Trypsin is as procoagulant as factor XIIa

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ABSTRACT

To help shed light on the roles of the contact pathway of blood clotting, we quantified the relative procoagulant activities of each of the serine proteases of the clotting cascade.

We added varying concentrations of the activated forms of different clotting proteases to normal human plasma and recorded the time to clot formation. We also compared these clotting activities to that of the nonspecific serine protease, trypsin. The activated proteases of the final common pathway of blood clotting exhibited relatively strong clotting activity and achieved 100-second clotting times at pM to very low nM concentrations. In contrast, factor XIIa and plasma kallikrein exhibited weak clotting activity such that it required nearly 100 nM factor XIIa to achieve a 100-second clotting time, and for plasma kallikrein this was not achieved even with 100 nM enzyme. Trypsin was slightly more procoagulant than factor XIIa.

We conclude that the enzymes that trigger the contact pathway of blood clotting have remarkably weak procoagulant activity. The implications for the roles of factor XII and trypsin in thrombotic disorders and pancreatitis are discussed.

Key words: blood clotting, contact pathway, pancreatitis, thrombosis, trypsin.

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Introduction

The contributions of the contact pathway to blood clotting have long been a source of confusion.[1] The two seminal 1964 papers that proposed the modern clotting cascade focused almost exclusively on the contact, or *intrinsic* pathway of clotting,[2,3] with Davie and Ratnoff writing that the "route by which thrombin forms in cell-poor plasma has been called the intrinsic pathway, since it does not require the participation of substances extrinsic to the blood."[3] Each of those landmark papers devoted just a single sentence to the tissue factor (TF) or *extrinsic* pathway of blood clotting, with MacFarlane stating simply, "Factor X can also be activated by tissue factor in the presence of factor VII (FVII)."

We now know that the process that initiates the contact pathway — the conversion of FXII to FXIIa — is triggered when plasma contacts artificial surfaces such as glass.[4] It is the TF pathway, not the contact pathway, that is essential for normal hemostasis,[5] since FXII deficiency in humans or animals is not associated with any bleeding tendency.[1,4] It is seemingly paradoxical, then, that FXII-deficient mice are protected from experimental thrombosis,[6] and targeting FXII(a) is thromboprotective in multiple animal models.[7-10] Those animal studies ignited a renewed focus on the contact pathway as a potential contributor to thrombotic disorders, and perhaps as a safer target for antithrombotic drugs. On the other hand, multiple published case reports and case series have described thrombosis in patients with FXII deficiency,[11,12] raising the question of whether FXII deficiency is truly thromboprotective in human patients. However, a recent large-scale population study found FXII haploinsufficiency to be significantly protective against venous thrombosis.[13]

Since FXII cannot have evolved just to cause thrombotic disorders, it must have protective roles, possibly unrelated to blood clotting. Indeed, it has long been known that there is crosstalk between FXII activation and the fibrinolytic and complement cascades.[4] More recently, multiple signaling/regulatory roles have been discovered for zymogen FXII, implicating it in such

processes as neoangiogenesis, fibrosis, wound healing, neutrophil recruitment, and neuroinflammation.[1] It is not clear, however, whether severely FXII-deficient human patients have any disease tendencies that result from lacking these non-clotting roles for FXII(a), although this could just be the result of insufficient study of this relatively rare population.

In pondering the roles of the contact pathway of blood clotting, we compared the circulating plasma concentrations of all the blood clotting zymogens and procofactors (Figure 1A).[14] Prothrombin (FII) circulates at quite a high concentration (1.4 μM) and as one moves, step by step, up the clotting cascade one sees that the earlier zymogen concentrations are more or less progressively lower, with FIX and FX at 90 and 170 nM, respectively, FVII at 10 nM, and FXI at 30 nM. The concentrations of the procofactors, FV and FVIII, are even lower, indicating that they are only needed in trace amounts. Because coagulation is an enzymatic cascade that results in amplification at each step, one might reasonably expect that the most abundant zymogen would be the one at the end of the cascade (prothrombin), with progressively lower concentrations of FX, FIX, FVII, FXI, and finally, plasma prekallikrein (PK) and FXII. It is striking, therefore, that the plasma concentrations of PK and FXII are both >300 nM, which is more than tenfold higher than that of the downstream substrate, FXI. Furthermore, high-molecular-weight kininogen (HK), the protein cofactor for the contact pathway, is present at 670 nM, which is far in excess of the FV or FVIII concentrations. Given their place at the pinnacle of the contact pathway-initiated clotting cascade, one might have expected FXII, PK and HK to circulate at far lower concentrations. This raises questions regarding the normal roles for these proteins relative to their ability to trigger the clotting cascade.

