The matching of oxygen supply with oxygen demand in metabolically active tissue is a fundamental physiological process. Although a number of theories to explain this critical function have been proposed, none have been either universally accepted or fully tested in the intact microcirculation. Any attempt to comprehend the mechanism(s) by which oxygen delivery and metabolic need are matched must, by necessity, be based on the combination of experimental observations and theoretical models. In 1919, August Krogh, in conjunction with a mathematician colleague, K. Erlang, proposed the first oxygen transport model based on the assumption that each capillary is the sole supplier to a cylindrical region of tissue surrounding it (the Krogh cylinder) (35). Under this simple model, oxygen is assumed to diffuse in the radial direction with a uniform diffusivity and to be consumed in the tissue at a uniform constant rate. FIGURE 1A, the current view is that the microcirculation supplies oxygen to tissue using multiple vessel types that are functionally connected through both convective oxygen flow (blood flow) and diffusive oxygen transfer (23, 37). Inherent in this complexity is the need for a mechanism to direct the convective oxygen flow to regions of the tissue where oxygen is required to satisfy metabolic needs. This directed distribution of peripheral blood flow is analogous to the mechanisms inherent in the pulmonary circulation that direct blood flow to those regions of the lung that are well ventilated (96).

One might expect that mechanisms associated with blood flow regulation such as wall shear stress and pressure (myogenic tone) would be sufficient to properly distribute blood flow and, consequently, O2 supply within the arteriolar tree. However, at the microvascular level, total blood flow may not accurately reflect local O2 supply. The convective distribution of oxygen within the arteriolar tree is impacted by the diffusional loss of oxygen to nearby erythrocytes in microvessels. Most of the diffusional loss of oxygen in the arteriole is from erythrocytes near the wall of the vessel, that is, at the edge of the cell free plasma layer. Thus these cells have a lower O2 saturation than those nearer to the center of the vessel (9, 25). At vessel bifurcations, this uneven distribution affects convective oxygen supply to a greater or lesser extent depending on the relative flow in the downstream branches. For example, if blood flow into a downstream branch is...
very low, only plasma and the erythrocytes with lower \( O_2 \) will be skimmed into this branch (FIGURE 2).

As flow into the side branch increases as a result of downstream vasodilatation, flow into that branch will be derived from a larger cross-sectional region of the lumen of the upstream vessel, allowing blood with higher hematocrit and erythrocytes with higher \( O_2 \) saturation to enter that branch. Thus an increase in \( O_2 \) demand in one region of tissue would induce a redistribution of erythrocytes (\( O_2 \) delivery) not solely described by the simple redistribution of blood flow. In light of these complexities, it becomes abundantly clear that the simplistic Krogh approach to oxygen delivery will not adequately explain the complex interactions apparent in the intact microvasculature. Therefore, a local control mechanism must exist that is capable of sensing \( O_2 \) need and adjusting flow within the small arterioles feeding the capillary network.

Numerous studies have focused on the blood vessels themselves or on discrete regions within the tissue as the sensor of \( O_2 \) requirements in a tissue (18, 23, 26, 27, 43, 49, 64, 72). However, the exquisite accuracy in matching \( O_2 \) supply with \( O_2 \) demand in skeletal muscle in vivo mandates a control system that is both more sensitive and responsive than those previously described. The system required must be able to sense localized need and to initiate an integrated response that results in appropriate increases in local oxygen supply. Could this controller be as simple as the erythrocyte itself?

