frequent being 8q24. However an increased interest in 14q32 rearrangements has occurred recently, given the fact that many patients with MM4,5 and most, if not all, human myeloma cell lines (HMCL) display illegitimate rearrangements of the immunoglobulin heavy chain (IGH) gene,6 as demonstrated by either fluorescence in situ hybridization (FISH) or Southern blot analyses.

Illegitimate IGH gene rearrangements

Human myeloma cell lines

Bergsagel et al.6 have developed a Southern blot assay for the evaluation of IGH gene rearrangements in which they select genomic probes flanking each switch region that is successively hybridized on HMCL DNA. This assay allows the identification of both legitimate (productive) and illegitimate (translocation) IGH rearrangements. Illegitimate recombinations occur in approximately 70% of HMCL (n = 21), some of which display two or three different illegitimate IGH recombinations. Moreover, five of the six HMCL lacking an illegitimate switch displayed 14q32 rearrangements, as determined by cytogenetics, that possibly involve other IGH sequences. Using fiber-FISH,7 these results have been recently confirmed in 100% (n = 17) of the HMCL,8 although switch regions were involved in ‘only’ 12 out of 17 HMCL. These studies show that virtually every HMCL displays a 14q32 abnormality, a situation comparable to that of other B-cell malignancies.

Patients with MM and primary plasma cell leukemia

Data on molecular IGH rearrangements in MM patients are difficult to obtain because of the large quantities of clonal PCs required for Southern blotting. A single study has analysed patients (n = 88) with either MM or primary plasma cell leukemia (PCL),9 reporting an illegitimate IGH rearrangement in only 21 patients. This low percentage (25%) can be explained by the use of unpurified PCs, with some samples containing as few as 20% PCs, digested with only one restriction enzyme. It is likely that some large restriction fragments were missed and that this percentage is an underestimate of the real incidence of illegitimate IGH recombinations.

It may be possible to circumvent the selection bias introduced by the analysis of patients with a high PC number by using interphase FISH, which allows the analysis of given genetic regions without the need for metaphases from the tumor clone. This strategy has been used to address the question of the incidence of illegitimate IGH rearrangements in MM and primary
PCL.\cite{4,5} By selecting probes that map on each side of the IGH constant domain, Nishida et al.\cite{4} identified 14q32 translocations in 74% of patients (n=42). This approach has also been applied to patients with newly diagnosed MM (n=143), primary PCL (n=15) or MM at relapse (n=28),\cite{10} with illegitimate IGH rearrangements occurring in 57, 73 and 39% of patients, respectively.

Patients with monoclonal gammopathy of undetermined significance

It is likely that illegitimate IGH rearrangements occur early in the evolution of monoclonal gammopathy of undetermined significance (MGUS) because the incidence of 14q32 abnormalities is identical in stages I, II and III.\cite{10} However, the question remains: are these recombinations observed in non-malignant monoclonal PCs found in individuals with MGUS, or are they present only in malignant PCs? FISH analysis of a series of 100 individuals with either indolent MM or MGUS\cite{11} revealed illegitimate IGH rearrangements in 46% of the cases. The abnormalities representing early genetic events are not likely to be sufficient for tumorigenesis, but may be involved in the first steps of PC deregulation.

Partner chromosomes and partner genes

Incidence of recurrent translocations

Translocations involving 14q32 differ in MM from those observed in other B-cell malignancies because of the variability seen in partner chromosomal regions. In most B-cell lymphomas, an almost perfect correlation is found between histological types and deregulated genes. In MM, more than 20 different partner chromosomal regions have been reported, most of them being described only once. However, some of them are recurrent [11q13, 4p16, 16q23, 8q24, 9p13\cite{12,13} and 20q12\cite{14} and may be more relevant for the pathogenesis of MM. Thus far, six partner genes have been cloned: (1) CCND1 at 11q13;\cite{15} (2) FGFR3 at 4p16;\cite{16,17} (3) MYC at 8q24; (4) MAF at 16q23;\cite{18} (5) IRF4 at 6p25;\cite{19} and (6) MUM2-MUM3 at 1q21,\cite{20} four of which are recurrently involved in 14q32 translocations in MM and HMCL (CCND1, FGFR3, MAF, MYC). The incidence of these four 14q32 translocations is clearly different in MM patients and in HMCL. Covering more than 90% of HMCL, these four translocations cover less than 30% of patients with newly diagnosed MM, and about half of patients with an illegitimate IGH rearrangement.\cite{10}

Translocation t(11;14) is the most recurrent and is observed with a similar incidence (16%) in overt MM and MGUS.\cite{10,11} This observation does not support the fact that this translocation is considered to be a poor prognostic indicator. In contrast, t(4;14) is observed in 12% of patients with overt MM, and in only 2% of MGUS. It is likely that this translocation can precipitate clonal PCs into malignant PCs. The other recurrent translocations, ie, t(8;14) and t(14;16), have been observed in sporadic cases only. Thus, the 11q13 and 4p16 chromosomal regions are the most frequent IGH partners in MM, but represent less than half of the partner chromosomal regions in these patients. Research dedicated to the discovery of unknown partners will be an important challenge for the future.

Conclusion

Studies focused on characterization of 14q32 abnormalities clearly highlight the high frequency of these chromosomal changes in PC dyscrasias. The most recent data indicate that these illegitimate IGH rearrangements play a major role in the oncogenesis and/or progression of PC malignancies. Data clearly demonstrate that 14q32 abnormalities are early events that are observed in individuals with MGUS. In addition, another conclusion is that 14q32 translocations, themselves, are not sufficient for malignant transformation. Another chromosomal abnormality, ie monosomy 13, is likely to make a major contribution in the transition from MGUS to MM.\cite{10} However, 14q32 translocations may play a role in the PC differentiation/survival regulation. Such a model suggests that the primitive important event would be IGH gene deregulation; a theory supported by the presence of multiple partners. It is none the less difficult to explain how the deregulation of so many genes could lead to a relatively homogenous disease. The theory identifying deregulation of the IGH gene (regardless of the partner) as the most important primary event has the advantage of proposing a unique mechanism for PC deregulation. Translocations may interfere with immunoglobulin production (by down-regulating the gene expression through a currently unknown mechanism), affecting a lower production of monoclonal immunoglobulins by malignant PCs, which is a major characteristic of MM. Another, less likely, hypothesis would be to attribute different clinical evolutive properties to each 14q32 translocation. It remains to address these questions with systematic prospective analyses of large series of patients.

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References

15. Chesi M, Bergsagel PL, Brents LA, Smith CM, Gerhard DS, Kuehl WM. Dysregulation of cyclin D1 by translocation into an IgH gamma switch region in two multiple myeloma cell lines. *Blood* **88**: 674, 1996.