ANTI-MODIFIED PROTEIN AUTOANTIBODIES IN RA DISPLAY IMPORTANT PEPTIDE CROSS-REACTIVITY BUT YET PROTEIN RECOGNITION SELECTIVITY

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Background: The continuing increase of anti-citrullinated protein autoantibodies (ACPA) titers together with epitope spreading close to onset of disease, suggests that antibody responses to different citrullinated antigens may be critical in rheumatoid arthritis (RA) pathogenesis. Interestingly, monoclonal antibodies demonstrate reactivity to multiple cit-antigens that can even expand to other protein modifications. The width of this cross-reactivity is still not understood.

Objectives: To characterize the targets of monoclonal ACPA in relation to amino acid motif recognition, cross-reactivity with others post-translational modifications, and cellular localization.

Methods: A peptide array (NimbleGen, Roche) containing 16aa arginine- or lysine in pairs with citrulline- or homocitrulline peptides (53019 and 49211 cognate peptide pairs, respectively) derived from 1610 extracellular proteins and known RA cit-targets was used to screen 12 monoclonal ACPA with CCP2 reactivity. In addition, these ACPA were also screened for reactivity to acetylated-histone peptides and for reactivity to acetylated HeLa cell-extracts from cytosome, membrane, nuclear and cytoskeleton fractions. Three of the described mAbs together with polyclonal anti-CCP2 G
ger were further evaluated on a macroarray platform (HExiselect, Engine) consisting of 20776 E.coli on-array expressed His-tagged protein fragments from 6909 genes originating from a human cDNA library. The array was enzymatically citrullinated with rabbit PADD and mAb-reactivity was scored from 0-3.

Results: On the peptide arrays, all 12 ACPA displayed low reactivity to unmodified peptides (<0.06%), while reacting to 1000s of synthetically citrullinated peptides (>3.4% of the peptides). Based on the sequence from the positive peptides, consensus amino acids motifs were created, identifying as-patterns with only a few critical citrulline-flanking residues (e.g. Cit-Gly- Oly-Cit- Arg-Cit-Asp). Intriguingly, five of the antibodies also reacted with the carbamylated peptides (>2.2%) and the recognition of certain homocitrulline-motifs also correlated with cross-reactivity to acetylated peptides. Interestingly, these AMPA reacted with acetylated-histones in NETs and apoptotic cells and in the nuclear fraction of in vitro acetylated cell-extracts. Three of the 12 ACPA were further screened on the macroarray and displayed multiple binding to citrullinated proteins and protein fragments identifying primarily previously unknown autoantibody targets (96, 210 or 917 positive hits for the mAbs, scoring 2-3), while limited binding was seen to native proteins.

Conclusion: ACPA display multi-reactivity to citrullinated peptides and proteins to a much greater extent than previously appreciated. Additionally, some ACPA, but not all, show distinct cross-reactivity to other post-translational modifications. Importantly, different auto-reactive clones display modified protein recognition patterns dominated by proteins from different cellular structures. These reactivity profiles are likely to have impact on functionality and pathogenesis.

Disclosure of Interests: Peter Sahlsström: None declared, Johanna Steen: None declared, Björn Forström: None declared, Philip Titcombe: None declared, Raghniidh Stålesen: None declared, Ute Nonhoff: None declared, Zoltán Konthu Shareholder of: Engine GmbH, Luca Piccoli: None declared, Karin Lundberg: None declared, Holger Bang Shareholder of: Engine GmbH, Daniel Mueller: None declared, Anca Catrina Grant/ research support from: Yes, but not for the presented study., Lars Klareskog Grant/research support from: Yes, but not for the presented study, Karl Skirner Shareholder of: Engine GmbH, Vivianne Malmström: None declared, Caroline Grönnwall: None declared


SAT0675B

SUPPORTING EARLY CAREER RESEARCHERS IN RHEUMATOLOGY AND MUSCULOSKELETAL MEDICINE: RESULTS FROM AN EMERGING EU-LERN SURVEY

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Background: Early career researchers (ECRs) across Europe face a number of challenges as highlighted by the European federation of education employers (EFFE) (1). Understanding the unmet needs of ECRs in rheumatology would allow development of targeted educational resources and support where required.

Objectives: To perform a Europe wide survey on the demographics of ECRs, current unmet needs and perceptions of possible solutions.

Methods: Clinical and non-clinical researchers who work in the field of rheumatology and under the age of 40, were invited to participate in an online-based survey. EMEUNET is a Europe-wide network of >2000 young researchers in rheumatology addressing educational needs and promoting research interests. Survey questions were devised and modified in collaboration with members of the EMEUNET education subgroup and steering committee. It was disseminated to EMEUNET members and national young rheumatology organisations. Participants were allowed to choose up to 4 answer options where applicable.