A Case for the Erythrocyte as a 
Variable Controller

Fundamental to any system that regulates the delivery of appropriate amounts of oxygen to meet changing tissue needs is the requirement that the oxygen need be detected, quantified, and subsequently coupled to a mechanism that will appropriately alter blood flow (\( O_2 \) delivery). Such a mechanism requires interplay among tissue gas exchange, tissue metabolism, and vascular smooth muscle function. Moreover, the process must be regulated within a narrow range (45). The vascular endothelium participates in controlling vascular caliber (7, 32, 54, 94) and coordinating the response to local, diverse stimuli initiated within the tissue (13, 17, 44, 77, 78, 94). It would be reasonable to suggest that one or more components of the oxygen transport pathway communicate directly or indirectly with the endothelium to appropriately alter microvascular perfusion. In 1993, Stein and Ellsworth suggested (80) that, in severe hypoxia, the oxygen content of the blood supplying the tissue was more important than its oxygen tension for the maintenance of oxygen supply in hamster skeletal muscle. Oxygen content (\( O_2 \) saturation), a reflection of the extent of binding of oxygen to hemoglobin within the erythrocyte, is related to oxygen tension by the characteristic oxyhemoglobin dissociation curve. Oxygen tension determines the diffusional transfer of oxygen from the erythrocyte to the tissue. Thus, if oxygen content rather than oxygen tension were the important factor in regulating oxygen delivery, then the erythrocyte itself would assume a central role in the process since it contains the only component of the oxygen transport pathway that is directly influenced by oxygen content, hemoglobin. The oxygen content of the erythrocyte as it traverses a tissue is directly linked to the level of oxygen utilization of that tissue (FIGURE 3). Therefore, if the erythrocyte itself were able to sense oxygen need and affect an alteration in vascular caliber leading to appropriate changes in blood flow, this property of the erythrocyte would provide an efficient means of matching oxygen delivery (blood flow) with metabolic need, eliminating the requirement for a diverse network of sensing sites throughout the vasculature. It is intriguing to think that the mobile erythrocyte, whose level of oxygen content at a particular point in a tissue is directly linked to the level of oxygen utilization by that tissue, could itself augment blood flow and oxygen delivery whenever and whenever the need might arise.

The establishment that the erythrocyte, the major supplier of oxygen, also functions as a sensor of oxygen requirements to local vascular beds was made possible by studies on the 

Vascular Controller

Strong evidence of ATP from erythrocyte energy metabolism and phosphodiesterase (85) activation to influence erythrocyte membrane deformation (85) has been demonstrated in these cells to mediate the response to erythrocyte membrane deformation (85).

Inhibition of ATP release from erythrocytes, such as a drop in oxygen tension (84), is an important factor in regulating oxygen supply to tissues. The finding that these effects are mediated by a signaling cascade involving the pertussis toxin-sensitive G proteins G(s) and G(i) (86) suggests that these proteins are 

A Proposal for a New 
Oxygen Transport Pathway from Erythrocytes to Tissue

A Case for the Erythrocyte as a Variable Controller

Fundamental to any system that regulates the delivery of appropriate amounts of oxygen to meet changing tissue needs is the requirement that the oxygen need be detected, quantified, and subsequently coupled to a mechanism that will appropriately alter blood flow (\( O_2 \) delivery). Such a mechanism requires interplay among tissue gas exchange, tissue metabolism, and vascular smooth muscle function. Moreover, the process must be regulated within a narrow range (45). The vascular endothelium participates in controlling vascular caliber (7, 32, 54, 94) and coordinating the response to local, diverse stimuli initiated within the tissue (13, 17, 44, 77, 78, 94). It would be reasonable to suggest that one or more components of the oxygen transport pathway communicate directly or indirectly with the endothelium to appropriately alter microvascular perfusion. In 1993, Stein and Ellsworth suggested (80) that, in severe hypoxia, the oxygen content of the blood supplying the tissue was more important than its oxygen tension for the maintenance of oxygen supply in hamster skeletal muscle. Oxygen content (\( O_2 \) saturation), a reflection of the extent of binding of oxygen to hemoglobin within the erythrocyte, is related to oxygen tension by the characteristic oxyhemoglobin dissociation curve. Oxygen tension determines the diffusional transfer of oxygen from the erythrocyte to the tissue. Thus, if oxygen content rather than oxygen tension were the important factor in regulating oxygen delivery, then the erythrocyte itself would assume a central role in the process since it contains the only component of the oxygen transport pathway that is directly influenced by oxygen content, hemoglobin. The oxygen content of the erythrocyte as it traverses a tissue is directly linked to the level of oxygen utilization of that tissue (FIGURE 3). Therefore, if the erythrocyte itself were able to sense oxygen need and affect an alteration in vascular caliber leading to appropriate changes in blood flow, this property of the erythrocyte would provide an efficient means of matching oxygen delivery (blood flow) with metabolic need, eliminating the requirement for a diverse network of sensing sites throughout the vasculature. It is intriguing to think that the mobile erythrocyte, whose level of oxygen content at a particular point in a tissue is directly linked to the level of oxygen utilization by that tissue, could itself augment blood flow and oxygen delivery whenever and whenever the need might arise.