In this study, we felt it would be instructive to directly com-

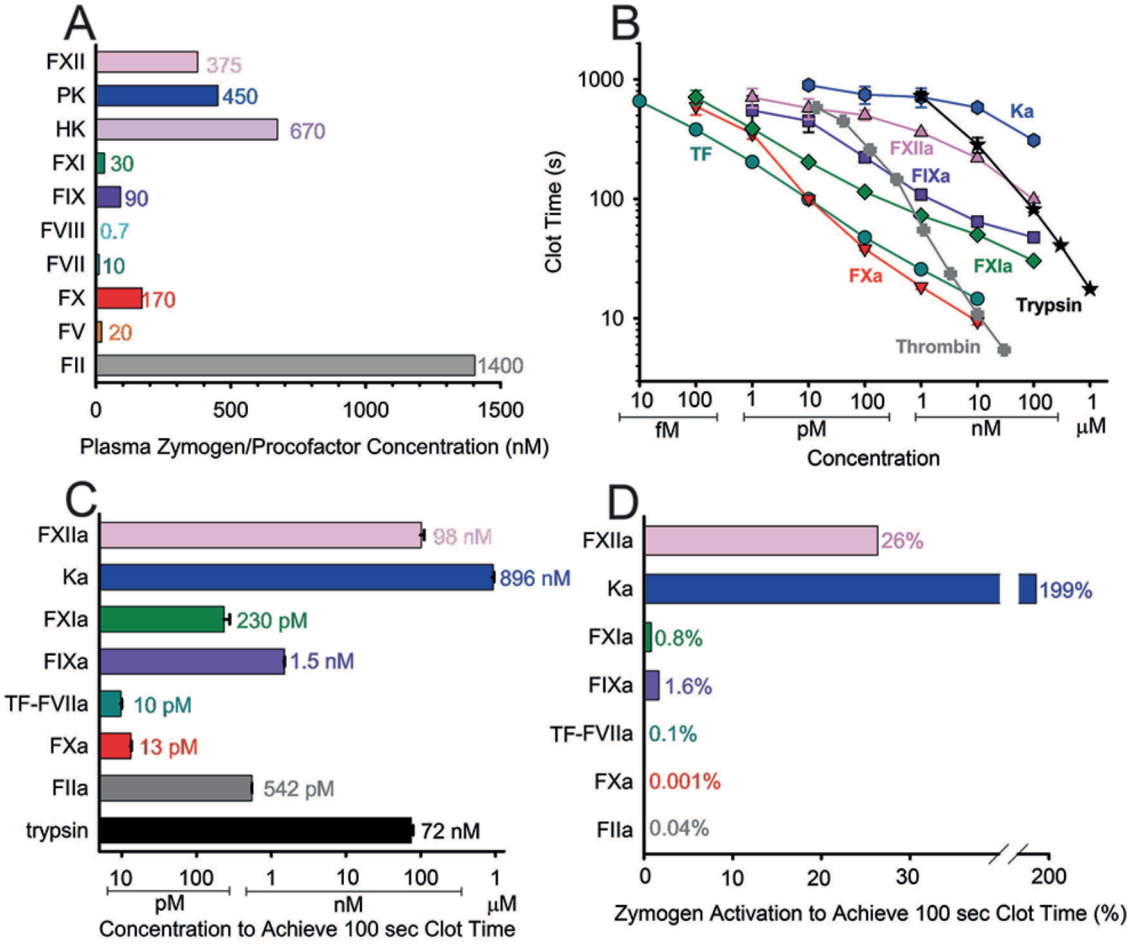

Figure 1. Plasma concentrations of clotting factors, and the relative procoagulant activities of activated clotting proteases. A) Literature values of the plasma concentrations of coagulation factor zymogens and procofactors.[14] B) Clotting times observed when the indicated concentrations of activated clotting proteases, relTF, or trypsin were added to citrated pooled normal plasma, followed immediately by recalcification. Data points are means ± standard error (n=4). C) Concentrations of the indicated enzymes or TF required to achieve a 100-second clotting time, interpolated from the assay results in panel B. Note that "TF-FVIIa" represents the TF concentration. For Ka, the data were extrapolated, since a 100-second clotting time was not achieved at the highest Ka concentration tested. D) The calculated percentage of circulating zymogens that would need to be converted into the corresponding active proteases to achieve 100-second clotting times. Values were calculated from mean values in panel C and the zymogen concentrations in panel A. The value for "TF-FVIIa" represents the relTF concentration that yielded a 100-second clotting time, normalized to the concentration of zymogen FVII in plasma. PK, plasma kallikrein; HK, high-molecular-weight kininogen; TF, tissue factor.

