

Maria Pospieszalska – Selected Recent Papers' Abstracts

Nature 488: 399-403 (2012)

'Slings' enable neutrophil rolling at high shear

Prithu Sundd¹, Edgar Gutierrez², Ekaterina K. Koltsova¹, Yoshihiro Kuwano^{1,3}, Satoru Fukuda⁴, **Maria K. Pospieszalska**¹, Alexander Groisman² & Klaus Ley¹

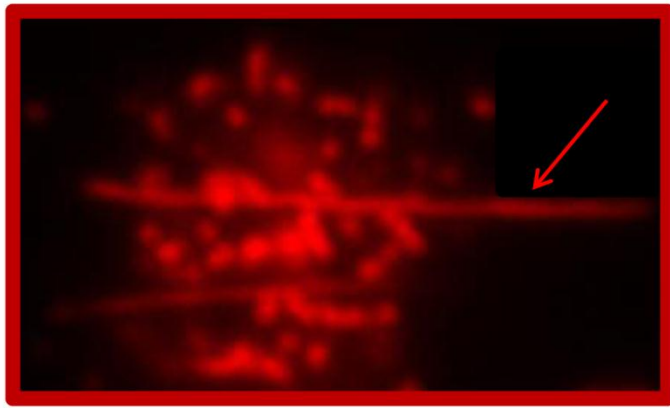
¹Division of Inflammation Biology, La Jolla Institute for Allergy and Immunology, La Jolla, California, USA

²Department of Physics, University of California San Diego, La Jolla, California, USA

³Department of Dermatology, University of Tokyo, Tokyo, Japan

⁴Laboratory of Electron Microscopy, University of Tokyo, Tokyo, Japan

Abstract: Most leukocytes can roll along the walls of venules at low shear stress (1 dyn cm^{-2}), but neutrophils have the ability to roll at tenfold higher shear stress in microvessels *in vivo*. The mechanisms involved in this shear-resistant rolling are known to involve cell flattening and pulling of long membrane tethers at the rear. Here we show that these long tethers do not retract as postulated, but instead persist and appear as 'slings' at the front of rolling cells. We demonstrate slings in a model of acute inflammation *in vivo* and on P-selectin *in vitro*, where P-selectin-glycoprotein-ligand-1 (PSGL-1) is found in discrete sticky patches whereas LFA-1 is expressed over the entire length on slings. As neutrophils roll forward, slings wrap around the rolling cells and undergo a step-wise peeling from the P-selectin substrate enabled by the failure of PSGL-1 patches under hydrodynamic forces. The 'step-wise peeling of slings' is distinct from the 'pulling of tethers' reported previously. Each sling effectively lays out a cell-autonomous adhesive substrate in front of neutrophils rolling at high shear stress during inflammation.

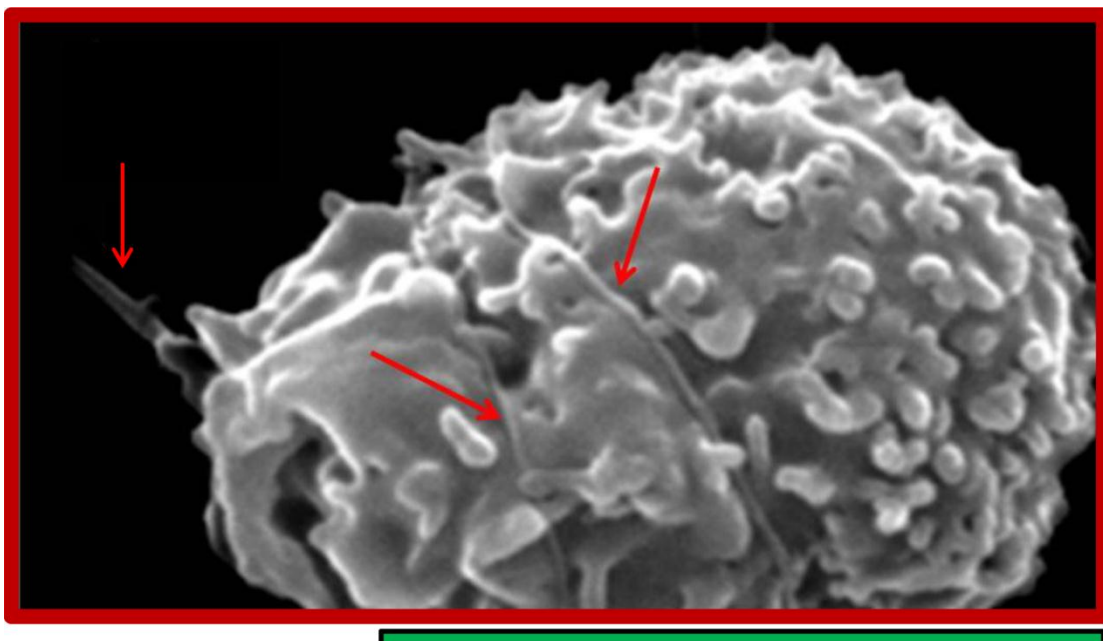


Tethers/slings wrapping around a rolling neutrophil: qDF image (left) and SEM image (bottom). Scale bars (green) 5 μm .