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genes localized to the Hb supply. Could this be an exonic event?

As a result, the delivery of oxygen to the tissue changes in response to a drop in oxygen saturation levels. Recent studies have demonstrated that ATP efflux is linearly related to reductions in oxygen tension, suggesting that the conformational change of hemoglobin, as it desaturates during a fall in oxygen levels, elicits the release of ATP. This conclusion was further supported by an observed inhibition of ATP release on exposure of the erythrocytes to carbon monoxide, which would prevent the conformational change of hemoglobin in response to a drop in oxygen tension. The importance of hemoglobin oxygen saturation in ATP release was later confirmed in human studies by González-Alonso and his collaborators (38, 39, 75). If release of ATP from erythrocytes is directly linked to a physiological stimulus, such as a decrease in oxygen saturation, then there must be a signal transduction pathway in the erythrocyte connecting the stimulus to the release.

A Proposed Signal Transduction Pathway for ATP Release from Erythrocytes

Strong evidence exists supporting the controlled release of ATP from erythrocytes in response to both physiological and pharmacological stimuli. Physiologically, erythrocytes release ATP in response to mechanical deformation (82, 83, 86), as would be encountered when these cells traverse the microcirculation, as well as in response to exposure to reduced oxygen tension (5, 15, 22, 50, 70). In both cases, the amount of ATP released is influenced by the magnitude of the stimulus. In addition to physiological stimuli, erythrocytes release ATP in response to receptor-mediated activation of erythrocyte membrane-bound β-adrenergic receptors or prostanycin receptors in a concentration-dependent manner (68, 80).

The finding that ATP is released in a controlled fashion suggests that erythrocytes possess a mechanism that directly links the stimulus to release of ATP. Over the past several years, Sprague’s group has delineated a signaling pathway for ATP release from erythrocytes (FIGURE 3). This pathway includes the heterotrimeric G proteins Gs and Gi (68, 69, 70, 81), adenylyl cyclase (AC) (86), protein kinase A (86), and the cystic fibrosis transmembrane conductance regulator (CFTR) (83). Studies have clearly shown that activation of Gs-coupled β-adrenergic receptors and prostanycin (IP) receptors in erythrocytes results in concentration-dependent increases in cAMP and ATP release from erythrocytes (6, 68, 80). However, Olearczyk et al. demonstrated that the G protein that is activated when erythrocytes are exposed to deformation or reduced oxygen requirements and affector of changes in oxygen supply would provide an important level of precision to local vascular control. How could such a small, anucleated bag of hemoglobin accomplish this task? Erythrocytes contain millimolar quantities of adenosine 5’ triphosphate (ATP) (65), which is produced primarily by membrane-bound glycolytic pathways. In 1992, Bregfeld and Forrester reported that human erythrocytes release ATP in response to the combined effects of hypoxia and hypercapnia (5). More recent studies have shown that exposure to reduced oxygen tension (~35 Torr) alone is sufficient to stimulate ATP release from erythrocytes of hamsters (24), rabbits (85), rats (50), and humans (84). Although these studies have examined ATP release in response to reductions in oxygen tension, Jagger et al. (50), demonstrated that ATP efflux was linearly related to hemoglobin O₂ saturation, suggesting that the conformational change of hemoglobin, as it desaturates during a fall in oxygen levels, elicits the release of ATP. This conclusion was further supported by an observed inhibition of ATP release on exposure of the erythrocytes to carbon monoxide, which would prevent the conformational change of hemoglobin in response to a drop in oxygen tension (50). The importance of hemoglobin oxygen saturation in ATP release was later confirmed in human studies by González-Alonso and his collaborators (38, 39, 75). If release of ATP from erythrocytes is directly linked to a physiological stimulus, such as a decrease in oxygen saturation, then there must be a signal transduction pathway in the erythrocyte connecting the stimulus to the release.

