Superactivated Platelets

Thrombus Regulators, Thrombin Generators, and Potential Clinical Targets

Marshall Mazepa, Maureane Hoffman, Dougald Monroe

Abstract—Platelets contribute to hemostasis by forming the platelet plug and then contributing to coagulation by providing a catalytic surface where thrombin generation occurs efficiently. This catalytic activity, known as the platelet procoagulant response, is being recognized as a nuanced response. This review examines platelets’ response to strong stimuli, which results in the formation of a platelet subpopulation (superactivated platelets) with several unique properties, including enhanced procoagulant activity. These platelets contribute uniquely to thrombus architecture and seem to have thrombus regulatory activity. Superactivated platelets’ role in diseases of thrombosis and hemostasis, as either potentiating or mitigating factors, is not currently known, but may be an important pharmacological target. (Arterioscler Thromb Vasc Biol. 2013;33:1747-1752.)

Key Words: activation ■ hemostasis ■ phosphatidylserine ■ platelet ■ procoagulant

A breach in the vasculature provokes a response in which platelets adhere, activate, aggregate, and serve as the catalytic surface for thrombin generation—this latter function is referred to as platelet procoagulant activity. With activation, one change that is key to the development of procoagulant activity is alteration of the membrane makeup, with exposure of phosphatidylserine (PS) on the outer leaflet of the membrane being of particular importance to driving the procoagulant reactions. Platelet activation also results in a conformational change in integrin αIIbβ3, which then binds fibrinogen, and contributes to the formation of platelet aggregates. Formerly, platelets were thought to be either in the resting state normally found in circulation, in which they neither support thrombin generation nor aggregate, or in an activated state, in which they aggregate and support thrombin generation. However, this notion is being challenged by the recognition of heterogeneity in the platelet response, and thus a binary view of platelet activation states is being replaced with a more nuanced one. Several investigators have identified a separate and discrete subpopulation of platelets with enhanced procoagulant activity after stimulation with strong agonists. They have attached several descriptive terms to this subpopulation on the basis of the context of their observations (eg, balloon platelets, procoagulant platelets, coated platelets, and sustained calcium-induced platelet morphology). Regardless of the context, the shared characteristics of this platelet subpopulation include bleb shape, sustained calcium influx, high surface PS exposure, inactivated integrin αIIbβ3, high levels of coagulation factors bound on the membrane surface, and ultimately higher procoagulant activity. We, therefore, think it likely that there is a single platelet subpopulation with enhanced procoagulant activity. In this review, this subpopulation of platelets with enhanced procoagulant activity will be referred to as superactivated platelets, a name chosen to be descriptive of the enhanced procoagulant function while avoiding terms already assigned by individual investigators. This review explores superactivated platelets’ (1) location and role within the thrombus architecture; (2) properties, including signaling pathways and procoagulant activity; and (3) potential clinical relevance in disorders of hemostasis and thrombosis and as a potential therapeutic target.

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Superactivated Platelets’ Niche in the Thrombus

In a hemostatic plug formed after a small injury, the platelet population is relatively uniform, with all platelets being activated, having similar characteristics and with fibrin associated with the platelets.1-3 By contrast, although activated platelets bound to fibrinogen can be found distributed throughout the thrombus, superactivated platelets are found in the minority, at sites of collagen exposure and scattered throughout the clot. This distribution of platelets into microdomains of activation states within the thrombus was described in experiments evaluating platelets’ response to collagen exposure (Figure).

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In these in vivo and in vitro studies, thrombi contained a majority of platelets in aggregates with activated integrin αIIbβ3 bound to fibrinogen, but some platelets were bleb shaped, had inactivated αIIbβ3, and high levels of PS exposure, and were found in strings or patches, with less platelet–platelet contact.4 Shi et al5 identified superactivated platelets on the basis of their enhanced PS exposure; annexin V only binds platelets with high levels of PS exposure (thus binding superactivated platelets only), whereas lactadherin binds platelets with both low and high PS exposure. In an in vivo experiment of thrombus formation, most aggregated platelets stained with lactadherin only, whereas superactivated platelets were labeled with annexin V, and were located primarily at the site of collagen exposure and thrombus initiation, and to a lesser degree were scattered throughout the thrombus.5 Furthermore, in infusion experiments, lactadherin inhibited both hemostasis and thrombosis, whereas, in contrast, infusion of annexin V did not inhibit hemostasis, but did inhibit thrombosis in a carotid artery occlusion thrombosis model.5

