To the editor:

Globin phenotype of erythroid cells derived from human induced pluripotent stem cells

The groundbreaking innovation of reprogramming adult cells to pluripotency has opened new avenues for patient-tailored treatments. The successful treatment of a humanized sickle cell anemia mouse model with induced pluripotent stem cells (iPSCs) from autologous skin illustrates this principle. Human iPSCs can be directed to undergo hematopoietic differentiation in a fashion similar to human embryonic stem cells (hESCs). However, the globin expression profile of iPSC-derived erythroid cells has not been fully explored and only partial results were mentioned in one study. An important question is whether the age of the cells used to derive iPSCs influences developmentally regulated globin expression.

We studied globin expression in erythroid cells derived from 6 different human iPSC lines generated in our laboratory with lentiviral vectors expressing OCT4, NANOG, LIN28, and SOX2 as described. Three lines (iPSC-MHF2) were derived from human fetal fibroblasts isolated at 20 weeks’ gestation (GM05387, Coriell Institute for Medical Research), and the other 3 (iPSC-OI12) were derived from human mesenchymal stem cells (MSCs) isolated from the spine of a 15-year-old patient. Two lines, iPSC-MHF2 C2 and iPSC-OI12 C7, were verified to have normal male karyotype (46X,Y). The ability of each iPSC clone used in this study to give rise to progenies of all 3 germ layers was established by teratoma assays in immunodeficient mice and staining of histologic sections for human microtubule associated protein–2 (MAP-2; ectoderm), human α–smooth muscle actin (SMA; mesoderm), or human α-fetoprotein (AFP; endoderm), as described (supplemental Figure 1). The iPSC lines were induced to undergo hematopoietic differentiation as previously described for human ESCs.

As was previously reported in hESC and iPSC lines, these 6 iPSC lines exhibited a wide range of hematopoietic differentiation potential, as demonstrated by the percentage expression of hematopoietic markers such as CD45 and glycophorin-A (Figure 1A) and by the formation of hematopoietic colonies (Figure 1B). In 2 of the lines with robust erythroid development (Figure 1C), we studied the globin expression pattern at the mRNA (Figure 1D) and protein levels (Figure 1E). We found that despite the original adult status of the cells from which they were derived, these iPSC-derived erythroid cells expressed mostly embryonic (ε) and fetal (γ) globins, similar to ESC-derived erythroid cells, consistent with complete reprogramming at the globin locus. This globin phenotype, if maintained in vivo, has an important implication for the treatment of hemoglobinopathies using patient-specific iPSC-derived hematopoietic cells in that correcting the defective β-globin gene may not be necessary. Furthermore, our data highlight the fact that iPSCs are highly heterogeneous in their hematopoietic potential as previously reported by Choi and colleagues. While this variation could reflect differential silencing and/or expression of reprogramming factors, it is similar to that observed in human ESC-derived cells, and demonstrates that large numbers of individual iPSC lines need to be screened before drawing conclusions related to the effects of cell origin on differentiation potential.

Further studies are needed to dissect these issues in iPSC-derived hematopoietic cells before their anticipated use in humans.

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The online version of this letter contains a data supplement.

References

To the editor:

Does IL-17 suppress tumor growth?

Numerous immune regulatory functions have been reported for the IL-17 family of cytokines, and, most notably, IL-17 is involved in inducing and mediating proinflammatory responses. In this context, the role of IL-17 in cancer initiation, growth, and metastasis is very controversial.1 This year, a brief report in Blood concluded that host IL-17 reduces tumor growth and metastasis.2 The authors’ conclusions relied entirely on one C57BL/6 mouse–derived adenocarcinoma cell line, MC38, in which they showed a 5-fold or greater enhancement in subcutaneous growth and metastases in IL-17–deficient mice compared with control wild-type mice. Their conclusions also contrasted sharply with 3 important previous papers that suggested that IL-17 promoted tumor growth.3-5 In particular, having worked extensively with the MC38 experimental tumor, we were surprised at the significant enhancement of MC38 tumor growth in IL-17–deficient mice compared with their wild-type controls.

We have now undertaken many studies of tumor initiation, growth, and metastasis in the same IL-17–deficient mice used by Kryczek (provided by Dr Yoichiro Iwakura) compared with wild-type controls. In particular, we would now like to share our results from an analysis of 3 different sources of MC38 tumor cells.
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