Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The lack of accurate biomarkers also hampers new drug development. Current intrathecal therapies usually rapidly clear visible leukemic cells in CSF but subclinical disease is likely to remain, explaining the need for prolonged intensive therapy. We are essentially "shooting blind" when treating the CNS. We need large numbers of patients and long follow-up to see the impact of new drugs on late CNS relapses, which are thankfully rare events. An ability to measure depth of remission at early time points would give a rapid surrogate end point. This would give confidence to treating clinicians and families when testing novel therapies that show promise in terms of reduced toxicity but still need to prove efficacy.

What about immunotherapy for the CNS? Unfortunately, many children with CNS involvement were excluded from early trials of chimeric antigen receptor-T cell therapy and blinatumomab because of concerns regarding neurological toxicity. Real-world data collection has established that chimeric antigen receptor T cells show some promise in this area,[7] but larger studies are awaited.

Finally, delivering intrathecal therapy via lumbar puncture is a hit-or-miss game. Drug distribution is variable and position dependent; at least 10% of intrathecal treatments miss the subarachnoid space and previous traumatic lumbar puncture can result in fibrous tissue, further hampering CSF flow from the lumbar spine to the brain.[8] The observation by Tang et al that use of general anesthesia appears to improve CNS control may be because of more accurate drug delivery. Unfortunately, rapid adoption of this approach is tempered by the recent observation that repeated general anesthesia in children with ALL is associated with increased neurotoxicity.[9] Another approach is the use of Ommaya reservoirs, which abolish the need for general anesthesia, result in more predictable pharmacokinetics, and, perhaps surprisingly, were often preferred by patients and families.[8] However, concerns regarding infection rates and difficulties in removing the device at the end of treatment have led to a low acceptance by treating physicians. Another possibility is to use systemic drugs with good CNS penetration. Indeed, one of the key advantages of switching from prednisolone to dexamethasone is the improved CNS control; however, dexamethasone is not without its own neurological and systemic toxicity. Interestingly, an increased focus on targeted drug delivery for brain tumors in children is driving innovation in CNS-delivery devices and novel routes of administration such as intranasal chemotherapy. Sharing of learning between the 2 communities will be important as we move forward.[10]

The time has come for an increased focus on how, where, and when we deliver CNS-directed therapy. Children with ALL deserve to have this done "just right."

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THROMBOSIS AND HEMOSTASIS

Comment on Wang et al, page 344

Novel mechanism regulating tissue factor activity

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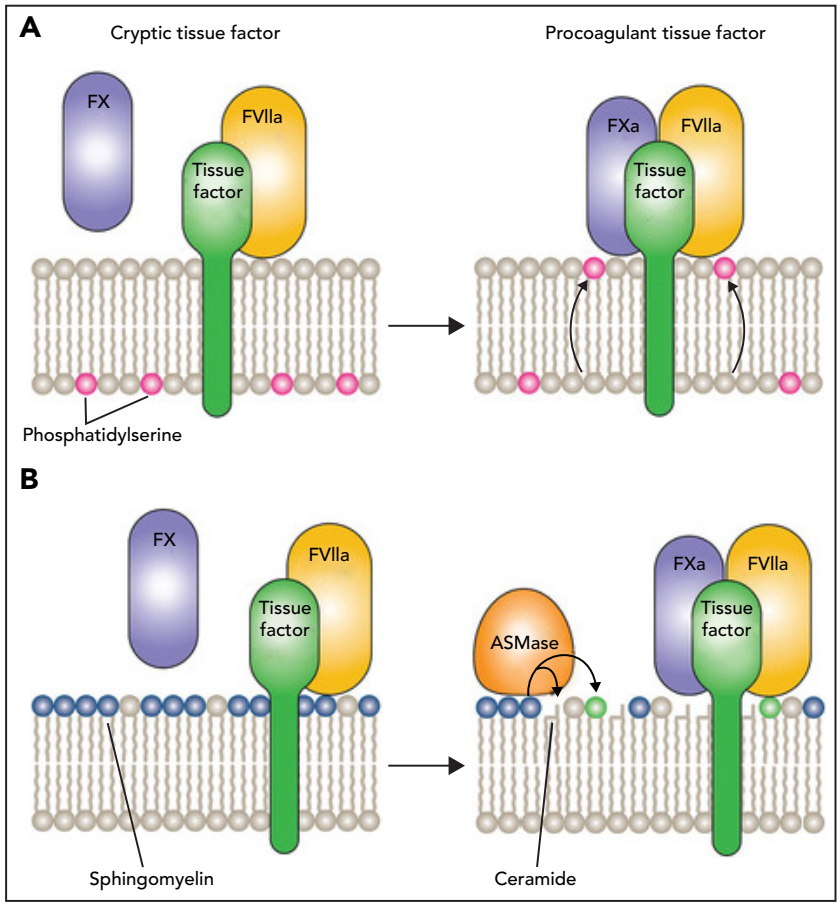
The phospholipid composition of plasma membranes and extracellular vesicles (EVs) affects coagulation in several ways. In this issue of *Blood*, Wang et al show that a phospholipid-degrading enzyme, acid sphingomyelinase (ASMase), translocates from lysosomes to the plasma membrane of macrophages upon infection with severe acute respiratory syndrome coronavirus 2 spike protein pseudovirus (SARS-CoV-2-SP-PV).[1]