Instead of inhibiting the procoagulant activity of superactivated platelets, Jobe et al6 studied cyclophilin D (a regulator of the mitochondrial permeability transition pore [MPTP]) knockout mice, which lack the ability to form superactivated platelets. Interestingly, in their experiments using a carotid artery injury model, they observed a decreased time to occlusion in the cyclophilin D−/− mice indicating an exaggerated thrombosis response in the absence of superactivated platelets.6 These seemingly conflicting findings in carotid artery injury models could be explained by postulating a regulatory effect of superactivated platelets on thrombus growth. This regulatory effect would have been retained in the experiments in which superactivated platelets' high procoagulant activity was abolished by annexin V leading to inhibition of carotid artery occlusion, whereas thrombosis was augmented in the experiments in CypD−/− mice where both the regulatory and the higher procoagulant activity were abolished. Clot retraction force, a measure of thrombus stability, was also noted to be higher in the knockout mice.6 Regulatory effects of superactivated platelets on thrombus growth were also observed in in vitro perfusion studies of whole blood over collagen.7 Therefore, despite their location at the breach, in vivo studies thus far have yet to show that inhibition or complete loss of superactivated platelets leads to a defect in hemostasis, but it does seem that superactivated platelets may have an important role in regulating the thrombus growth, stability, and architecture.

Properties of Superactivated Platelets
Superactivated platelets can be identified in suspension by flow cytometry after stimulating platelets with strong agonists. Alberio et al8 described a platelet subpopulation termed COAT (COllagen And Thrombin) platelets after stimulation with both thrombin and with a collagen receptor agonist (fibrillar collagen, a collagen-related peptide, or the glycoprotein VI agonist convulxin). This population of platelets has high levels of factor V bound on their surface (Figure) and enhanced procoagulant activity, consistent with superactivated platelets.8 In experiments in which the FcRγ chain, a key component of

Figure. Left, Platelet subpopulations can be identified in suspension by flow cytometry after stimulation with strong agonists. Discrete populations are identified by degree of surface phosphatidylserine (PS) exposure or factor V (FV) binding, with superactivated platelets (red, bleb shaped) having high PS exposure and high FV binding, and activated platelets (blue, contacted and with pseudopods) having less PS exposure and less FV binding. Right, Platelet subpopulations as they contribute to thrombus architecture. Superactivated platelets are located primarily at the site of collagen (orange) exposure and then scattered at the surface of the thrombus. In contrast, activated platelets are found in aggregates and make up the majority of platelets in thrombi.
the glycoprotein VI receptor and collagen-induced platelet activation responses,8,10 was knocked out, there was near complete loss of the superactivated platelet population by flow cytometry and by procoagulant activity assays, indicating a key role for FcRγ chain to signal for the generation of superactivated platelets with dual agonist stimulation.11 In vitro flow experiments identified superactivated platelets after adhesion to collagen matrices as well, suggesting that collagen alone, perhaps in combination with shear stress, may be sufficient to produce this platelet phenotype.7 Similarly, Fager et al12 showed that high concentration of thrombin is sufficient to generate superactivated platelets in comparable proportions and with comparable procoagulant activity to platelets activated by thrombin and convulxin. Stimulation with thrombin coupled with an activator of the platelet Fc Receptor, FcγRIIIA, similarly generates a population of superactivated platelets (although it was also noted that this agonist combination consistently produced a smaller proportion of superactivated platelets than stimulation with collagen and thrombin).13 ADP release from activated platelets may also enhance development of superactivated platelets in the growing thrombus. ADP (via the P2Y12 receptor), in concert with thrombin stimulation, generates superactivated platelets and enhances platelet-dependent procoagulant activity.14 Taken together, the data suggest that several receptor-mediated platelet activation conditions can result in superactivated platelets, but either high concentrations of single agonists or dual agonists are required to generate superactivated platelets. Signaling via thrombin (likely via protease-activated receptor-1 and protease-activated receptor-4) and collagen (via glycoprotein VI) receptors play key roles in this process, and FcRγ chain is essential for glycoprotein VI-mediated superactivation of platelets.

