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Inflammation as a cause of venous thromboembolism

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SUMMARY

Inflammatory markers are highly amenable to appraise and adjust and could already serve as a diagnostic indicator and also as a predictor of prognosis over the management of many health problems. Inflammation is implicated in venous thromboembolism (VTE). However there is still an intense curiosity about whether it is a cause or only a consequence of the thromboembolic process. The more likely scenario is that some inflammatory mediators contribute to the development of VTE, which per se induces an inflammatory reaction. Here we will review evidences supporting the role of inflammation as a cause of VTE. Genetic association studies have provided possible links between inflammation-related genetic variants, especially cytokines (e.g. IL-1, IL-4, IL-6, IL-10, and IL-13), and VTE, leading to establish the fundamental role of genetic background in predisposition to VTE and variable inflammatory processes in individuals. Additionally, several inflammation-related conditions including aging, autoimmune disease, cancer, cardiovascular diseases, hormone replacement therapy, infectious diseases, metabolic diseases, overweight or obesity, pregnancy or postpartum, respiratory diseases, and trauma have been associated with an increased risk of VTE. At this moment, despite their theoretical potential, to achieve the implementation of the inflammation-related laboratory tests in practice is a long task and future studies

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with larger sample sizes are required to address whether the properties of the inflammatory process, particularly intensity and duration, are useful in determining the risk of VTE and following outcomes.

1. Introduction

Venous thromboembolism (VTE) is consisted of deep vein thrombosis (DVT) and pulmonary embolism (PE) with a totally estimated incidence rate of 70–113 cases per 100,000 people per year in the U.S (White, 2003). The data available for the incidence rate of VTE covers the full spectrum of male/female ratio (Goldhaber and Bounameaux, 2012; Parambil et al., 2005) (Fig. 1). A still growing concern exists about asymptomatic PE patients and related sudden deaths; because they are as many as that they can absolutely change the mathematical comparison statement between symptomatic DVT and PE cases (White, 2003) (Fig. 1). PE, known as the most common cause of pulmonary infarction, is more fatal than DVT due to a 2-fold increased mortality rate among PE patients compared to DVT patients within the first month (White, 2003). PE has been reported in more than 1% of total death certificates in the U.S within 20 years from 1979 to 1998 (Parambil et al., 2005; Horlander et al., 2003). It is expected that the age-adjusted PE-related mortality rate (AAMPE) should be still on the decrease; due to its reduction by greater than 50% from 1979 to 1998 (Horlander et al., 2003). The AAMPE is notably related to ethnicity (Horlander et al., 2003), and for this reason there is a spectrum for AAPEM in the various ethnic compositions (Fig. 1). During the first two years after DVT, about half of all patients develop post-thrombotic syndrome (PTS), that nearly 40 percent of these, i.e. 10% of all DVT cases, experience the moderate and severe forms of PTS (Shbaklo et al., 2009). In comparison with PTS, chronic thromboembolic pulmonary hypertension (CTEPH) is relatively rare, as shown to affect up to 4% of patients during two years after PE (Pengo et al., 2004). The factors associated with the increased risk of PTS and CTEPH (Pengo et al., 2004; Bonderman and Lang, 2011; de Wolf et al., 2012; Bouman et al., 2012; Bonderman et al., 2005; Heit et al., 2000) are summarized in Fig. 2.

Inflammation helps to pave enormously the way not only for VTE, but also for its subsequent possible complications e.g. CTEPH and PTS. In this way, the origin (e.g. aging, autoimmune diseases, cancer, diabetes, heart and respiratory diseases, hormone replacement therapy, infections, overweight or obesity, pregnancy, surgery, superficial venous thrombosis, and trauma) is not different to inflammation, but the one important thing is arriving at that known destination of VTE as illustrated in Fig. 3. Accordingly, it is well-expected that the properties of involved inflammatory process, particularly its intensity and duration, help to determine the chief characteristics of VTE, importantly its risk, severity, mortality and recovery. DVT patients who had increased inflammatory cytokines experienced worsened recanalization, and as well the short-term mortality and severity of PE were predictable from systemic inflammatory response syndrome (SIRS) and leukocytosis criteria (Jo et al., 2013; Jezovnik and Poredos, 2012).

Although its efficacy is far from satisfactory, the use of existing prophylaxes divided into anticoagulant (e.g. low-molecular weight heparin and unfractionated heparin) and mechanical compression (e.g. stocking and pneumatic compression) therapy for prevention of VTE in high risk patients is statistically better than none at all. However, less than half of high-risk medical populations deliver appropriate prophylaxis (Baser et al., 2013; Stinnett et al., 2005). Several risk factors of VTE in the various medical populations have been identified (Figs. 4–8). However, many of them cannot be included in designing the prophylactic and/or therapeutic settings of VTE, i.e. the age of patients or type of a traumatic injury are off one's hands. The issue that how inflammation is implicated in VTE has been discussed elsewhere, however whether inflammation is a cause or only a consequence of VTE is still an open question (Saghazadeh et al., 2015). Here we will present the evidence suggesting the role of inflammation as a cause VTE. Addressing what inflammation-related conditions are associated with the increased risk of VTE may help us in designing more effective VTE prophylaxis and treatments.

2. Genetic investigations

2.1. Genetic association studies

It has been demonstrated that some variants of inflammation-related genes including pro- and anti-inflammatory cytokines, pathways, chemokines and other inflammation-related genes are in association with the first occurrence or recurrence risk of VTE in humans (Table 1) (Tang et al., 2014; Mahemuti et al., 2012; Inanir et al., 2013; Mustafa et al., 2008; Bean et al., 2012; Beckers et al., 2010; Zee et al., 2009a; Zee et al., 2009b; van Minkelen et al., 2007). Some of them have been performed in the confined medical populations, such as cancer or Behçet's disease, to discover individual inflammation-related genetic factors of VTE (Inanir et al., 2013; Bagratuni et al., 2013). For example, the variant NFκB1 (rs3774968) gene was associated with the increased risk of VTE in myeloma patients on lenalidomide regimen, who received aspirin as prophylaxis (Bagratuni et al., 2013). In addition, these studies have highlighted the importance of sex and ethnicity in predisposing patients to develop VTE. In regard with ethnicity carrying of two L allele of HMOX1 repeat length polymorphism has been shown to leave black individuals, but not whites, more susceptible to occurrence or recurrence of VTE (Bean et al., 2012). Regarding the significance of sex, some polymorphisms, i.e. IL-4 -589C/T and IL-13 intron 3C/T, were proved to make women susceptible to the VTE event, while IL-6 174C/G was associated with the increased risk of VTE among men (Beckers et al., 2010). More interestingly, VTE women had represented higher T allele frequency for the polymorphism IL-4 -589C/T compared to their healthy counterparts, whereas VTE men had lowered ones (Beckers et al., 2010). In addition, it has been proved that the IL-1β rs1143634 variant could provide a protective effect against VTE development in white women (Zee et al., 2009a). Haplotype analysis has showed a 4-fold increased development of DVT among people who were homozygous for haplotype 5 of IL-1RN (tagged by SNP 13888T/G) (van Minkelen et al., 2007).

2.2. Gene-targeted animal studies

These studies are depicted to address that how these inflammatory markers contribute to VTE.

For instance, it has been shown that the deletion matrix metalloproteinase 9 (MMP-9) led to decreases in the amount of vein wall collagen and as well proinflammatory cytokines, might explaining an increased resolution of VTE (Deatrick et al., 2013). Further,

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