pare the relative potencies of the activated forms of all the blood clotting proteases in clotting of plasma. During this study, we included trypsin as a non-specific protease for comparison. We now report that FXIIa and PK, the two proteases that initiate the contact pathway, had the lowest procoagulant activity of all the clotting proteases tested. Furthermore, trypsin was approximately as procoagulant as FXIIa. We discuss possible implications of these results regarding roles of the contact pathway in blood clotting, and possible pathophysiologic roles for activation of clotting by trypsin in various disease states.

Materials and Methods

Purchased materials were from the following suppliers: porcine trypsin and powdered kaolin, Sigma-Aldrich (St. Louis, MO, USA); human FXIa, plasma kallikrein (Ka), and FXIIa, Enzyme Research Laboratories (South Bend, IN, USA); human FIXa, FXa, α-thrombin, and citrated human plasmas immunodepleted of individual clotting factors, Prolytix (Essex Junction, VT, USA); citrated pooled normal human plasma, George King Biomedical (Overland Park, KS, USA); egg phosphatidylcholine (PC) and porcine brain phosphatidylserine (PS), Avanti Research (Alabaster, AL, USA). Phospholipid vesicles containing 80% PC/20% PS (PC/PS) were made via sonication. Recombinant human TF was produced and relipidated into 80% PC/20% PS liposomes (relTF) using 15 mM deoxycholate and Bio-Beads (Bio-Rad, Hercules, CA, USA), as described.[15] Long-chain polyP was produced as described and had a modal length of 1200 phosphates (range, 595-1935 phosphates long).[16] For assays with kaolin, the desired concentration of kaolin powder was suspended in liquid with vigorous mixing immediately before use.

Clotting assays were performed in a STart 4 coagulometer (Diagnostica Stago, Parsippany, NJ, USA), with all solutions and plasmas prewarmed to 37°C. Enzymes or relTF were diluted to the desired concentrations in HBSAL (20 mM HEPES-NaOH pH 7.4, 100 mM NaCl, 0.1% bovine serum albumin, 0.02% NaN_3, 75 μM PC/PS). Clotting assays without kaolin or polyP were conducted by dispensing 50 μL of a solution of the desired enzyme or relTF (in HBSAL) into the coagulometer cuvette, after which 50 μL citrated plasma and 50 μL 25 mM $CaCl_2$ were immediately added and mixed. Clotting assays with kaolin or polyP were conducted by dispensing 25 μL of kaolin suspension or polyP solution (in HBSAL) into the coagulometer cuvette, followed immediately by 25 μL enzyme or relTF (in HBSAL), 50 μL citrated plasma, and 50 μL 25 mM $CaCl_2$, then mixing. In both assay configurations, the total volume was 150 μL, and the time to clot formation was recorded from the moment of $CaCl_2$ addition. Concentrations of enzymes, relTF, kaolin and polyP are graphed as their final concentrations in the 150 μL clotting mixture.

Results

Comparative procoagulant activities of the blood clotting proteases and tissue factor

We compared the relative procoagulant potency of blood clotting serine proteases by adding varying concentrations of the activated versions of each protease to citrated plasma that had been supplemented with a sufficient concentration of PC/PS vesicles to fully support blood clotting reactions. We then immediately recalcified the samples and recorded the clotting time from the point of calcium addition. Since FVIIa has very little clotting activity without TF, we conducted clotting assays with varying concentrations of relTF instead of FVIIa. The results in Figure 1B showed that, as expected, TF was extremely potent at initiating plasma clotting, with detectable shortening of the clotting time at TF concentrations as low as 100 fM. The potency of FXa was rather similar to that of TF, although the slope of concentration-dependence curve was slightly different. FXIa and FIXa were next in potency, but both were less potent than TF or FXa. At nM concentrations, thrombin had similar potency to TF and FXa. However, at subnanomolar concentrations thrombin had less activity than TF or FXa, possibly because it was inhibited by any of its many inhibitors in plasma. FXIIa was substantially less potent than TF, FXa, FIXa, FXIa, or thrombin. Ka was the least potent clotting factor by far, showing relatively little ability to shorten the plasma clotting time even at 100 nM Ka.

