ACR 2017 - Systemic Sclerosis Highlights - Basic Science

A EUSTAR Young Investigator Group Report

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Sixty-two basic science abstracts were presented at the meeting. The following selection provides a synopsis of some of the recurring themes and notable findings reported at the meeting.

In further displays of how far the field of transcriptomics has progressed, there were several important abstracts presented of RNA-sequencing that provide additional support to our understanding of the inter-relationship between autoimmunity, vascuolpathy and fibrosis in SSc. Assassi et al. (from the PRESS cohort) reported a global gene expression profiling study using nextGen RNA Sequencing of skin obtained from a large multicentre cohort of very early diffuse cutaneous SSc (dcSSc). The study reported upregulated genes concerning fibrosis but also a prominent adaptive immune signature, not identified in an earlier study of established disease [1]. The work suggests there may be a relatively short window of opportunity within which we can maximise the benefits of immunomodulatory therapy in SSc. Apostolidis et al. (Lafyatis & Kahaleh collaboration), meanwhile, reported the findings of single cell RNA sequencing of endothelial cells isolated from SSc and healthy donor skin biopsies. An pro-fibrotic endothelial cell gene signature was identified in SSc that would be expected to support extracellular matrix generation, negative regulation of angiogenesis and epithelial-to-mesenchymal transition [2]. Mehta et al. (Whitfield group) has reported the conservation of intrinsic RNA-sequencing signatures in SSc patients who had provided at least 4 different biospecimens (skin, eosophagus, fundus, duodenum, and/or blood) highlighting the truly multi-system nature of the disease and potential to target shared pathways across different organ systems [3]. Cai et al meanwhile used RNA-sequencing to identify genetic variants associated with SSc gene expression subsets, and their potential relevance to innate immune responses and extracellular matrix deposition [4]. Potentially deleterious variants of the IL37 gene were enriched in patients with dcSSc and correlated with increased gene expression of IL6 and STAT3 in patient samples [4].

Nada et al. (Altorok & Kahaleh group) characterized the genome wide DNA methylation signature in SSc Microvascular Endothelial Cells (MVECs). The study identified significant genome-wide DNA methylation differences that could form the target of future therapies with relevance to cell adhesion, angiogenesis, Wnt signaling pathways, vascular smooth muscle contraction and adherens junctions [5]. Other epigenetic studies examined the potential roles of antisense long noncoding RNAs (HAND2-AS1 and OTUD6B-AS1) and the long noncoding RNA H19X in SSc pathogenesis [6, 7].

The relationship between vasculopathy, tissue ischaemia and fibrosis received further attention in work reported by Watanabe et al. (Feghali-Bostwick group) that has demonstrated the anti-fibrotic effects of endostatin-derived peptides on lung fibroblasts and in pre-clinical murine models of SSc [8]. Endostatin inhibits the pro-angiogenic effects of fibroblast growth factor and vascular endothelial growth factors and it is intriguing to consider the potential opposing effects of drugs targeting this pathway on vasculopathy and fibrosis in SSc.

There were 2 abstracts reporting the potential contribution of induced cellular autophagy in the pathogenesis of SSc. In vivo evidence of enhanced TGF-β-mediated cellular autophagy was identified in both the skin and myocardium of SSc patients compared with health donors [9, 10]. Zehender et al. (J Distler group) undertook studies demonstrating the process is driven by SMAD3-dependent downregulation of the H4K16-histoneacetlytransferase MYST1 and it appears, these pro-fibrotic effects can be abrogated through forced expression of MYST1 [9]. Stellato et al. (O Distler group), meanwhile, suggested fra-2 silencing might offer an alternative approach to targeting autophagy activity in SSc [10].

A number of clinical research studies have highlighted severe disease and poorer outcomes in black people with SSc. The Genome Research in African American Scleroderma Patients consortium (GRASP) presented the first genome-wide association study (GWAS) in African Americans with SSc in which they have confirmed MHC as a susceptibility locus but also identified a novel non-MHC locus (TGFβ3) as a SSc susceptibility gene. TGFβ3 is involved in fibrosis and Th17 cell function. The TGFβ3 locus variants are non-polymorphic in Europeans which might offer an explanation for the increased prevalence and severity of SSc in African Americans and bespoke treatment targets within this group of patients [11]. In another valuable genetic study of an enriched population of SSc patients, Stern et al. (Denton group) have identified 2 genes (CTNND2 and GPATCH2L) in patients with anti-RNA Polymeras III autoantibodies and a history of scleroderma renal crisis that may shed light on SRC aetiopathogenesis and provide new therapeutic targets [12].

Anti-nuclear antibodies in SSc are typically mutually exclusive which has led to

interest in the recently described autoantibodies targeting Cytoskeleton-Like Bicaudal D Protein Homolog 2 (BICD2) that appear to co-exist with anti-centromere antibodies in many patients. Epitope mapping has revealed homology between the core epitope of BICD2 and CENP-A peptides resulting in potential cross-reactivity [13]. It remains to be seen whether anti-BICD2 antibodies have diagnostic and prognostic importance beyond existing SSc-specific autoantibodies [13].

A large number of presented abstracts proposed a number of new potential candidate therapeutic targets (and treatments) for fibrosing disease in SSc. These include Retinoic-acid related Orphan Receptor-alpha (RORα) [14], MYST1 [9], Histone Demethylase Jumonji Domain-Containing Protein 3 (JMJD3) [15], fucosyltransferase-1 (Fut1) (derived from post-translational fucosylation) [16], Methyl-CpG-binding protein 2 (MeCP2) [17], IRF7 (a key transcription factor in type I interferon signalling pathways) [18], signal transducer and activator of transcription 3 (STAT3) [19], bone morphogenetic proteins-9 (BMP-9) [20], Insulin-like growth factor-II [21], the histone methyltransferase enhancer of zeste homolog 2 (EZH2) [22], Toll-like receptor 8 [23], hedgehog acyltransferase (Hhat) [24] and non-canonical WNT5A signalling [25] amongst others.

Conclusions

The selection of abstracts reported here provides a synopsis of some of the exciting and influential research presented for the first time at the 2017 American College of Rheumatology Annual Meeting. Inevitably, an exercise such as this is inherently subjective and will inadvertently omit important research findings whose significance will have important and far-reaching effects on our understanding of scleroderma and related disorders in the future. Nonetheless, we hope we have compiled a selection of some of the meeting's highlights whose full manuscripts we shall eagerly await. We hope this synopsis will be of interest to investigators who could not attend the meeting in person and alert interested clinicians and investigators to eagerly awaited manuscripts that shall provide a more detailed account of the important work being undertaken globally to better understand, investigate and manage this unyielding disease.

References

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