Unravelling extracellular matrix biomarkers in systemic sclerosis

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Systemic sclerosis (SSc) is a prototypic fibrotic disease characterised by accumulation of excessive extracellular matrix (ECM) in affected tissues including skin, lung, and in the wall of blood vessels that may lead pulmonary hypertension, scleroderma renal crisis or digital ischaemia. The constellation of clinical manifestations makes SSc one of the most challenging of the immune mediated rheumatic diseases. One of the hallmarks of the disease is its clinical diversity and it is increasingly appreciated that the natural history of progression, improvement or stability in the skin and lung is an important predictor of outcome and disease burden. Serum markers that predict future outcomes are an attractive proposition and the ability to sample ECM fragments in the blood or other biological samples has opened up possibilities to develop better ways to stratify cases at an early stage that could be applied in clinical trials or practice.

To develop and validate such an approach, Dobrata et al have used technically robust immunoassays to measure the levels of ECM fragments in the circulation [1]. The immunoassays target specific epitopes generated by enzymatic cleavage of ECM by metalloproteinase and can be used to determine targets that reflect biosynthesis, which are released as procollagen and as markers that reflect the enzymatic degradation of ECM components. In this way it is possible to assess both synthesis and degradation of fibrillary collagens and derive a ratio that may reflect net collagen turnover at a point in time. Building upon promising earlier studies of this technology [2], this approach has been applied to a derivation and validation cohort of SSc and healthy controls. Further analysis of the pooled samples has also been undertaken.

Their findings support previous literature showing markers of type I and type III collagen synthesis, designated C1 and C3 respectively, differ between SSc and healthy controls (HC), and these have been correlated in cross-sectional analysis to measurements such as the modified Rodnan skin score (mRSS) [2]. mRSS has been validated as a trial outcome measure but has substantial limitations especially related to reproducibility and reliability [3] and so a blood measure that reflects global skin fibrosis burden would be useful [4]. The present work uses longitudinal disease behaviour to classify cases as progressive and this is aligned to approaches that have proven valuable beyond SSc such as in lung fibrosis.

Although such an approach has enormous potential relevance to clinical management it also has limitations. The added value to measuring degradation as well as synthesis is not completely clear as most of the statistical associations seem to be driven by the individual marker. Synthesis and degradation may not correlate with total ECM burden. Compelling recent longitudinal studies have shown good baseline cross sectional correlation but interestingly markers of ECM synthesis may increase with clinical improvement perhaps reflecting that matrix turnover is dynamic and can associate with improvement as well as worsening [5]. This is important other serum tests, such as the composite ELF (enhanced liver fibrosis) test, developed for liver fibrosis, also appear to reflect skin severity and lung fibrosis [6].

In addition, baseline cross sectional analysis does not consider longitudinal changes in these markers, and further understanding on how collagen neoepitopes are impacted by the disease's natural history or treatment response is required. In this way it will be important to demonstrate the advantages of having a measure in the serum that reflects total disease as compared to sampling other distinct compartments (such as urine, BAL or skin blister fluid) [7], especially as these results only reflected changes in skin, and not lung fibrosis.

Another important question from the present study is why the most abundant collagen in skin, lung and fibrosis, type I collagen, did not perform as well as III and IV. Collagen I is the predominant fibrillar collagen in fibrotic skin or lung and total burden may be especially relevant. Other

approaches such as isotopic labelling of proteins in ECM [8] have been tested applicable and have the advantage that multiple proteins can be measured simultaneously.

Although the ease and simplicity of a serum marker is attractive, it is of course also possible to biopsy skin in SSc which enables high dimensional transcriptomic profiling and intrinsic molecular subset classification [9] that has been shown to associate with clinical response in recent trials [10]. However non-invasive tools to stratify cases are needed to reduce inclusion of non-informative cases, likely to remain stable or improve spontaneously, in early stage trials makes the search for simple markers of progressive disease important. A marker that predicts future worsening in skin, and especially in internal organs or blood vessels would help to target the patients with greatest need for treatment and possibly also those more likely to respond to emerging novel therapies including direct antifibrotic drugs that may have applicability well beyond systemic sclerosis.

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