We note that Chatterjee *et al*.[17] conducted somewhat similar titrations of various clotting protease *versus* clotting times, although with fewer proteases and under somewhat different conditions. For one, they tested the proteases in fivefold-diluted whole blood, not plasma. Nevertheless, their findings broadly match ours.

Procoagulant activity of trypsin relative to blood clotting proteases

Since the procoagulant activities of FXIIa and Ka were so much weaker than any of the downstream clotting proteases, we thought it might be instructive to compare their procoagulant activities to that of a *generic* serine protease. All blood clotting proteases have trypsin-like substrate specificities, so we chose to extend these clotting assays to testing varying concentrations of porcine trypsin. We found that trypsin did indeed shorten the clotting time of plasmas in a concentration-dependent manner. In fact, the procoagulant activity of trypsin was rather comparable to that of FXIIa, although the shapes of the concentration-dependence curves differed somewhat.

Protease concentrations that yielded 100-second clotting times

To directly compare the relative potencies of these enzymes in clotting plasma, for each enzyme we calculated the protease concentration that would yield a clotting time of 100 seconds (Figure 1C). This was done by interpolation of the clotting curves for all proteases except Ka. Since Ka did not achieve a 100-second clotting time even at the highest concentration tested (100 nM), we resorted to extrapolation to estimate the Ka concentration that would yield a 100-second clotting time. We found that TF, FXa, FXIa, and thrombin all achieved 100-second clotting times at pM protease concentrations, while FIXa required 1.5 nM. In contrast, FXIIa required nearly 100 nM enzyme to achieve this clotting time, and we estimate that it would take close to 1 μM Ka to do so. Thus, the concentrations of FXIIa or Ka to achieve a 100-second clotting time are multiple orders of magnitude higher than the concentrations required for FXa or thrombin, the two proteases of the final common pathway. The trypsin concentration calcu-

lated to result in a 100-second clotting time was 72 nM, which compares favorably to the FXIIa concentration (98 nM) required to achieve the same clotting time.

Percent zymogen activation that would yield 100-second clotting times

Another way to consider the potencies of the clotting proteases is to calculate the percentage of each zymogen that would need to be converted into active enzyme to yield a 100-second clot time. When we did this exercise (Figure 1D), we found that much less than 1% of FX or prothrombin would need to be activated into FXa or thrombin to achieve this clotting time. For FIX or FXI, the percentage of the zymogen that would need to be activated was 1.6% and 0.8%, respectively. In sharp contrast, 26% of plasma FXII would need to be converted into FXIIa to achieve a 100-second clotting time, and this is despite the relatively high concentration of zymogen FXII in plasma. For PK, we estimate that it would not be possible to achieve a 100-second clotting time even if 100% of the plasma zymogen were converted into Ka.

Effect of contact activators as cofactors for the procoagulant activity of factors XIIa, FXIa and plasma prekallikrein

It occurred to us that the clotting activities of the enzymes of the contact pathway are typically tested in the presence of contact activators, which function essentially as cofactors. Accordingly, we evaluated whether these enzymes would be more procoagulant if contact activators were present. We did this by observing the concentration-dependence of their clotting activities alone or in the presence of powdered kaolin or long-chain polyP (two known activators of the contact pathway). When we varied the Ka concentration in normal plasma, we found that polyP shortened the plasma clotting times (Figure 2A). However, even at 100 nM Ka the clotting time was longer than 100 seconds. Adding kaolin to these clotting reactions also shortened the clotting times, but this effect was essentially independent of added Ka. Since activation of the contact pathway by kaolin likely confounded the results by activating FXII to FXIIa which would then generate more Ka from endogenous PK, we repeated the tests by adding varying concentrations of Ka to PK-deficient plasma, with or without the contact activators (Figure 1B). In this setting, the presence of either polyP or kaolin shortened the Ka-driven clotting times in PK-deficient plasma across the nM range of Ka concentrations, with polyP being more effective than kaolin. Again, however, even in the presence of polyP, the clotting time of 100 nM Ka was longer than 100 seconds. When we repeated these tests by adding varying concentrations of FXIIa, we obtained similar results. Thus, polyP and kaolin shortened the FXIIa-driven clotting times with normal plasma (Figure 2C) or FXII-deficient plasma (Figure 2D).

