Reviewer's report

**Title:** Transforming growth factor beta receptor 1 is a new candidate prognostic biomarker after acute myocardial infarction

**Version:** 1  **Date:** 7 October 2011

**Reviewer:** Timothy McCaffrey

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Overall: This is an interesting and potentially important transcriptomic analysis of patients that presented with MI and then went on to maintain, or to lose LV function. The potential predictive value of TGFBR1 in whole blood is potentially important to prognosis, as well as to understanding the LV remodeling process.

Major compulsory revisions:

1) The method of blood collection and profiling needs to be more clearly specified. Was the blood collected before or after mechanical reperfusion? Via arterial line? It was collected into Paxgene tubes?

2) Likewise, the array analysis needs details. What kind of array? How was the RNA purified and labeled/amplified? The 1.3 fold change had no statistical confidence, ie t-test?

3) Demographic features were similar between groups, except infarct size. So was TGFBR1 predicting or somehow responsive to infarct size?

4) There needs to be some words of caution around the angiogenesis ‘filtering’ of the data. On the one hand, pathway-based analysis can somewhat minimize the multiple testing problem, but, on the other hand, it takes a method such as microarrays, which derive much of their strength from their broad, hypothesis/bias-free quantitation, and then immediately re-imposes an overt bias for a particular theory: angiogenesis. While angiogenesis is certainly important to the development of collateral circulation, there are many other legitimate pathways that would affect LV remodeling: fibrosis, inflammation, and thrombosis, to name just a few.

5) The angiogenesis theory is also relatively thin even on experimental grounds. If we argue that the arrays on blood are picking up TGFBR1 levels in endothelial progenitor cells (EPC) circulating in blood, their frequency in blood is vanishingly small and unlikely to produce a usable signal. It is more plausible, a priori, that TGFBR1 levels in leucocytes is related to inflammatory activity, or in monocyte-derived macrophages it might predict wound repair functions. These alternate theories deserve mention.

6) While whole blood profile has certain clear advantages, such as avoiding ex vivo artifacts, it leaves open the possible confound of changing populations of cells within blood. Are there CBCs to determine whether there are shifts in cell populations in the 2 groups?
7) Given that the authors speculate as to the potential therapeutic potential, it would be reasonable to inform the reader about potential modes by which the TGFBR1 could be clinically modulated: existing small molecule inhibitors, siRNA, or neutralizing antibodies/ligands for TGF-B.

Minor compulsory revisions:

8) The third person narrative would be preferred: “Patients with MI were enrolled…” as opposed to “We enrolled patients with MI…”

9) This sentence is confusing. Is it meant to say that these germline diseases suggest that blocking the receptor systemically would have adverse outcomes, or that you would not be able to use this as a diagnostic in people with germline defects? “In addition, mutations in TGFBR1 gene, known to affect vascular integrity in Marfan and Loeys-Dietz syndromes [34, 35], may limit the use of TGGR1 as either a marker or a therapeutic target after acute MI.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests. I do have financial interests in genomics companies that are using blood profiling, but LV function after MI is not a current target, and so I do not see how this paper helps, or hurts me.