To the Editor:

Multiple myeloma (MM) is characterized by the expansion of malignant plasma cells (PCs) within the bone marrow. Although such malignant PCs can be easily identified by their high expression of CD38 and B-B4, their purification and in vitro expansion remain difficult. Therefore, established human myeloma cell lines (HMCL) are still essential to study the biology of MM. Eighteen years ago, it was elegantly documented by Nilsson that the establishment of continuous cell lines from the bone marrow or the peripheral blood of MM patients actually leads to the obtention of two completely different types of cell lines, most frequently lymphoblastoid cell lines (LCL), which result from the immortalization of nonmalignant B cells by Epstein-Barr virus (EBV), and true HMCL, which represent the immortalization of tumor cells sharing the same Ig gene rearrangement as fresh tumor cells. We and others have recently reevaluated this critical point thoroughly and confirmed it. Of note, some EBV+ LCL established from the bone marrow of MM patients can produce Igs sharing the same isotype, public idiotype, and epitopic specificity (ie, anti-DNA) as the myeloma protein, although using completely different VL, VH, and CDR sequences, showing their complete irrelevance to the myeloma clone.

A lot of studies devoted to the biology of MM based on the use of several putative HMCL have recently been published. These interesting studies pointed towards major topics related to the MM biology. Clearly, the two types of cell lines, ie, LCL and HMCL, have been used indiscriminately in these studies, making some of the conclusions irrelevant to the biology of MM. Therefore, it appears very important to clearly establish the criteria for differentiating them. Based on recent phenotypic data, the European Myeloma Research Network examined eight discriminant surface markers making it possible to determine the myeloma nature (or not) of the cell lines commercially available and routinely used in the majority of studies. Some XG HMCL recently established by ourselves have been included. As expected, the phenotypic analysis outlined in Table 1 shows clearly that two types of cell lines can be distinguished: (1) on the one hand, LCL, which are positive for CD19 and CD20, surface Ig, and the adhesion molecules CD11a and CD49e, but negative for B-B4, CD38 and CD28; and (2) on the other hand, the other cell lines negative for CD19, CD20, CD11a, and CD49e but positive for the antigens characterizing the HMCL, ie, B-B4, CD38 and CD28. Attention has to be focused on the fact that one of these differentiation antigens is not sufficient to establish the nature of the cell line but that all these markers taken together allow an accurate conclusion. The clear-cut phenotypic dichotomy is also supported by the EBV status and the karyotype of these two types of cell lines, which have been previously published. Indeed, the LCL have all been described as EBV+ and the karyotype of these two types of cell lines, which have been previously published. Moreover, it should be noticed that no
direct proof has ever been published that the LCL harbor the same karyotypic abnormalities and/or Ig gene rearrangements as primary tumor cells in the patients from whom they were derived.

Considering that the LCL ARH-77, IM9, HS-Sultan, and MC-CAR listed at the ATCC as HMCL have been used frequently in recent reports to study the biology of MM (in place of HMCL), we would like to address some concerns about the conclusions related to the studies regarding (1) the expression of adhesion molecules by myeloma cells and the interaction of myeloma cells with stromal cells through these adhesion molecules; (2) the mechanisms of bone disease in MM; (3) the role of the CD40 molecule in MM; and (4) the role of soluble CD16 in MM as relevant to the biology of MM.

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REFERENCES


Human myeloma cell lines as a tool for studying the biology of multiple myeloma: a reappraisal 18 years after [letter]

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