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oxygen tension is not Gs but rather Gi (68, 70). The direct activation of Gi with the wasp venom extract mastoparan 7 stimulates increases in cAMP and ATP release from erythrocytes (68, 70). Although the α subunit of Gi is well known to inhibit the activity of some AC isoforms, its associated β subunits, specifically subunits 1 through 4 (4, 28, 33, 60, 89, 91), have been shown to activate AC isoforms II, IV, and VII. Importantly, Giα, β subunits 1 through 4, and AC II are all components of human erythrocyte membranes (81). A central role for Gi in the pathway for ATP release from erythrocytes in response to reduced oxygen tension was demonstrated by the finding that incubation of erythrocytes with pertussis toxin, which binds to Gi preventing its dissociation into the component subunits, prevented ATP release in response to this physiological stimulus (70). Although Gi activation is clearly involved in ATP release from erythrocytes exposed to reduced oxygen tension, the mechanism that directly couples the decrease in oxygen saturation of the hemoglobin molecule to the activation of Gi remains under investigation. One possibility is that the conformational change in the hemoglobin molecules bound to the erythrocyte membrane directly activates Gi or some other aspect of the release pathway (50).

Vascular Control by ATP

If we accept that ATP is released from erythrocytes in a controlled manner as they perfuse a region of tissue with a low SO2, then this ATP must initiate a conducted vasodilation that extends beyond the site of initiation for there to be an effective increase in vascular perfusion (O2 delivery) (56) (FIGURE 3). Using arterioles in the intact hamster cheek pouch retractor muscle, McCullough et al. (59) demonstrated a dose-dependent conducted vasodilator response to the intraluminal ATP, which would be most consistent with ATP as the vasoactive mediator of such a response (50).

When ATP is released from erythrocytes in the microcirculation, it can interact with endothelial purinergic receptors, resulting in the production of mediators that initiate vasodilation. This vasodilation is conducted in a retrograde fashion, resulting in increased blood flow (oxygen supply) to areas of increased oxygen demand. Gi, heterotrimeric G protein; ATP, adenosine triphosphate; cAMP, 3’5’-adenosine monophosphate; PKA, protein kinase A; CFTR, cystic fibrosis transmembrane conductance regulator; ?, an as yet unidentified conduit for ATP release; PR, purinergic receptors; +, stimulation; endo, endothelium; SMC, smooth muscle cell.
The increase in oxygen tension at the vessel tip initiates a conducted response in the arterioles within fractions of a second after entering the hypoxic vessel (15). Although not all studies have detected the drop in oxygen tension associated with neuronal activation (79), there is increasing evidence suggesting that, in the brain, ATP released from erythrocytes could contribute to a rapid initial increase in blood flow in response to neuronal activity. When ATP is released into the vascular lumen, it can interact with receptors present on the endothelium that can elicit both endothelium-dependent and smooth muscle cell-dependent vasoactive responses, which would be conducted along the vasculature. Endothelial cells possess purinergic receptors that, when activated, stimulate the synthesis and release of several vaso dilators. These vaso dilators include nitric oxide (NO) as well as products of arachidonic acid metabolism. Although the receptor activated and the mediator released may vary in different tissues, the receptors present in the cerebral circulation have been particularly well characterized. In the cerebral circulation, ATP and its related breakdown products, including adenosine, are vasoactive mediators. Forrester et al. found that intraluminal ATP was a potent vaso dilator in the baboon cerebral circulation (28) and that topically applied ATP dilated cat pial vessels at a much lower concentration than adenosine (30). These reports led to the hypothesis that ATP, or a closely related breakdown product rather than adenosine, is the vasoactive purine in the cerebral circulation (38). Although in the cerebral microcirculation ATP, ADP, and adenosine are all potent vaso dilators (14, 53), only ATP and ADP consistently caused conducted vasomotor responses (14, 53). Since at equimolar concentrations ADP was slightly less potent in causing dilatory local and conducted responses (53) than ATP, it is likely that ATP may be the primary agonist. This corresponds with observations by Ikeuchi and Nishizaki where, in brain artery endothelial cells, ATP caused stronger potassium currents than ADP, whereas AMP had no effect (48).