Translocation of ASMase reduces membrane staining for sphingomyelin (SM), the phospholipid substrate of ASMase, confirming that the translocated enzyme remains active. Concurrently, an increase of tissue factor (TF) activity is observed, which is sensitive to pharmacological inhibition, gene silencing, and inhibition of virus entry, but insensitive to inhibition of phosphatidylserine (PS), another



Phospholipid-dependent mechanisms regulating TF procoagulant activity. (A) Resting cells have an asymmetric phospholipid distribution. PS is located in the inner leaflet of the membrane but translocates upon cell activation. In turn, FX binds to the membrane and is activated by the TF and FVIIa complex to FXa. (B) Upon infection with SARS-CoV-2-SP-PV, ASMase translocates from lysosomes to the plasma membrane. SM, the substrate of ASMase, is present in the outer leaflet and is hydrolyzed by SM into ceramide and phosphorylcholine, thereby triggering the TF procoagulant activity and activating FX to FXa. Professional illustration by Patrick Lane, ScEYEnce Studios.

phospholipid involved in regulating TF activity. Earlier, the authors described a similar involvement of ASMase in lipopolysaccharide- and cytokine-induced TF activation.[2]

TF is the transmembrane receptor for coagulation factor VII (FVII). TF is expressed by extravascular cells under physiological conditions, and TF is present on EVs in normal human body fluids such as saliva, urine, and milk.[3,4] TF is also found in the blood, where it is expressed by monocytes and endothelial cells during infection and inflammation. TF triggers coagulation by binding FVII, thereby promoting the formation of active FVII (FVIIa). Often, however, TF does not trigger coagulation, and several posttranslational mechanisms have been described regulating the procoagulant activity of "cryptic" TF, including homodimerization, glycosylation, oxidation of disulfide bonds, and exposure of PS.[5] Exposure of PS also provides a negatively charged membrane surface to which coagulation factors such as FVa can bind in the presence of calcium ions.

In resting cells, PS and other charged phospholipids are present in the inner leaflet of the phospholipid bilayer of the membrane, whereas uncharged phospholipids such as SM are present in the outer leaflet (see figure). This phospholipid asymmetry is actively maintained by phospholipid transporters; for example, upon platelet activation, a PS-specific transporter is inhibited, resulting in the exposure of PS on platelets and EVs.[6] Earlier, Del Conde et al showed that EVs bearing TF from human monocytic cells interact and fuse with activated platelets, thereby depositing TF in a PS-rich environment that promotes coagulation.[7] The Wang study now provides evidence for an SM-dependent but PS-independent mechanism regulating this TF procoagulant activity.

The present study does not address the mechanism underlying translocation of ASMase. When the translocated ASMase is enzymatically active, cell lysis may occur, as described previously for bacterial sphingomyelinases,[8] which may potentially give access to intracellular TF. Infection with pseudovirus is reported to result in the release of TF-exposing EVs. However, more evidence is needed as nanoparticle-tracking analysis detects all particles above the detection limit in suspension, not just EVs, and conventional flow cytometry is too insensitive to detect single EVs with a diameter of 150 nm and smaller.[9]

There is ample evidence that SM is attacked by sphingomyelinases secreted by pathogenic bacteria.[8] To which extent lysis of SM by intracellular (eg, virus induced) and extracellular (eg, bacteria-secreted) sphingomyelinases contributes to decryption (ie, activation) of TF and thrombosis in pathological conditions requires further investigation. Recently, Lacroix and coworkers reported that the TF activity of EVs in patients with severe COVID-19 is strongly increased compared with patients with septic shock, and this increased TF activity is associated with an increased thrombotic risk.[10]

Whether ASMase played a role in the decryption of TF activity observed by Lacroix and coworkers is unknown, but investigating the presence of bacterial (extracellular) sphingomyelinases and determining the lipid composition of EVs in patient blood may provide evidence for involvement of intracellular and extracellular sphingomyelinases in decryption of TF activity in vivo. If proven, this may offer new therapeutic targets against thrombosis.

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