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ORAL PRESENTATION

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Defective removal of ribonucleotides from DNA promotes systemic lupus erythematosus

C Günther^{1*}, B Kind², MAM Reijns³, N Berndt¹, M Martinez-Bueno⁴, C Wolf², V Tüngler², O Chara⁵, YA Lee⁶, N Hübner⁶, YA Lee⁶, L Bicknell³, S Blum², C Krug², F Schmidt², C Krug², S Kretschmer², S Koss², KR Astell³, G Ramantani⁷, A Bauerfeind⁶, DL Morris⁸, DS Cunninghame Graham⁸, D Bubeck⁹, A Leitch³, SH Ralston¹⁰, EA Blackburn¹¹, M Gahr², T Witte¹², TJ Vyse⁸, I Melchers¹³, E Mangold¹⁴, MM Nöthen^{14,15}, M Aringer¹⁶, A Kuhn¹⁷, K Lüthke¹⁸, L Unger¹⁹, A Bley²⁰, A Lorenzi²¹, JD Isaacs²¹, D Alexopoulou²², K Conrad²³, A Dahl²², A Roers²³, ME Alarcon-Riquelme^{4,24}, AP Jackson^{3,24}, MA Lee-Kirsch^{2,24}

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Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disease in which environmental exposures like virus infection and UV-irradiation trigger activation of the innate and adaptive immune system in genetically predisposed individuals. Heterozygous mutations of the 3' repair exonuclease 1 (TREX1) are associated with SLE. Biallelic mutations in TREX1 and the three subunits of ribonuclease H2 (RNASEH2A-C) cause Aicardi-Goutières syndrome, an inflammatory encephalopathy with clinical overlap with SLE. We therefore investigated the role of RNase H2 in SLE pathogenesis. RNase H2 is responsible for the removal of misincorporated ribonucleotides from DNA and is indispensable for genome integrity. We demonstrated a genetic association for rare RNase H2 sequence variants with SLE. RNase H2-deficient fibroblasts of AGS and SLE patients accumulated ribonucleotides in genomic DNA resulting in chronic low-level DNA damage, constitutive p53 phosphorylation and senescence. Patient fibroblasts proliferated slower than fibroblasts from healthy individuals and showed impairment of cell cycle progression. In addition, patient fibroblasts exhibited constitutive up-regulation of interferon-stimulated genes and an enhanced type I interferon response to the nucleic acid poly(I:C) and UV-irradiation. UV-irradiation induced enhanced cyclobutane pyrimidine dimer formation in ribonucleotide-containing DNA. This suggests that innate immune activation may be

caused by immune recognition of DNA metabolites of DNA damage repair and may also explain photosensitivity in SLE patients with RNase H2 mutation. In summary, our findings implicate RNase H2 in the pathogenesis of SLE, and suggest a role of DNA damage-associated pathways in the initiation of autoimmunity.

Authors' details

¹University Hospital Dresden, Department of Dermatology, Dresden, Germany. ²University Hospital Dresden, Department of Pediatrics, Dresden, Germany. ³MRC Institute of Genetics and Molecular Medicine, Medical Research Council Human Genetics Unit, Edinburgh, UK. ⁴Pfizer-Universidad de Granada-Junta de Andalucía (GENYO), Centro de Genómica e Investigación Oncológica, Granada, Spain. ⁵Technical University Dresden, Center for Information Services and High Performance Computing, Dresden, Germany. ⁶Max Delbrück Centre for Molecular Medicine, Buch, Berlin, Germany. ⁷University of Freiburg, Epilepsy Center, Freiburg, Germany. ⁸King's College London, Genetics & Molecular Medicine, London, UK. ⁹Imperial College London, Department of Life Sciences, London, UK. ¹⁰MRC Institute of Genetics and Molecular Medicine, University of Edinburgh, Rheumatic Diseases Unit, Edinburgh, UK. ¹¹Centre for Translational and Chemical Biology, School of Biological Sciences, University of Edinburgh, Edinburgh, UK. ¹²Hannover Medical School, Hannover, Germany. ¹³University Medical Center, Clinical Research Unit for Rheumatology, Freiburg, Germany. ¹⁴University of Bonn, Institute of Human Genetics, Bonn, Germany. ¹⁵Life & Brain Center, Department of Genomics, Bonn, Germany. ¹⁶University Hospital Dresden, Rheumatology, Department of Internal Medicine III, Dresden, Germany. ¹⁷University of Münster, Department of Dermatology, Münster, Germany. ¹⁸Schwerpunktpraxis Rheumatologie, Dresden, Germany. ¹⁹Städtisches Klinikum Dresden-Friedrichstadt, Dresden, Germany. ²⁰University of Hamburg, Department of Pediatrics, Hamburg, Germany. ²¹Newcastle University, Institute of Cellular Medicine, Newcastle-upon-Tyne, UK. ²²Technical University Dresden, Center for Regenerative Therapies Dresden, Dresden, Germany. ²³Technical University Dresden, Institute for Immunology, Dresden, Germany. ²⁴Oklahoma Medical Research Foundation, Arthritis and Clinical Immunology Program, Oklahoma City, OK, USA.

¹University Hospital Dresden, Department of Dermatology, Dresden, Germany

Full list of author information is available at the end of the article

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