Numerous studies have attempted to link neuronal activation, local oxygen tension, and cerebral blood flow. Neuronal activation can lead to a small, but significant, drop in local oxygen tension, which is followed by an increase in local blood flow (2). This neuronal activation-induced decrease in oxygen tension could elicit ATP release from erythrocytes, resulting in an increase in blood flow. Indeed, ATP is released from erythrocytes perfusing isolated cerebral arterioles within fractions of a second after entering the hypoxic vessel (15). Although not all studies have detected the drop in oxygen tension associated with neuronal activation (79), there is increasing evidence suggesting that, in the brain, ATP released from erythrocytes could contribute to a rapid initial increase in blood flow in response to neuronal activity. ATP released from erythrocytes is known to activate specific P2 purinergic receptors on the vascular endothelium. Although it is simpler to consider two distinct classes of these P2 receptors, P2x and P2y, more recent evidence indicates that the mammalian P2x and P2y receptors are actually families of receptors consisting of seven P2x receptors (P2x1–7) and eight P2y receptors (P2y1–12) (1, 34). Studies in cerebral microvessels have delineated the specific receptors present and the vasoactive response to their stimulation. In isolated nonpreserved pial arterioles, Lewis et al. concluded that P2x7 receptors and P2y2-like receptors are responsible for the observed vessel constriction (57). In isolated and pressurized rat penetrating arterioles, Horiuchi et al. reported that ATP constricts the vessels transiently via smooth muscle P2x7 receptors and dilates the vessels via endothelial P2y2 (47). Similarly, You et al. found that, in larger size cerebral arterioles, dilation to intraluminal ATP results from P2y1 stimulation (98). These receptors were confirmed to exist on hamster skeletal muscle arterioles (unpublished observations).

Regardless of the receptor that is activated, ATP-induced vasodilation is the result of the synthesis and activity of endothelium-derived relaxing factors. In skeletal muscle, McCulloch (59) and Collins (10) each observed that the conducted vasodilation to intraluminal ATP was eliminated following administration of a NO synthase inhibitor implicating NO as an important vascular mediator in these vessels. In addition, in large cerebral arterioles, endothelial P2y2-specific stimulation was shown to release NO as well as a non-NO, non-cyclooxygenase-dependent factor (97, 98). Similarly, it was reported that in cerebral arterioles, endothelial P2y2-specific stimulation releases both NO and a non-NO, non-cyclooxygenase-dependent factor, whereas P2x7-specific stimulation releases only the
non-NO, non-cyclooxygenase-dependent factor (46), possibly a cytochrome P450 monooxygenase product such as epoxyeicosanoids (EETs) (16). EETs can activate calcium-sensitive potassium channels, resulting in hyperpolarization (8, 31). In brain artery endothelial cells, purines induced strong potassium currents with ATP > ADP > AMP (48). In cerebral arteries, the dilution of ATP was preceded by hyperpolarization, and the dilution to ATP depended on large conductance BKCa and intermediate conductance IKCa calcium-sensitive potassium channels but not small conductance IKCa channels (16). Thus the mediator released in response to activation of endothelial purinergic receptors by ATP will depend on the identity of the specific receptor activated and the signaling pathway present in a particular vessel (FIGURE 3).