After stimulation sufficient to generate superactivated platelets, a rapid and prolonged rise in intracellular Ca2+ occurs. In experiments of flowing platelets across collagen matrices, bound platelets varied in intracellular calcium, and correspondingly, those platelets with high levels of intracellular calcium developed the characteristics of superactivated platelets, including a blebbled, or balloon-shaped morphology, high levels of PS exposure, and enhanced capability for thrombin generation.7,15 When these experiments were performed in the presence of an intracellular Ca2+ chelator or prostaglandin E1 (raising cAMP), the morphological changes and subsequent procoagulant properties of the platelets were abolished.15 Although the mechanism for this degree of intracellular Ca2+ rise has not been completely determined, it is known that Ca2+ entry into platelets can be triggered by receptor-mediated calcium entry and store-operated calcium entry (SOCE). In vitro flow experiments identified superactivated platelets after adhesion to collagen matrices as well, suggesting that collagen alone, perhaps in combination with shear stress, may be sufficient to produce this platelet phenotype.7 Similarly, Fager et al12 showed that high concentration of thrombin is sufficient to generate superactivated platelets in comparable proportions and with comparable procoagulant activity to platelets activated by thrombin and convulxin. Stimulation with thrombin coupled with an activator of the platelet Fc Receptor, FcγRIIIA, similarly generates a population of superactivated platelets (although it was also noted that this agonist combination consistently produced a smaller proportion of superactivated platelets than stimulation with collagen and thrombin).13 ADP release from activated platelets may also enhance development of superactivated platelets in the growing thrombus. ADP (via the P2Y12 receptor), in concert with thrombin stimulation, generates superactivated platelets and enhances platelet-dependent procoagulant activity.14 Taken together, the data suggest that several receptor-mediated platelet activation conditions can result in superactivated platelets, but either high concentrations of single agonists or dual agonists are required to generate superactivated platelets. Signaling via thrombin (likely via protease-activated receptor-1 and protease-activated receptor-4) and collagen (via glycoprotein VI) receptors play key roles in this process, and FcRγ chain is essential for glycoprotein VI-mediated superactivation of platelets.

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The discovery of the STIM1–Orai1 pathway led to an important new understanding of the mechanism of how the release of intracellular stored calcium was paired with Ca2+ entry from outside the cell; after Ca2+ stores are depleted, STIM1, a Ca2+ sensor located on the endoplasmic reticulum membrane, interacts with Orai1.16 Then, Orai1, which is a Ca2+ channel located on the cell membrane, opens, allowing rapid influx of Ca2+.16 Interestingly, when examining the effect of both STIM1 and Orai1 in knockout mice, superactivated platelets did not form when blood was flowed over collagen; however, in the presence of thrombin, superactivated platelets did form, indicating that the Orai1–STIM1 pathway for Ca2+ entry likely accounts for one of several mechanisms for Ca2+ entry in superactivated platelets.17 Once the initial rise in cytosolic Ca2+ occurs, the process is reinforced with further loss of intracellular Ca2+ homeostasis. In superactivated platelets, elevated cytosolic Ca2+ leads to the formation of the MPTP and loss of the mitochondrial membrane potential, which further exacerbates the rise in Ca2+.18 Jobe et al19 demonstrated that cyclophilin D, a key regulator of the MPTP, is essential for superactivated platelet formation, and others have shown that pharmacological inhibition of the MPTP inhibited platelet superactivation.18 Formulation of the MPTP leads to a rise in intracellular calcium and calpain activation, resulting in cleavage of phospholipases and membrane and cytoskeletal proteins, contributing to the shape changes and blebbing seen in superactivated platelets.7