We next tested whether the procoagulant activity of FXIa is enhanced by kaolin or long-chain polyP, by adding varying concentrations of FXIa to normal plasma (Figure 2E) or FXI-deficient plasma (Figure 2F) in the presence or absence of these contact activators. The results were clearest with FXI-deficient plasma, in which adding neither kaolin nor polyP shortened the clotting times observed with FXIa. Although we tested two agents (kaolin and polyP) that can activate the contact pathway, there are other contact activators, and it is possible that different results might be obtained with different activators.

The step at which trypsin activates the clotting cascade

Lastly, we did clotting tests to identify the step of the plasma clotting cascade at which trypsin acts. We did this by adding 100 nM trypsin and PC/PS vesicles (followed immediately by recalcification) to various clotting factor-deficient plasmas and compared their clotting time to that obtained with pooled normal plasma. The results in Figure 3 show that 100 nM trypsin successfully shortened the clotting time of plasmas deficient in FXII, FXI, FIX or FVIII. When this concentration of trypsin was added to plasmas deficient in FX, FV or prothrombin, the clotting times were all in excess of 1000 seconds. These results are consistent with the idea that trypsin activates clotting of plasma at the level of FX.

Discussion

In the widely used aPTT clotting test, the contact pathway of blood clotting is initiated by the surface-mediated, reciprocal activation of FXII to FXIIa and PK to Ka. However, our in vitro clotting assays showed that FXIIa and Ka are much weaker initiators of blood clotting than any of the downstream clotting proteases, such that it was difficult to achieve even 100 second clotting times with relatively high concentrations of FXIIa or Ka. Given this, why is the aPTT clotting time of normal plasma typically in the range of 25 to 40 seconds? The answer is that the aPTT is performed under highly artificial conditions that include a preincubation period in which the citrated plasma sample is mixed with the contact activator and then held at 37°C, typically for around 3 minutes, after which the sample is recalcified. This preincubation step allows the calcium-independent reactions of the contact pathway to proceed, namely the reciprocal activation of FXII and PK as well as the activation of FXI to FXIa. Even with this relatively prolonged preincubation step to allow FXIa to accumulate before recalcification, a typical aPTT clotting time of normal plasma is around 30 seconds. In contrast, the normal clotting time of a PT assay is usually 11 to 13.5 seconds. Given that there is a log-log relationship between clotting protease concentration and clotting time (Figure 1B), and given that FXIa has substantial procoagulant activity (Figure 1C), this means that the aPTT assay is being driven by the production of orders of magnitude lower enzyme concentrations than the PT assay. Furthermore, the aPTT clotting time is recorded from the moment of calcium addition, ignoring the preincubation time, so the actual clotting time is effectively minutes long. This underscores the idea that FXIIa and Ka have very weak clotting activity.

In addition to the relatively weak potency of FXIIa and Ka as triggers of coagulation, the fact that the plasma concentrations of FXII and PK are more than tenfold higher than that of FXI (the substrate for FXIIa) suggests that FXI is not the most important substrate for FXIIa. This situation is in sharp contrast to the downstream clotting cascade, where the zymogen concentrations increase with each step amplifying the cascade (*i.e.,* FXI < FIX < FX < prothrombin; Figure 1A).

