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ANOMALIES DE LA VOIE DU FACTEUR TISSULAIRE EN PATHOLOGIE THROMBOTIQUE VEINEUSE

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RESUME (FRANÇAIS)

Le couple facteur tissulaire/facteur VII (FT-FVII) et son inhibiteur le tissue factor pathway inhibitor (TFPI) jouent un rôle important dans l'initiation de coagulation et la thrombogénèse. Des facteurs environnementaux et génétiques modifient les composants de la voie du FT. Notre travail a été consacré à la recherche d'anomalies de la voie du FT en pathologie thrombotique veineuse.

L'expression monocytaire du FT, le FVII et le TFPI plasmatiques ainsi que différents polymorphismes des gènes de ces 3 facteurs ont été mesurés chez 92 malades avec un accident thromboembolique veineux et chez 82 sujets témoins appariés par le sexe et l'âge. Des mutations dans les exons 2 à 5 du FT ont été recherchées par SSCP et séquençage.

Chez les témoins, l'activité FT tend à être plus élevée chez les femmes prenant des contraceptifs oraux (CO) que chez les autres, ceci est significatif chez les porteuses du génotype -603GG. Chez les malades, il n'y a pas de différence d'expression du FT selon le sexe et le statut hormonal (pas de CO), ni d'effet global du génotype -603AG. L'expression du FT tend à être plus faible chez les malades que chez les témoins. Ceci est lié à une diminution du FT chez les patients traités par héparine et antivitamines K. L'analyse des exons du FT a révélé un profil de migration différent en SSCP chez un témoin sans mutation dans l'exon 5 ou les sites de splice intron-exon adjacents.

Le TFPI est diminué chez les femmes sous CO par rapport à celles sans CO et augmente après la ménopause. Il n'y a pas de différence entre patients et témoins pour le TFPI libre et le TFPI total. La mutation C536T du TFPI n'a été trouvée que chez un témoin.

Pour le FVII, il n'y a pas de différence entre malades et témoins, mais une augmentation de l'antigène du FVII et du FVII activé chez les femmes témoins sous CO, indépendamment des polymorphismes 5'F7 et 353R/Q.

Les dosages des composants de la voie du FT doivent tenir compte de différents facteurs environnementaux et génétiques.

RESUME (ANGLAIS)

The tissue factor/factor VII pathway (TF/FVII) and its inhibitor the tissue factor pathway inhibitor (TFPI) have an important role in the initiation of coagulation and in thrombogenesis. Environnemental and genetic factors can change the components of the TF pathway. Our work was to assess the disorder of the TF pathway in venous thromboembolic disease.

We measured the TF expression in monocytes, the FVII and TFPI plasmatic levels and different polymorphisms of the genes of these 3 factors in 92 patients with an history of venous thromboembolic disease and in 82 healthy volunteers related to sex and age. We screened the TF gene for mutation in exons 2 at 5 by SSCP and sequencing.

In controls the TF activity tends to be higher in women taking oral contraceptives (OC) than in other women, these difference is only significant in women with the –603GG genotype. In patients there is no difference of TF expression regarding sex and hormonal status (no women with OC) and no global effect of the –603AG genotype. The TF expression tends to be lower in patients than in controls. This is linked with a decrease of TF levels in patients taking heparin or antivitamin K. The analysis of the TF gene showed a difference in SSCP in one control subject without related mutation in exon 5 or in the splice junctions.

TFPI decreases in women taking OC in comparison with women not taking OC and increases after menopause. There is no difference between patients and controls for free and total TFPI. The C536T mutation was only found in a control subject.

There is no difference between patients and controls for FVII, but in women with OC FVII antigen and activated FVII were higher than in women without OC, independantly of the genotypes of the 5'F7 and 353R/Q polymorphisms.

The evaluation of the components of the TF pathway must take care of several environnemental and genetic factors.

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