Although there is significant evidence to suggest that NO is a regulator of vascular perfusion, controversy remains as to its source and mechanism of action. In 1996, Stamler and colleagues (51) proposed that the erythrocyte was responsible for regulating O2 delivery to tissues, especially in response to hypoxia. This concept is supported by evidence that deoxyhemoglobin acts as a nitrite reductase, converting nitrite to NO, and hence making it possible that the erythrocyte is a source of NO under physiological conditions (35, 36, 71, 74). Recent work from the laboratories of Gladwin and Patel has provided evidence that deoxyhemoglobin acts as a nitrite reductase, converting nitrite to NO, and hence making it possible that the erythrocyte is a source of NO under physiological conditions (35, 36, 71, 74).

Control of ATP Release In Vivo: Feedback Mechanisms

Although ATP can stimulate the synthesis and release of multiple endothelium-derived vasodilators, ATP-induced increases in NO are important in both the cerebral and skeletal muscle microcirculations. It is important to recognize that NO synthesized in endothelial cells diffuses not only to vascular smooth muscle, where it stimulates vasodilation, but is also released into the vascular lumen. When erythrocytes enter a microcirculation in which large amounts of NO are already present, additional ATP release would be unnecessary. Indeed, NO was shown to attenuate agonist-induced ATP release from erythrocytes in a negative-feedback fashion.
In these studies, incubation of erythrocytes with the NO donor nitroprusside results in inhibition of ATP release from rabbit and human erythrocytes exposed to decreased oxygen tension (67). It has also been proposed that ADP, the first degradation product of ATP, can inhibit ATP release from erythrocytes (95). Under this hypothesis, ATP released from the erythrocytes in response to physiological stimuli is metabolized by ecto-enzymes, resulting in the generation of ADP. ADP can then activate P2Y1 receptors present on erythrocytes resulting in decreases in intracellular cAMP and derived vasodilator released from the endothelium in response to ATP (NO3) as well as the first degradation product of that nucleotide (ADP) demonstrates the potential for negative feedback regulation of this physiological important signaling pathway.

**Pathological Consequences of a Defect in this Control Mechanism**

Recently, it was reported that erythrocytes of humans with Type 2 diabetes (DM2), a condition in which cardiovascular disease accounts for nearly one-half of deaths, express decreased amounts of the endothelial nitric oxide synthase enzyme (NO3). Interestingly, decreased expression is present in animal models of diabetes as well (40-42, 83, 86, 99). In humans, Gs2 expression was decreased selectively; that is, expression of other Gi subtypes, Gso, and AC II was unaltered (86). This selective decrease in Gs2 expression in human erythrocytes was associated with impaired cAMP synthesis as well as decreased ATP release in response to physiological stimuli is metabolized by ecto-enzymes, resulting in the generation of ADP. ADP can then activate P2Y1 receptors present on erythrocytes resulting in decreases in intracellular cAMP and released vasodilator released from the endothelium in response to ATP (NO3) as well as the first degradation product of that nucleotide (ADP) demonstrates the potential for negative feedback regulation of this physiological important signaling pathway.

*...the erythrocyte could be a novel target for the development of drugs for the treatment of vascular insufficiency.*
include 1) whether there is a primary location within the network where the need for changes in O2 supply are sensed or controlled is exercised throughout the arteriolar tree to ensure proper distribution of O2 supply; 2) the inherent time scale of the regulatory system (i.e., determining how fast can the system respond and what the limiting factors are); 3) the vessels in the network that are involved in the response to a given stimulus; and 4) the limitations of the system's ability to control local O2 delivery. Future progress toward understanding the role of erythrocyte-derived ATP in the regulation of O2 delivery within the microcirculation will depend on a combination of new in vitro experiments, detailed computational modeling, and model testing and validation using in vivo systems under a range of physiological and pathophysiological conditions.

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