hemoglobin concentration was measured. As expected, mortality rates were significantly higher in black and white participants missing hemoglobin data compared to those with hemoglobin information. Because the proportion missing from the black enrollees is almost twice that of the whites (20.5% vs 11.8%), it is possible that this could have led to an underestimation of the effects of anemia in blacks. Other important prospective studies on anemia in older adults had missing data as well, including the study referenced by Drs Artz and Dong where more than 50% of the original cohort were missing hemoglobin information. Differences in overall disease burden may account for differences in our study findings and those reported by Denny and colleagues.

Finally, we believe that epidemiologic studies can make valuable contributions in understanding the implications of abnormal health conditions. Epidemiologic studies have been key to defining risk thresholds for several conditions, including diabetes, hypercholesterolemia, and hypertension. The WHO criteria for anemia, established in 1968, were based on hemoglobin distributions from relatively small studies that did not account for race or health status. Over the past few decades, several population-based studies have demonstrated significantly lower hemoglobin concentration in blacks compared with whites, and there has been discussion of race-specific criteria for defining anemia. Our outcomes-based results are provocative and support reconsideration of anemia cutpoints. However, given our study limitations, we agree that a definitive statement based on our data may have been premature. More outcomes-based research in representative samples of older blacks and in blacks with comorbid conditions, such as diabetes or renal disease, is required before establishing alternative hemoglobin cutoffs. This is particularly needed in the wake of recent findings of potential harm associated with using erythropoiesis-stimulating agents to achieve higher hemoglobin concentration in certain patient populations.

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References


To the editor:

Life is plastic

Paolo Bianco’s comment, “Life in plastic is fantastic,” criticizes our paper “Multipotent cells can be generated in vitro from several adult human organs (heart, liver, and bone marrow)” from many standpoints. Our article describes a method to generate in vitro, from many human tissues, a population of cells characterized by clonogenicity and multipotency. Moreover, differentiating these cells into multiple definitive cell types is possible only if this assay is mandatory to define a cell as a stem cell, the only entities that would satisfy this criterion, apart from embryonal carcinoma cells, embryonic stem cells (ES), and embryonic germ cells, are hematopoietic stem cells, spermatogonial stem cells, and tumor initiating cells. This raises the semantic question on how to define cells showing either the in vitro properties of hMASCs or cells for which, in addition, it has been shown a robust in vivo engraftment (eg, mesenchymal stem cells [MSCs], cardiac stem cells, etc). (2) Considering multipotency, first it is imperative to specify that we demonstrated it at both polyclonal and clonal levels, excluding its contingency on clonal growth. Moreover, differentiation was not only demonstrated by “the expression of divergent differentiation markers,” but documenting the acquisition of specific functional activities (ie, among the others, spontaneous contractile activity for myocytes, voltage dependent ionic currents for neural cells, albumin release for hepatic cells). Bearing in mind this elucidation, we would like to underline that our paper does not deal with the existence, in postnatal tissues, of cells with transgenic potential, as stated by Dr Bianco, but with the possibility to generate, in culture, from human adult tissues, cells characterized by a robustly proven ability to differentiate into multiple functionally competent cell types.

(3) To dismiss the importance of generating cells predifferentiated in vitro for regenerative purposes would be in contrast with many works that use ES-derived mature cells to treat diseases ranging from Parkinson to myocardial infarction or that use cells in engineered tissues. Moreover, we agree that, from a theoretical point of view, “a cell pushed to express hepatocyte features might not survive if transplanted in vivo,” but recent data on MSCs used for liver regeneration point in the opposite direction.
(4) Finally, we agree with the statement that the immediate translation of hMASC use from the in vitro assays to clinical settings is, at present, less than prudent. Confidence on their safety and usefulness will require extensive in vivo animal studies, such as those that are ongoing in our laboratory. Therefore, before expressing a priori preconceptions, it will be better to wait for in vivo data.

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To the editor:

Association between persistent lymphatic infection by hepatitis C virus after antiviral treatment and mixed cryoglobulinemia

Hepatitis C virus (HCV) is closely related to the development of mixed cryoglobulinemia (MC). Occult HCV infection in sustained virologic responders (SVRs) after antiviral treatment has been shown,1,2 but MC patients have never been investigated.

We studied 102 HCV patients (64 males, mean age 50.8 ± 12.1 years), who were SVRs after interferon-based anti-HCV therapy, consecutively recruited at our Center from July 2003 to July 2004 and followed-up until July 2007. Patients included 13 subjects with MC syndrome (group A, Table 1) and 89 patients without MC (58 males, mean age 50.2 ± 12.5 years; group B). Blood samples were collected at least twice a year.

Positive-strand and negative-strand (replicative intermediate) HCV RNA was detected by highly sensitive, previously described methods: transcription mediated amplification (TMA; Bayer Healthcare, Tarrytown, NY); reverse transcriptase–polymerase chain reaction [RT-PCR]-nucleic acid-hybridization assay, Real-time PCR, 5'-UTR-HCV RNA negative-strand PCR with Tth polymerase, with appropriate controls.2,3 Peripheral blood mononuclear cells (PBMC) were cultured with mitogens as previously described.2,4 T(14;18) was determined in PBMC by MBR bcl-2/J H PCR as described.5

In all patients, serum samples were persistently HCV RNA-negative. HCV RNA was repeatedly detected in stimulated cells (mainly lymphocytes) from 12 patients (8 group A, Table 1, and 4 group B; P < .001), whereas posttreatment liver biopsies scored HCV RNA-negative. Negative-strand HCV RNA was shown in PBMC from MC cases.

PBMC infection was shown in 5 patients with persistent MC syndrome and in no subject in whom MC syndrome completely disappeared. Persistence of t(14;18)-positive B-cell clones was associated with persistence of MC syndrome (P = .021; Table 1).

We, and others, previously detected positive- and negative-strand HCV RNA in PBMC, and observed the increased detection of viral sequences after mitogen stimulation.6,7 HCV lymphotropism is generally interpreted as a key factor in HCV-related lymphoproliferative disorders, but this hypothesis was never confirmed, probably due to the difficulty in enucleating the role played by lymphatic infection in patients also with liver infection and circulating HCV. In this study, persistence of HCV infection was observed in PBMC (mainly lymphocytes) in the absence of serum or liver HCV-positivity and was significantly associated with MC syndrome. This isolated PBMC infection may be explained by previous data showing that HCV compartmentalization may occur, in which HCV is confined to a given “compartment” not able to “infect” other compartments.8 Of note, serum samples were thoroughly mixed and warmed to resolubilize cryoglobulins before HCV RNA testing.9 Further studies are needed to clarify the mechanisms possibly linking HCV lymphatic infection with MC. The association between persistence of t(14;18) and lymphatic infection and, in turn, between persistence of t(14;18) and MC syndrome add value to the hypothesis of a pathogenetic role also played by t(14;18).

From a clinical point of view, this study emphasizes the relevance of a complete eradication of HCV for the resolution of MC syndrome, even if the presence of (one or more) “point of no return” in the natural history of such lymphoproliferative disorder, with progressive independence from the etiologic agent, cannot be excluded. Actually, cases of persistent syndrome in spite of viral eradication have been described,10 including some personal observations. If this interpretation is correct, the current indication for an early etiologic treatment of HCV-positive MC11 will be clearly reinforced.

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References

Life is plastic

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