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Response

Chemotherapy versus allogeneic transplantation in adult patients with acute lymphoblastic leukemia in first remission: not a time for dogma

Isakoff and colleagues highlight in their letter that young adults with acute lymphoblastic leukemia (ALL) treated with a pediatric-inspired regimen do not need a bone marrow transplant in first remission. Their assumption is based on comparisons of published outcomes of young patients with ALL treated with adult and pediatric-inspired regimens mainly in the age group of 15 to 20 years. Although the outcomes of pediatric-inspired regimens in young adults 15 to 20 years old with ALL are encouraging, several factors should be taken into consideration before any valid conclusions can be drawn.

In our report, a young adult is defined as <35 years old.¹ It is highly speculative that the findings of patients treated in the age group of 15 to 20 years can be generalized to those >20 years old.

The best chemotherapy regimen for young adults with ALL is unknown. A pediatric-inspired regimen may be better than a standard adult regimen, but comparison of these regimens has never been prospectively studied. One has to question the real causes of differences in outcomes with these regimens. There are minimal data on the comparison of drug dosages delivered in pediatric- vs adult-type regimens.² Is it truly the impact of intensity of a pediatric-inspired regimen or a pediatric culture of maintaining a prescribed dosage and schedule strictly with minimal interruptions?³ In addition to these physician practice patterns, the issue is further confounded by referral patterns and patient compliance.

In summary, we present an individual patient data meta-analysis according to a well-defined study protocol (available at: <http://www.ctsu.ox.ac.uk/research/meta-trials/leukaemia-metaanalyses/protocol-2009>). Of course, we agree that if the outcomes of chemotherapy improve (in the absence of a concomitant improvement in the transplant), this could abrogate the need for a transplant, but we wish to emphasize that this needs to be demonstrated in prospective randomized studies, which, to our knowledge, have not yet been done. The key to the future would seem to be continued study of modern chemotherapy protocols vs allogeneic transplantation as part of well-designed prospective studies.

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To the editor:

Coordinate expression of transcripts and proteins in platelets

Published reports have demonstrated coordinate expression between messenger RNA and proteins in platelets.¹⁻³ It was therefore surprising that, comparing our RNA-seq data set⁴ to their quantitative proteomics

data set, Burkhardt et al⁵ concluded that "in platelets, the occurrence of proteins is not interrelated to the presence of transcripts." The accompanying highlight article reiterated that "the protein profile

does not correlate at all with earlier published transcriptome analyses.”⁶ Are these statements valid and to what extent? Can transcript profiling be used to predict protein expression and differences in platelets? Because transcript profiling forms the basis of many published and ongoing platelet studies, the answers to these questions are critical.

Two lines of evidence led to their conclusion. First, no correlation in expression was found between the top 20% of proteins and transcripts. Second, transcript expression for a limited number of receptor complexes did not match the expected stoichiometry. To further evaluate these, we remapped the proteomics data set onto our published RNA-seq data set (supplemental Table 1, see the *Blood* Web site). Of the 3992 detectable proteins with an ID match, 96% are detected within the RNA-seq data set and 87% expressed at >0.3 reads per kilobase of exon model per million mapped reads (RPKM; 0.3 RPKM is an expression threshold well above background). Thus, the presence of protein is highly predictive of the presence of transcript. Conversely, 30% of the detected transcripts correspond to a detectable protein. Furthermore, as the transcript abundance threshold increases, so does the likelihood that the protein is present (Figure 1A). For example, of transcripts expressed above 300 RPKM, 84% correspond to a detectable protein. This overlap is remarkable considering “undetectable” (by the assay) is not equivalent to “unexpressed.”

Figure 1B demonstrates a clear correlation in protein vs RNA expression when both the protein and transcript are detectable. This coincides with a Spearman correlation of 0.40 between protein (>500 count) and RNA expression (>0.3 RPKM). Bearing in mind that the RNA/protein measurements were generated from different individuals, that RNA/protein methodologies are different, and that the platelet proteome contains many plasma derived proteins,⁵ we conclude that transcript expression correlates well with protein expression in platelets.

Our correlation analysis considered all values quantitatively assessed above background. In contrast, Burkhart et al analyzed a

smaller subset of the data. In addition, their ID mapping strategy may have introduced occasional, yet significant, discrepancies. For example, as evidence for the nonstoichiometric expression of GPIb/IX/V in our RNA-seq data set, they reason that “GPIb α is missing in the transcriptome data.” However, as found within our published supplementary data set, GPIb α is abundant (198 RPKM). To avoid “missing” information (ie, because of different naming conventions; even UniProt’s ID mapper⁷ “missed” mapping GPIb α between the data sets), we recommend visualization of our RNA-seq data by genomic location. This can now be done directly in GNomEx⁸ (<https://bioserver.hci.utah.edu/gnomex/>), which includes links to the University of California Santa Cruz genome browser⁹ (Figure 1C, see figure legend for access instructions).

Proteomics technologies boast the opportunity to quantitatively assess thousands of proteins at once. RNA-seq provides sensitive expression and sequence-level information. Together, these complementary technologies provide unprecedented capabilities to assess the imperfect yet correlated relationship between RNA, protein, platelet function, and ultimately disease.

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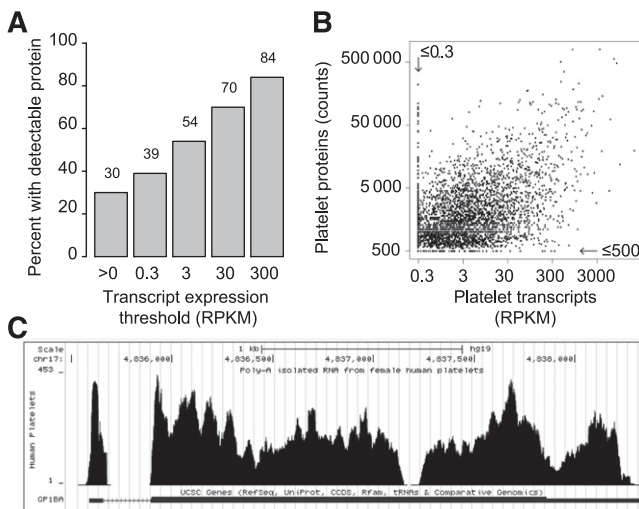


Figure 1. Transcript and protein expression in platelets is correlated. (A) The percentage of transcripts where the coordinate protein is detected is plotted for each threshold of transcript expression. (B) Scatter plot comparing log-adjusted transcript expression (x-axis) with log-adjusted protein expression (y-axis) for all proteins with an ID match to a transcript. For visual simplicity, transcripts or proteins below the arbitrary background threshold (0.3 RPKM or 500 count, respectively) were adjusted to the threshold. Values were left unadjusted for the correlation analysis described in the text. (C) Visualization of our RNA-seq data for GPIIb/IIIa in the UCSC genome browser (<http://genome.ucsc.edu>) via direct links in GNomEx (<https://bioserver.hci.utah.edu/gnomex/>). To view the data, sign in as a guest, type “platelet” in the search box, double click on the track of interest, and then click the University of California Santa Cruz browser link next to the data track title.

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