FIBROBLAST-MATRIX-VESSEL: THE UNHAPPY TRIAD

WHAT S100-ALARINS: POTENTIAL THERAPEUTIC TARGETS

Is there an universal translator? Which health professionals in rheumatology

TGF-beta, PDGF, FGF beta and VEGF. Among these are nintedanib and a more novel approach involves inhibition of tyrosine kinases which, in turn, affect socializumab (an IL-6 inhibitor), abatacept (affecting CD8 receptors) and rituximab.

Multiple therapies are being tested which modify the immune system and the vascular pathogenetic node underlying the pathogenesis of SSC. Among these are important in pathogenesis and represent appropriate targets for therapeutic intervention. It is likely that some emerging therapies can attenuate the pathogenesis of SSC by acting on multiple cell type sand this is perhaps especially relevant to an approach such as autologous haematopoietic stem cell transplant. However is likely that individual pathways or mediators can be modified in a less extreme manner and have benefit as potential disease modifying therapy. A number of key mediators and pathways are emerging including IL6, TGFbeta and intracellular pathways linked to nuclear hormone receptors. These are being targeted experimentally. Another strategy for treatment would be targeting the initiating cells such as monocytes, especially those with a proinflammatory phenotype, or the effector cells in fibrosis such as myofibroblasts. Evidence supporting these strategies is emerging and it is likely that restoration of a more balanced interaction between vessels, extracellular matrix and fibroblasts would underpin effective therapies for the fibrotic and vascular components of SSC.

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IS THERE AN UNIVERSAL TRANSLATOR? WHICH (ANIMAL) MODELS TELL US MOST?

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We will review the key features of currently available preclinical models of SSC, highlight their strengths and limitations and analyse, which subset of SSC patients individual models mimic. We will also discuss how to employ models to evaluate drug candidates with different modes of actions and how to combine different models for an optimal preclinical portfolio.

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NOVEL THERAPIES THAT MAY MAKE IT INTO THE CLINIC IN SYSTEMIC SCLEROSIS

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Introduction: Many therapies have been tested in systemic sclerosis (SSc), often failing but new approaches to measuring effect may improve the probability of success. The Combined Response Index for Systemic Sclerosis (CRI SS) combines measurement of the skin, lungs, activities of daily living and global assessments of disease activity into a single number. Like the DAS 28, this measure may be more powerful than any single outcome measure such as modified Rodnan skin score (mRSS) or forced vital capacity (FVC).

Novel approaches: Multiple therapies are being tested which modify the immune system and the vascular pathogenetic node underlying the pathogenesis of SSc. Among these are tocolizumab (an IL-6 inhibitor), abatacept (affecting CD8 receptors) and ruximab (a CD20 inhibitor), all of whom are being tested in late phase studies and for whom results can be expected soon.

A more novel approach involves inhibition of tyrosine kinases which, in turn, affect TGF-beta, PDGF, FGF beta and VEGF. Among these are nintedanib and a nanoparticle preparation delivering imatinib selectively. Encouraging animal studies and early human studies are resulting in larger studies in SSC patients.

Other drugs affecting fibrosis and inflammation are also being tested, including a cannabinoid which has shown encouraging early results.

While hematopoietic stem cell therapy will soon become a standard of care, other cellular therapies such as adipose derived mesenchymal cells and mesenchymal products such as exosomes and microparticles are being tested in systemic sclerosis.

There may or may not be enough time to discuss even more novel approaches to treating systemic sclerosis, with good rationale and some early results, which may reach the clinic.

Overall, this is an encouraging time for novel therapies to treat systemic sclerosis.

Disclosure of Interest: None declared


S100-ALARINS: POTENTIAL THERAPEUTIC TARGETS FOR ARTHRITIS

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Innate immunity is a pivotal factor in the pathogenesis of rheumatic diseases. During the last years there is growing evidence that pro-inflammatory alarmins of the family of calcium-binding S100-proteins promote inflammation in rheumatic, auto-inflammatory and auto-immune diseases. Serum concentrations of S100A8/S100A9 correlate with disease activity in several rheumatic diseases and are useful surrogate markers for monitoring disease activity predicting response to treatment, systemic organ involvement, or relapses in autoimmune diseases.

We have now identified a novel mechanism of auto-inhibition in mice and man restricting S100-alarmin activity to local sites of inflammation. We identified specific peptide sequences within the second calcium-binding EF-hands of S100A8 and S100A9 binding to TLR4/MD2 and triggering inflammation. However, biological activity of S100A8/S100A9 is locally restricted by calcium-induced (S100A8/S100A9)2-tetramer formation hiding the TLR4/MD2-binding site within the tetramer interphase. This auto-inhibitory mechanism is essential to prevent fatal inflammation in mice in vivo. Since S100A8/S100A9 complexes are the most abundant alarmins in arthritis, blocking of active S100A8/S100A9-dimers may represent an innovative approach for local inhibition of inflammatory processes in rheumatic diseases.

Disclosure of Interest: None declared


HEALTH PROFESSIONALS WELCOME SESSION

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An increasing amount of people are diagnosed with Rheumatic and Musculoskeletal Diseases (RMDs). EULAR Health Professionals in Rheumatology (HPR) can through substantial knowledge and clinical expertise contribute significantly to better lives with RMDs. Examples of important HPR core competencies are education, evidence-based treatment, prevention, team-based rehabilitation, and the support of individuals to participate in work, or education. The presentation will address some of the important multidisciplinary contributions to reduce the individual and societal burden of RMDs in the future.

Disclosure of Interest: None declared


WHAT’S NEW? PRESENTATION OF THE HPR NEWSLETTER

K. Betteridge, N/A, London, UK

The presentation will aim to showcase HPR News – the newsletter for EULAR’s Health Professionals in Rheumatology. HPR News is available twice a year and is published to support EULAR’s commitment to enable networking and learning.