Results: 339 participants’ anonymised responses were collected from 53 countries. The majority of participants were between 31-35 years (38.1%), and female (63.4%). Most were clinical researchers (including 33.8% rheumatology trainees) and 24.1% were non-clinical, including allied health professionals. The area of research of the participants was as follows: Epidemiology (40.0%), basic science/translational (39.6%), clinical trials (38.1%), imaging (17.7%), health services research (14.7%), other (7.5%). 48.6% did not feel they had adequate educational resources to develop their research skills locally. Obtaining grant funding as ECRs was deemed to be difficult (43.3%) or very difficult (31.4%) in their respective institutions/countries. Reasons listed are presented in figure 1. 98% were interested in developing new European collaborations in their research area either through: face to face interactions at conferences (82.1%), website forum (50.8%), email interactions (61.1%), teleconferences (43.5%). In addition, 93.7% felt they would apply for small European grants for ECRs, 81.6% would be interested in funding to spend short periods (4-8 weeks) at another European institute and 87.5% in focussed deep dive sessions on a topic of interest. The top 3 research skills that participants felt they would benefit from having more resources for as ECRs were: 1. Writing a study protocol (64.9%), 2. Writing a first grant application (64.0%), 3. Performing a systematic review (51.1%) (Figure 2).

Conclusion: A large proportion of ECRs in rheumatology felt they lack resources to develop their research skills locally. Small grant funding, research opportunities for pan-European collaborations, short periods of exchange to other institutions and targeted support to develop research skills can help address some of the current needs of ECRs.
HETEROGENEITY OF STRATEGIES AND METHODS FOR DEVELOPMENT AND VALIDATION OF A SELF-

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Background: The structure and content of Rheumatology training programs vary widely among European countries. Harmonization of assessment methods of competences across EULAR countries could contribute to ensure a minimal standard of care.

Objectives: To identify and review the evidence on competence assessment methods and strategies in postgraduate medical training in rheumatology and other specialties.

Methods: As part of the EULAR project to develop points to consider on assessment of competences in rheumatology training, a systematic literature review (SLR) was performed. Two reviewers (AA and AN) independently identified eligible studies according to the PICO framework: P (population): trainees, fellows; I (instrument of interest): assessment strategies and methods; C (comparative group): M (measurement of properties of interest): validity, discrimination, feasibility. Two searches were conducted: (i) for rheumatology, retrieving original studies; (ii) for related medical specialties, retrieving SRs through which we identified original studies. Risk of bias was assessed using the medical education research study quality instrument (MERSQI) and the tool by Daly et al for qualitative studies. Studies were too heterogeneous to allow for any form of pooling, so descriptive results are presented.

Results: Of the 6276 articles from the rheumatology search, 4 met the inclusion criteria; of the 2,265 SRs in other specialties, 36 were included, corresponding to a total of 133 original studies included. Studies on the assessment of competences in rheumatology were at variable risk of bias and explored only 2 methods: direct observation of practical skills (DOPS) and objective structured clinical examination (OSCE) (Table 1). Rheumatology OSCEs have been used to assess clinical and communication skills, professionalism and practical skills on musculoskeletal ultrasound, with conflicting evidence on internal consistency, reliability and inter-rater reliability. However, OSCEs including clinical, laboratory and imaging stations performed best, with a good to very good internal consistency (Cronbach’s α = 0.83-0.92) and inter-rater reliability (r correlation coefficient= 0.80-0.95). A fair to moderate correlation (r= 0.44-0.52) between OSCEs and other assessment tools, including DOPS, has been found. The study on DOPS but not those on OSCE provided evidence for feasibility. Studies in other specialties were more heterogeneous for strategy/tools investigated, type and comprehensiveness of the analysis. The majority of studies on OSCEs to assess clinical skills showed a good to very good inter-rater reliability (r=0.60-0.95), while those on OSCEs to assess communication skills consistently demonstrated a good to very good internal consistency (Cronbach’s α=0.7-0.80). Other tools such as multisource feedback (MSF) and mini-clinical evaluation exercise (mini-CEX) showed feasibility and a good to very good internal consistency, but results on validity and reliability were conflicting.

Conclusion: Although there is a consistent body of evidence about assessment of competence in postgraduate medical training in several specialities, data in rheumatology is scarce and this partial picture indicates some conflicting evidence. OSCEs represent an appropriate tool to assess clinical competences and correlate fairly well with other assessment strategies; DOPS, MSF and mini-CEX are other feasible alternatives. A mapping of European countries and a qualitative alternative will be additionally performed.

Disclosure of Interests: None declared.


Development and Validation of a Self-Administered Questionnaire Measuring Essential Knowledge for Patients with Spondyloarthritis: The Spondyloarthritis Assessment Knowledge Questionnaire(SPAKE):

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Background: Patient education is recommended for patients with inflammatory arthritis to enhance self-management. Only one Knowledge