Modulation of Thrombophilia Genes by Environmental Factors

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Key Words

Thrombophilia, functional polymorphisms, transcriptional control, environmental factors, factor levels

Abstract

The control of coagulation factor levels has a pivotal role in thrombophilia and known functional polymorphisms explain only a minor part of the coagulation factor level variance.

Several studies provide evidence for i) interaction of polymorphisms and their combination with environmental factors; ii) molecular mechanisms mediating activation of coagulation proteins by environmental factors; iii) molecular mechanisms mediating transcriptional control of thrombophilia genes by environmental factors. However, the vast majority of molecular regulation by environmental factors is still unknown. Understanding of gene-gene and gene-environment interactions will require a detailed knowledge of regulatory regions of thrombophilia genes and of regulatory proteins.

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There is currently a large interest in defining the genetic components of thrombotic disease. Knowledge of genes and gene variations making humans prone to thrombosis could help to define the mechanisms of disease, thus improving the design of innovative therapy or prophylaxis.

A number of well-characterized defects or polymorphisms in genes of the coagulation cascade (factor V, prothrombin, fibrinogen) and of natural inhibitors (protein C, protein S and antithrombin) have been found associated with venous thromboembolism, thus supporting its multigenic nature.

The gene variations or conditions producing hypercoagulable states are generally associated with hyperactivity of the coagulation system caused by increased function (FV Leiden)

Functional Polymorphisms and gene expression

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- Transcription
 - RNA processing (PT 20210G/A)
 - Protein maturation
 - Protein function
 - Protein inactivation (FV Leiden)

Fig. 1. Functional polymorphisms modulate the expression of coagulation factors at different steps.

or levels (PT, FVIII, FIX, FXI, fibrinogen) of procoagulant proteins or decreased functional levels of inhibitors (protein C, protein S and antithrombin). The estimate of heritability of hemostatic factor levels [1-3] shows a large genetic component both for procoagulant and anticoagulant factors.

Beside gene lesions, functional polymorphisms are able to modulate the factor levels through interaction with gene expression at different steps (figure 1), i.e. RNA processing (PT 20210G/A,) [4] and protein inactivation (FV Leiden) [5].

Combination of polymorphisms, linked in a single gene (haplotype) or located in different genes can synergize to produce a procoagulant condition. The FV HR2 haplotype [6] provides a paradigmatic example. This haplotype encodes for several aminoacid changes and has been found associated to decreased FV levels, increased FVa1/FVa2 isoform ratio, slightly increased APC resistance and FVIII-related APC resistance. All these associated phenotypes might contribute to increase the risk for thrombosis. Combination of prothrombin 20210G/A with FV Leiden and with three FV mutations (R506Q, H1299R, Y1702C) have been documented in thrombophilic patients [7-10]. The combinatorial interactions among thrombophilic defects and polymorphisms might account for the variable clinical phenotype observed among carriers of the same abnormality, even within a single family, and further demonstrate that thrombosis is a complex genetic trait.

New genetic components contributing to thrombotic disease could be hardly detectable because of small individual effect on thrombosis and complex interplay with environmental factors. The predominant role of environmental factors, and of their unexpected interactions has to be taken into account, particularly for arterial thrombosis. The recent epidemic history of thrombotic disease, as compared with the very ancient presence of gene variations in human populations, suggests that polymorphisms able to produce deleterious gene-environment interactions are likely to contribute significantly to the disease. The weak relationship between several genetic markers and variation of biological phenotypes, which does not favour the interpretation of results obtained in association studies, is probably explained by interaction of functional polymorphisms with various environmental factors. The combinatorial and gene-environment issues (Figure 2) complicate the detection of genetic components and require an ad-hoc design of epidemiological and molecular genetic studies.

Interaction between functional polymorphisms and environmental factors could produce fluctuation of coagulation factor activation and/or levels.

An example of coagulation factor activation is provided by the relationship between FVII R353Q polymorphism and postprandial triglyceridemia [11]. Serum cholesterol and triglyceride concentrations were found to correlate positively with FVIIc level and the postprandial increase in FVIIa levels was stronger in carriers of R353Q genotype than in R353 homozy-

gotes. Plasma lipoproteins could enhance TF-independent FVII activation [12].

A reasonable prediction is that most acquired influences exert their effect on factor levels by altering expression of genes. In particular, several evidences have been provided for transcriptional control.

Inflammation components - Responsive elements to IL-6 have been found in the promoter of several coagulation proteins (reviewed in [13]), and IL-6-mediated transcriptional activation of the factor of FVIII gene [14] and of α_2 -fibrinogen gene [15] in liver cells have been demonstrated.

Hormones - Regulation by steroid hormones has been suggested for FIX [16], FXII [17] and FVII genes [18-19]

Circadian rhythm - Diurnal variations in levels of coagulation cascade components, prothrombin fragment F1+2 and circulating FVIIa, [20] and of natural coagulation inhibitors (protein C protein S and antithrombin) [21] have been documented. Clear circadian oscillation of PAI-1 activity peaking in the early morning has been observed and transcription factor CLIF appears to regulate circadian oscillation of PAI-1 gene expression in endothelial cells [22].

Age - Stimulating models have been provided by genetic elements responsible for age-related stable or increasing expression patterns of genes relevant for thrombophilia (factor IX and protein C) [23-24].

Vascular-bed-specific expression [25] of some procoagulant and anticoagulant factors could provide differential substrates for interaction with such environmental factors.

Taken together these findings indicate that understanding of gene-gene and gene-environment interactions will require a detailed knowledge of regulatory regions of thrombophilia genes and of regulatory proteins.

Fig. 2. Interplay between genetic and environmental factors. Multiple genetic factors, increasing procoagulant activity or decreasing anticoagulant function, produce a gradient of risk for thrombosis in combination with environmental factors.

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