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Original article

Independence of carbohydrate-deficient isoforms of transferrin and cyclic citrullinated peptides in rheumatoid arthritis

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ABSTRACT

Objective: The aim of this study was to assess the relationship between the two types of posttranslational modifications of proteins in RA: glycosylation on the example of carbohydrate-deficient transferrin and citrullination by means of autoantibodies to cyclic citrullinated peptides.

Methods: The study was carried out in 50 RA patients. CDT was measured using N Latex CDT immunonephelometric test, the results were presented in absolute and relative units. Anti-CCP were measured using the chemiluminescent method and rheumatoid factor by immunoturbidimetric method.

Results: 80% of RA patients were positive for anti-CCP, 70% for RF and 62% for both, anti-CCP and RF. The level of %CDT was significantly elevated, but absolute CDT level was not changed. The mean absolute CDT concentration was higher in anti-CCP positive patients than that in anti-CCP negative. CDT (absolute and relative concentration) did not correlate with anti-CCP and RF. However, serum RF significantly correlated with anti-CCP. %CDT did not correlate with anti-CCP, but absolute level correlated with anti-CCP only in anti-CCP negative and RF negative patients. CDT did not correlate with RF, but solely with anti-CCP in anti-CCP negative patients. Anti-CCP correlated with DAS 28 only in anti-CCP negative RA, but CDT (absolute and relative units) correlated with DAS 28 in all patients and in anti-CCP positive RA.

Conclusions: These results suggest that the changes in CDT and anti-CCP concentrations are not associated with oneself and indicate on the independence of these posttranslational modifications in rheumatoid arthritis. Only the alterations in transferrin glycosylation reflected the activity of RA.

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Independência de isoformas de transferrina deficiente em carboidrato e peptídeos citrulinados cíclicos na artrite reumatoide

Palavras-chave:
Anticorpos antipeptídeo citrulinado cíclico
Transferrina deficiente em carboidrato
Fator reumatoide
Artrite reumatoide

RESUMO

Objetivo: O objetivo deste estudo foi avaliar a relação entre os dois tipos de modificações pós-translacionais de proteínas na AR: glicosilação no caso da transferrina deficiente em carboidrato (TDC) e citrulinação por meio dos anticorpos no caso do antipeptídeo citrulinado cíclico (anti-CCP).

Métodos: O estudo foi realizado em 50 pacientes com AR. A TDC foi medida utilizando o teste imunonefelométrico N Latex CDT, e os resultados foram apresentados em unidades absolutas e relativas. O anti-CCP foi mensurado usando o método quimioluminescente e o fator reumatoide (FR) pelo método imunoturbidimétrico.

Resultados: 80% dos pacientes com AR foram positivos para anti-CCP, 70% para FR e 62% para ambos (anti-CCP e FR). A percentagem de transferrina total (%TDC) esteve significativamente elevada, mas o nível absoluto de TDC não esteve alterado. A concentração média de TDC absoluta foi maior nos pacientes anti-CCP positivos do que naqueles anti-CCP negativos. A TDC (concentração absoluta e relativa) não se correlacionou com o anti-CCP e o FR. No entanto, o FR sérico se correlacionou significativamente com o anti-CCP. O percentual de TDC não se correlacionou com o anti-CCP, mas seu nível absoluto se correlacionou com o anti-CCP apenas em pacientes FR negativos e anti-CCP negativos. A TDC não se correlacionou com o FR, somente com o anti-CCP em pacientes anti-CCP negativos. O anti-CCP se correlacionou com o DAS 28 apenas nos pacientes com AR anti-CCP negativos, mas a TDC (unidades absolutas e relativas) se correlacionou com o DAS 28 quando considerados todos os pacientes com AR e em pacientes com AR anti-CCP positivos.

Conclusões: Estes resultados sugerem que as alterações na TDC e as concentrações de anti-CCP não estão associadas entre si e indicam a independência destas modificações pós-translacionais na artrite reumatoide. Apenas as alterações na glicosilação da transferrina refletem a atividade da AR.

Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune disease of connective tissues, with the appearance of several types of autoantibodies.[1] The specific autoantibodies generated in RA have been associated with the posttranslational modifications of proteins and peptides.[2] These modification involve glycosylation, citrullination, methylation, acetylation and ubiquitination occur in physiological conditions and have an important role in the normal function of the immune system.[3] The first type of autoantibodies founded in RA patients was rheumatoid factor (RF), which is an autoantibody to Fc domain of IgG. The changes in glycosylation (galactosylation/sialylation) IgG have been found to be associated with a pathogenesis of RA and can be diagnostically and therapeutically useful.[4] The several studies were conducted to recognize the alterations in glycosylation of others glycoproteins such as IgA, alpha 1-acid glycoprotein, fibronectin, haptoglobin and transferrin. Human transferrin exists as an heterogeneous population glycosylated variants differing in carbohydrate composition.[5] In healthy people mostly occur tetrasialylated glycoforms and glycoforms which lack one or both of complete N-glycans are called carbohydrate-deficient transferrin (CDT).[5] It has been assumed that CDT is the sum of three isoforms: asialo-, monosialo- and disialotransferrin. The glycosylation of plasma transferrin changes in RA and can lead to increase the CDT level.[6] The newly known posttranslational modification in RA is citrullination.[7] It is an enzymatic conversion of arginine to citrulline catalysed by peptidylarginine deiminases (PAD). In patients with RA, PAD may leak out of the dying cells in the synovial joints which can citrullinate of arginine and generate an cyclic citrullinated peptides (CCP).[8,9] Autoantibodies against CCP are considered as early diagnostic and prognostic biomarker of RA.[10] Their presence in RA-negative patients testifies for the early RA with worse prognosis.[8] In RA patients many citrullinated proteins have been detected, as fibrinogen, vimentin, enolase and type II collagen.[3] The aim of this study was to assess the relationship between different types of posttranslational modifications – glycosylation and citrullination – in RA by means of the concentration of CDT and anti-CCP.

Material and methods

The study was carried out in 50 RA patients (41 females, 9 males; mean age 53) recruited from the Department of Rheumatology and Internal Diseases (Medical University in Bialystok). The diagnosis of RA was confirmed according to criteria which were set by the American College of Rheumatology (ACR). All patients were interviewed regarding their use of alcohol. The patients drank alcohol only occasionally.

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