Exactly how these 2 mechanisms of Ca2+ entry contribute to the sustained rise in cytosolic Ca2+ in superactivated platelets has not been defined, but they may act synergistically and may also involve receptor-mediated calcium entry. These ligand-activated signaling mechanisms (formation of the MPTP, loss of Ca2+ homeostasis, membrane blebbing, etc) seem to have been adapted from pathways involved in necrosis in nucleated cells. Interestingly, there also seem to be a second, independent pathway for generation of superactivated platelets adapted from apoptosis-like signaling, which is Bak/Bax and caspase dependent.19 Experiments in which platelets were exposed to ABT-737 (a BH3 mimetic) lead to the formation of superactivated platelets without other evidence of platelet activation, including formation of the MPTP.19 When other BH3-mimetics (gossypol and methoxy-antimycin) were investigated, these compounds did not generate superactivated platelets unless platelets were costimulated with thrombin, and in these platelets MPTP formation occurred.20 Furthermore, these BH3-mimetics also enhanced superactivated platelet formation when costimulated with convulxin and thrombin,20 suggesting that although the apoptosis-like and necrosis-like pathways may act independently, they may also act synergistically.

After sustained Ca2+ entry, superactivated platelets take on their final phenotype with enhanced PS exposure and procoagulant activity and inactivated αIIBβ3. Because activation of αIIBβ3 is a hallmark feature of platelet activation, the observation that the αIIBβ3 complex is transiently activated and then inactivated (without being cleaved from the platelet surface) is both surprising and remains without a clear mechanism. Munnek et al21 showed that, despite αIIBβ3 being blocked, platelets still exposed PS after stimulation with strong agonists, indicating that αIIBβ3 does not regulate PS exposure, and furthermore that sustained tyrosine phosphorylation led to integrin inactivation and PS exposure. Kulkarni and Jackson22 showed that calpains and factor XIII serve to regulate αIIBβ3 adhesion; however, others have shown that factor XIII is not required to form superactivated platelets.18 Although αIIBβ3 inactivation and PS exposure are consistently observed after Ca2+ entry, the mechanism for this loss of adhesive property and gain of procoagulant activity remains incompletely understood.

Finally, platelet membranes take on enhanced PS exposure and procoagulant activity. Before identification of superactivated platelets as a platelet subpopulation, it was observed that higher levels of PS exposure occurred in platelets
after costimulation with convulxin and thrombin compared with single agonists (Figure)\(^{21}\). A correlation between the amount of PS exposed and the ability for the lipid surface to promote thrombin generation was also observed, and that the procoagulant activity of these membranes is lost with the treatment with phospholipases that cleaves the head groups of PS\(^{22,23}\). In a canine model of Scott syndrome (in which cell membranes lack the ability to expose PS), an impaired ability to generate superactivated platelets was observed\(^{24}\). Because superactivated platelets expose more PS, which is the binding site for factor Va (FVa) of the prothrombinase complex,\(^{25}\) higher thrombin generation by these platelets can be anticipated. However, there may be more than higher levels of PS exposure to account for enhanced binding of FVa to the membrane surface. It was noted by Fager et al\(^{12}\) that when superactivated platelets were washed, a significant amount of platelet-derived FVa could not be removed from the platelet surface, leading the authors to conclude that FVa was tethered to the membrane surface by the heavy chain of the cofactor that was bound to the surface, potentially through a glycosylphosphatidylinositol anchor. An alternative hypothesis was proposed by Dale et al\(^{26}\), which was based on the observation that not only was FVa bound on the platelets’ surface but there was retention of other \(\alpha\)-granule contents as well, including von Willebrand factor, fibrinogen, and thrombospondin, and therefore described the superactivated platelets as coated. The finding that fibrinogen was bound to the platelet surface, although \(\alpha_{\text{m}}\beta_3\) was not activated, suggested that the contents of the \(\alpha\) granules were retained on platelets by an alternative mechanism\(^{26}\). This conclusion was strengthened by the observation that PAC-1, an antibody to the activated \(\alpha_{\text{m}}\beta_3\) with much higher affinity for activated \(\alpha_{\text{m}}\beta_3\) than fibrinogen, was unable to displace fibrinogen from the platelet surface\(^{26}\). It was noted that the bound molecules shared the characteristic of being potential substrates for transglutamination and their work ultimately led to a model of superactivated platelets in which \(\alpha\)-granule contents are coupled and linked in a matrix via serotonin as the results of an unknown transglutaminase\(^{26}\). Beyond the binding of \(\alpha\)-granule contents, superactivated platelets have also been found to increase 4- to 6-fold in expression of adhesive proteins integrin \(\beta_3\), integrin \(\alpha_{\text{m}}\), and GPIb\(_\alpha\), suggesting a possible compensatory mechanism for incorporation in the clot given the inactivation of \(\alpha_{\text{m}}\beta_3\)\(^{12}\). In addition to FV, work from several investigators has demonstrated that factor VIII, factor IX, and factor X are also bound in increased quantities on the platelet surface\(^{27,28}\).