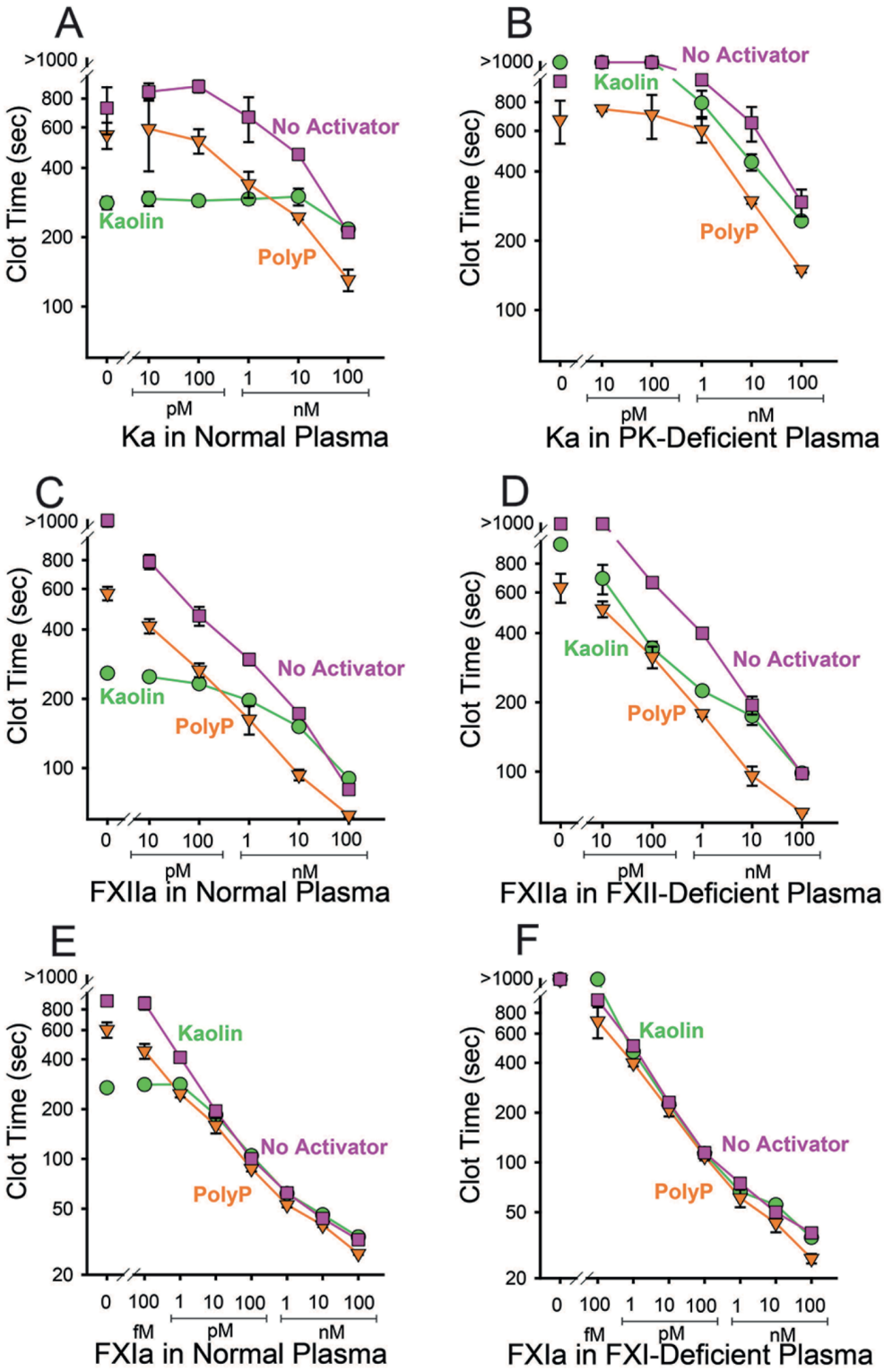

Figure 2. Procoagulant activities of Ka, FXIIa, and FXIa in normal versus factor-deficient plasmas, with or without the contact activators, kaolin or polyP. In each panel, clotting times are plotted versus enzyme concentration when the indicated concentrations of Ka, FXIIa or FXIa were added to normal or factor-deficient plasma, followed immediately by recalcification. Additives included 1 µg/mL kaolin (Kaolin), 10 µM long-chain polyP (PolyP) or no contact activator, as indicated. A) Ka-triggered clotting of pooled normal plasma. B) Ka-triggered clotting of PK-deficient plasma. C) FXIIa-triggered clotting of pooled normal plasma. D) FXIIa-triggered clotting of FXII-deficient plasma. E) FXIa-triggered clotting of pooled normal plasma. F) FXIa-triggered clotting of FXI-deficient plasma. Data represent mean ± standard error (n=5).

