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LETTER TO THE EDITORS

Comment on "Epigenetics in the pathogenesis of RA"

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Dear Editors,

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that affects between 0.5 and 1% of individuals in the more economically developed countries [1]. The cause of the disease is yet to be determined, but environmental and genetic factors have been shown to be associated. For this reason, investigating epigenetic mechanisms in RA has received serious attention over the last decade. The recent review published in *Seminars in Immunopathology*, written by Ospelt and colleagues [2], aimed to provide a timely overview of this rapidly developing field.

In the abovementioned review, different epigenetic mechanisms and existing studies and results of relevance for RA were described. In the context of DNA methylation, being a key epigenetic marker, the respective quantification—and dissociation—of genetic and epigenetic contributions is a major question, and twin studies are necessary to discern them. It was concluded that in non-twin studies, mainly the major histocompatibility complex (MHC) regions have been identified as differentially methylated, while no differences have been found in twin studies. Regarding the latter, work on monozygotic twins discordant for RA by Gomez-Gabrero et al. was discussed and concluded that this study also did not present significant differential methylation between twins discordant for RA [3]. However, after discussions between the authors of the two mentioned papers, we came to the conclusion that the view presented in the mentioned review should be revised and the data should be described in greater detail.

When performing differential analysis of arrays, it is indeed possible to characterize differential methylated probes (DMPs) and sets of consecutive (regions) differentially methylated probes (DMRs). While it is true that in the discussed study [3] no significant DMPs were observed within healthy and RA twin pairs, the existence of DMPs cannot be excluded because of the small number of twin pairs considered and the correction for multiple testing (approximately 2 million probes). However, statistically significant DMRs were discovered, which were validated and replicated by pyrosequencing. The changes in the pyrosequencing experiments were directionally consistent but without statistical significance. Importantly, the array methodology used in the study (CHARM) has been designed to identify DMRs rather than DMPs, and this is one reason why evidence of high DNA methylation profile correlation between close CpG sites was obtained [4]. This explains how it was possible to obtain sufficient statistical power for the identification of DMRs associated with the EXOSC1 gene, despite the small number of samples. Importantly, to gain enough power and to obtain robust results, the DMR search protocol was updated as described in [4], which was another achievement of the study, besides novel DMRs.

These results are important for two reasons. Firstly, from the identified candidates, none was located within an MHC region, which was expected considering the genomic background, but it stressed the idea of the existence of epigenetically driven changes. Secondly, DMRs in ACPA+ pre-RA twin pairs were also studied and the PCDHB14 gene was identified, which was found to be of relevance also in RA

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through a projection analysis [3]; this provided the first insight of DNA methylation in pre-stages of RA.

Hence, we conclude that indeed differences in DNA methylation in twins discordant for rheumatoid arthritis were found in the discussed paper [3].

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