

## Flow and ICAM1 initiate leukocyte extravasation

To obtain credit, you should first read the journal article. After reading the article, you should be able to answer the following, related, multiple-choice questions. To complete the questions (with a minimum 75% passing score) and earn continuing medical education (CME) credit, please go to <http://www.medscape.org/journal/blood>. Credit cannot be obtained for tests completed on paper, although you may use the worksheet below to keep a record of your answers. You must be a registered user on <http://www.medscape.org>. If you are not registered on <http://www.medscape.org>, please click on the "Register" link on the right hand side of the website. Only one answer is correct for each question. Once you successfully answer all post-test questions you will be able to view and/or print your certificate. For questions regarding this activity, contact the accredited provider, [CME@medscape.net](mailto:CME@medscape.net). For technical assistance, contact [CME@medscape.net](mailto:CME@medscape.net). American Medical Association Physician's Recognition Award (AMA PRA) credits are accepted in the US as evidence of participation in CME activities. For further information on this award, please go to <https://www.ama-assn.org>. The AMA has determined that physicians not licensed in the US who participate in this CME activity are eligible for AMA PRA Category 1 Credits™. Through agreements that the AMA has made with agencies in some countries, AMA PRA credit may be acceptable as evidence of participation in CME activities. If you are not licensed in the US, please complete the questions online, print the AMA PRA CME credit certificate, and present it to your national medical association for review.

Wang S, Wang B, Shi Y, Möller T, Stegmeyer RI, Strlic B, Li T, Yuan Z, Wang C, Wettschureck N, Vestweber D, Offermanns S. Mechanosensation by endothelial PIEZO1 is required for leukocyte diapedesis. *Blood*. 2019;140(3):171-183.

**1. Based on the in vitro and mouse model study by Wang and colleagues, which of the following statements about how low flow and leukocyte-induced intercellular adhesion molecule 1 (ICAM-1) clustering interact to mechanically activate endothelial PIEZO1 is correct?**

- Low flow and leukocyte-induced ICAM-1 clustering have opposing effects on mechanical activation of endothelial PIEZO1, a mechanosensitive cation channel
- Downstream signaling through ICAM-1 requires coactivation of PIEZO1 by fluid shear stress and ICAM-1-induced reorganization of the cortical cytoskeleton
- Changes in actomyosin cortical tension are unlikely to directly affect plasma membrane tension
- Small interfering RNA (siRNA)-mediated knockdown of  $\alpha$ -actinin-4 and cortactin had no effect on ICAM-1-mediated increases in membrane tension

**2. Based on the in vitro and mouse model study by Wang and colleagues, which of the following statements about the role of PIEZO1 activation in signaling processes leading to opening of the endothelial barrier and leukocyte extravasation is correct?**

- Activation of PIEZO1 initiates signaling processes that block opening of the endothelial barrier
- PIEZO1 activation leads to decreases in  $[Ca^{2+}]_i$
- PIEZO1 activation leads to activation of downstream signaling events, including phosphorylation of SRC, PYK2, and myosin light chain
- The study showed involvement of PIEZO1 in transendothelial migration of leukocytes in vitro but not in vivo

**3. Based on the in vitro and mouse model study by Wang and colleagues, which of the following statements about pathophysiologic and clinical implications of how molecular mechanisms underlying the initial interactions between leukocytes and endothelial cells are linked to opening of the endothelial barrier is correct?**

- Findings from this study are likely applicable only to hematologic disorders
- Mice with endothelium-specific *Piezo1* deficiency show increased leukocyte extravasation in different inflammation models
- Inflammation does not require leukocyte extravasation
- Leukocytes and the hemodynamic microenvironment synergize to mechanically activate endothelial PIEZO1 and subsequent downstream signaling to initiate leukocyte diapedesis