Alberio et al\(^{15}\) first described the enhanced procoagulant activity of platelets using a thrombin generation assay which included fixed concentrations of FVAs and factor Xa, prothrombin, and a chromogenic thrombin substrate added to platelets activated by thrombin and convulxin. The finding of higher thrombin generation by these platelets has been verified by other groups\(^{5,28}\). A cell-based model of coagulation was used to investigate the procoagulant activity of superactivated platelets, in which convulxin was added to the system in addition to tissue factor to initiate coagulation and platelet activation, which may more closely model superactivation of platelets that occurs at the site of collagen exposure in vivo\(^{28}\). Thrombin generation was increased in this model, and thrombin was generated more rapidly with a higher peak than in platelets activated by tissue factor alone\(^{28}\). Interestingly, an increase in both factor Xa and thrombin activity occurred in parallel at low concentrations of convulxin, but a disproportionate rise in factor Xa activity over thrombin activity occurred at high maximal concentrations of convulxin\(^{28}\). These studies of the procoagulant activity of superactivated platelets reveal that while thrombin generation is increased, the platelet surface also regulates thrombin generation by an unknown mechanism. One regulator of the procoagulant response, tissue factor pathway inhibitor, has been shown to be present on the surface of superactivated platelets to the exclusion of activated platelets\(^{29}\). In a mouse knockout model, tissue factor pathway inhibitor\(^{−/−}\) mice developed larger thrombi in response to a standardized injury\(^{30}\). In comparison with wild-type mice, the knockout mice had similarly sized thrombi in the early phase of thrombus formation, but the knockout mice continued to accumulate thrombus in the late phase, whereas thrombus size was declining in the wild-type mice\(^{30}\).

### Clinical Studies and Therapeutic Potential of Superactivated Platelets

Even when maximally stimulated with strong agonists in vitro, only a proportion of platelets take on the superactivated phenotype, whereas others simply become activated. Therefore, a given platelet may or may not have the capacity to become a superactivated platelet, a fate which cannot be determined before stimulation. It has been observed that there are differences between individuals’ platelets’ capacity to become superactivated after maximal stimulation, which here we have termed superactivated platelet potential (SPP). Data about the distribution of SPP are sparse; however, Dale found 30% of platelets became superactivated on average (range of 15%–50%) among healthy volunteers and noted that a given individual’s SPP seems to be conserved over time\(^{31}\). The threshold for platelets to become superactivated also seems to follow a dose–response relationship that rises with increasing convulxin concentrations in experiments using the combination of thrombin and convulxin, and plateaus at the subject’s SPP\(^{28}\). Several investigators have noted that young (reticulated) platelets have a higher probability of becoming a superactivated platelet and suggest a role of platelet aging in the capacity for superactivation; however, the mechanism linking platelet aging and capacity to become superactivated has not been determined\(^{4,12}\).

Although the characteristics of superactivated platelets have been described both in vitro and in vivo, individual differences in SPP in both healthy and disease states lack robust clinical data. Some associations between cerebrovascular disease risk have been made, including hemorrhagic transformation and spontaneous intracranial hemorrhage in patients with low SPP\(^{32,34}\). Conversely high SPP has been correlated with transient ischemic attack and ischemic stroke\(^{35,36}\). There are limited data, as well, in severe hemophilia that suggest an association between a milder hemorrhagic phenotype and higher SPP\(^{37}\). Clearly, more clinical data linking hemorrhagic and thrombotic phenotypes are needed to draw conclusions about how individual differences in SPP contribute to disease states.
The potential role for manipulation of SPP will clearly rely first on good clinical evidence about these platelets’ role in disease, but could offer an exciting therapeutic target. Elevated SPP has been correlated with arterial thrombotic disease, and if SPP can be identified as an independent risk factor for arterial thrombotic disease, drugs that specifically inhibit the mechanisms for platelet superactivation, such as formation of the MPTP, or the proteins involved in Ca\(^{2+}\) entry, such as SOCE, would be potential new therapies for the treatment or prevention of arterial thrombosis. Cyclosporine and coenzyme Q are known to be inhibitors of the MPTP and have been shown in vitro to inhibit formation of superactivated platelets; thus, both of these drugs are potential candidates for therapeutically and specifically downregulating superactivated platelet formation in vivo. Furthermore, the identification of Orai1 as a key mediator of SOCE has led to the first in vitro studies of pharmacological inhibition of platelet superactivation and the possible role of these compounds in downregulating SPP in cerebral artery disease.