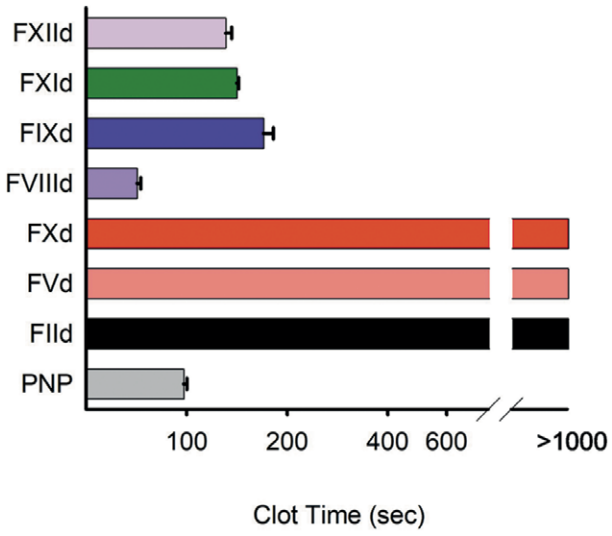

Figure 3. Procoagulant activity of trypsin in normal human plasma and various factor-deficient plasmas. The time to clot formation was recorded following addition of 100 nM trypsin followed immediately by recalcification to either pooled normal plasma (PNP) or plasmas that were immunodepleted of the indicated clotting factor. Each immunodepleted plasma is indicated with a lower-case "d" after the name of the deficient clotting factor. Data represent mean ± standard error (n=3).

Could the weak clotting activity of FXIIa help explain how it could contribute to thrombosis but not hemostasis? Possibly – especially since the time courses of blood clotting can be very different in hemostasis *versus* thrombosis. To prevent serious blood loss, it is essential that hemostatic clots form within seconds to minutes after vascular injury. Therefore, hemostasis depends upon very rapid initiation of the blood clotting cascade. In typical thrombotic disorders, however, thrombi develop over time courses of hours to days. For this reason, even a very weak activator of clotting such as FXIIa can be significant for slowly driving the accumulation of thrombi, while being unable to meaningfully contribute to the rapid formation of hemostatic plugs.

Given the very weak procoagulant activity of FXIIa, we decided to compare its clotting activity with that of the general serine protease, trypsin. Surprisingly, we found that trypsin and FXIIa have roughly the same potency with regard to clotting plasma. Trypsin has, in fact, long been known to clot blood.[18] Trypsin is generally considered a promiscuous serine protease, produced in the pancreas as trypsinogen and activated to trypsin in the lumen of the small intestine for the purpose of digesting dietary proteins. Very early in the twentieth century, pancreatic extract was first reported to clot plasma or whole blood,[19,20] and over the ensuing decades, multiple studies explored the blood-clotting effects of trypsin.[18,21,22] Trypsin was even tested intravenously in animals and humans,[23,24] and in the 1970s it was used as the clot-initiating agent in clotting assays such as the K-test (trypsin clotting time).[25] In the 1960s, trypsin was reported to trigger clotting by activating FX,[22,26] which we confirmed in this study (Figure 3).

The pathophysiology of pancreatitis is due in large part to the uncontrolled proteolytic activity of trypsinogen that becomes prematurely activated to trypsin within the pancreas itself. Disseminated intravascular coagulation and thrombosis can both be important clinical features of pancreatitis.[27,28] The current paradigm is that such sequelae – including thrombosis and coagulopathy – are secondary to tissue necrosis and the systemic inflammatory response. However, given the procoagulant activity of trypsin it seems reasonable to propose that direct activation of coagulation by trypsin could be a contributing factor to disseminated intravascular coagulation and thrombosis in pancreatitis. Interestingly, vascular endothelial cells and a variety of cancer cells have been reported to secrete trypsinogen, which can be activated to trypsin and whose procoagulant activity might therefore contribute to the pathophysiology of thrombosis in cancer and vascular disease.[29]

Conclusions

In summary, the plasma concentrations of zymogen FXII and PK are far higher than those of the downstream zymogens, while the corresponding activated enzymes, FXIIa and Ka, have remarkably low procoagulant potency. Our conceptual reexamination of the coagulation cascade provides a plausible explanation for how a very weak clotting enzyme, FXIIa, can contribute significantly to thrombosis but not at all to hemostasis. Furthermore, we report that the relatively nonspecific digestive enzyme, trypsin, is as least as procoagulant as FXIIa. This finding raises the possibility that trypsin's clotting activity may contribute directly to the pathology of pancreatitis and cancer. And finally, in spite of FXIIa being primarily thought of as a clotting enzyme, our findings question whether coagulation is actually the primary function of this enzyme.

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