Conversely, if low SPP is shown to either cause a hemorrhagic phenotype or modulate a hemorrhagic phenotype, upregulating or potentiating SPP would have therapeutic potential. In vitro studies of the bypassing agent recombinant factor VIIa (rFVIIa) show that rFVIIa preferentially binds to superactivated platelets. Therefore, one could hypothesize that SPP may predict individual differences in hemostatic response to the drug, which is currently poorly understood. The mechanism of the hemostatic effect of rFVIIa, while still debated, seems to have convincing evidence for a tissue factor–independent mechanism that relies on binding of rFVIIa to the platelet surface, where Xa and thrombin can be generated. Similar preferential binding to superactivated platelets was also found in studies of vatreptacog alfa (formerly NN1731), a rFVIIa variant with enhanced proteolytic activity. If effective hemostasis with rFVIIa and rFVIIa variants relies on both drug dose and the individual’s SPP, then SPP would be an important component of predicting response to the drug and a potential therapeutic target for modulating these drugs’ hemostatic effect. There are no currently identified therapies that potentiate the formation of the MPTP or SOCE; however, these would be logical targets for increasing SPP. The apoptosis-inducing agents (BH3-mimetics, currently under investigation for hematologic malignancies), ABT-737 and ABT-263 (Navitoclax), have provided some insight into the potential for manipulating the SPP in patients. These agents could potentially increase SPP by 2 mechanisms: (1) directly inducing PS exposure and enhanced procoagulant activity; and (2) selectively affecting older platelets (reticulated platelets are relatively resistant to the drugs’ effect), leading to a larger proportion of circulating young platelets. Unfortunately, the effect of these drugs on SPP was not measured, and furthermore, these drugs also seem to induce thrombocytopenia and platelet dysfunction. The authors acknowledged the potential for enhanced hemostasis or even thrombosis by agents that directly induce PS exposure, but instead found platelet dysfunction and prolonged tail bleeding times in mice treated with the drugs. They speculated that because platelets are in circulation when PS is exposed (rather than at a site of thrombus formation), this likely then leads to clearance of these platelets and leaves behind dysfunctional platelets (a dose-dependent effect of these drugs). Instead, if SPP could be more specifically enhanced by either lowering the threshold for superactivation (such as by potentiating formation of the MPTP or enhancing SOCE) or alternatively by increasing the proportion of younger platelets (such as with TPO-mimetic drugs), then platelets would remain in circulation and have an enhanced response to a hemostatic challenge under conditions that naturally lead to platelet superactivation.

Conclusions

The roles of platelets in hemostasis and thrombosis seem to be more nuanced than simple formation of the platelet plug and provision of a catalytic surface for thrombin generation. A strong signal for activation, such as dual agonist activation or a high concentration of thrombin or collagen, leads to the development of a subpopulation of platelets with enhanced procoagulant activity (while integrin \(\alpha_{IIb}\beta_3\) is inactivated), which here we have termed superactivated platelets. In vivo, superactivated platelets are primarily localized to sites of collagen exposure and in strings along the clot surface. The formation of this specialized platelet subpopulation also has the potential to modulate clot architecture and regulate thrombus growth. After sufficient stimulation to create the superactivated state, high and sustained Ca\(^{2+}\) entry, with contributions from the formation of the MPTP and SOCE, leads to morphological changes in the platelet and enhanced PS exposure. On the superactivated platelet surface there is enhanced coagulation factor binding and thrombin generation. The role of superactivated platelets in diseases of thrombosis and hemostasis is still to be determined, but modulation of an individual’s SPP, possibly by targeting Ca\(^{2+}\) entry or balance young and older platelets, may have important therapeutic implications.

Disclosures

None.

References


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