Editor's Choice: Academic Journal

Shu Chien, UC San Diego: "These findings not only have fundamental importance in the mechanobiology of the cell, but also in understanding the pathophysiology of many disease states."

Sussan Nourshargh, WHRI, London School of Medicine "This is a completely new cellular concept that will now be added as an additional step to the leukocyte adhesion cascade that describes the sequential cellular responses involved in guiding neutrophils to sites of inflammation. This pioneering work will without doubt pave the way for other researchers to explore the occurrence of "slings" in a wide range of inflammation scenarios."



Mathematical Models and Methods in Applied Sciences 22: 1250035 (2012)

Well-posedness and exponential decay of the energy in the nonlinear Jordan-Moore-Gipson-Thompson equation arising in high intensity ultrasound

Barbara Kaltenbacher¹, Irena Lasiecka^{2,3} & Maria K. Pospieszalska^{4,5}

¹Alps-Adriatic University, Klagenfurt, Austria

²Department of Mathematics, University of Virginia, Charlottesville, Virginia, USA

³Systems Research Institute, Polish Academy of Sciences, Warsaw, Poland

⁴Division of Inflammation Biology, La Jolla Institute for Allergy and Immunology, La Jolla, California, USA

⁵Department of Mathematics and Statistics, American University, Washington DC, USA

Abstract: We consider a third order in time equation which arises, e.g. as a model for wave propagation in viscous thermally relaxing fluids. This equation displays, even in the linear version, a variety of dynamical behaviors for its solution that depend on the physical parameters in the equation. These range from non-existence and instability to exponential stability (in time) as was shown for the constant coefficient case in Ref. 23. In case of vanishing diffusivity of the sound, there is a lack of generation of a semigroup associated with the linear dynamics. If diffusivity of the sound is positive, the linear dynamics is described by a strongly continuous hyperbolic-like evolution. This evolution is exponentially stable provided sufficiently large viscous damping is accounted for in the model. In this paper, we consider the full nonlinear model referred to as Jordan–Moore–Gibson–Thompson equation. This model can be seen as a “hyperbolic” version of Kuznetsov’s equation, where the linearization of the latter corresponds to an analytic semigroup. This is no longer valid for the presently considered third-order model whose linearization is associated with a group structure. In order to carry out the analysis of the nonlinear model, we first consider time and space-dependent viscosity which then leads to evolution rather than semigroup generators. Decay rates for both “natural” and “higher” level energies are derived. Relevant physical parameters that are responsible for spectral behavior (continuous and point spectrum) are identified. The theoretical estimates proved in the paper are confirmed by numerical simulations. The derived energy estimates are then used in order to establish global well-posedness and exponential decay for the solutions to the nonlinear equation.

Biorheology 48:1-35 (2011)

Biomechanics of leukocyte rolling

Prithu Sundd¹, Maria K. Pospieszalska¹, Luthur S. Cheung², Konstantinos Konstantopoulos² & Klaus Ley¹.

¹Division of Inflammation Biology, La Jolla Institute for Allergy and Immunology, La Jolla, California, USA

²Department of Chemical and Biomolecular Engineering, John Hopkins University, Baltimore, Maryland, USA

Abstract: Leukocyte rolling on endothelial cells and other P-selectin substrates is mediated by P-selectin binding to P-selectin glycoprotein ligand-1 expressed on the tips of leukocyte microvilli. Leukocyte rolling is a result of rapid, yet balanced formation and dissociation of selectin-ligand bonds in the presence of hydrodynamic shear forces. The hydrodynamic forces acting on the bonds may either increase (catch bonds) or decrease (slip bonds) their lifetimes. The force-dependent 'catch-slip' bond kinetics are explained using the 'two pathway model' for bond dissociation. Both the 'sliding-rebinding' and the 'allosteric' mechanisms attribute 'catch-slip' bond behavior to the force-induced conformational changes in the lectin-EGF domain hinge of selectins. Below a threshold shear stress, selectins cannot mediate rolling. This 'shear-threshold' phenomenon is a consequence of shear-enhanced tethering and catch bond-enhanced rolling. Quantitative dynamic footprinting microscopy has revealed that leukocytes rolling at venular shear stresses (>0.6 Pa) undergo cellular deformation (large footprint) and form long tethers. The hydrodynamic shear force and torque acting on the rolling cell are thought to be synergistically balanced by the forces acting on tethers and stressed microvilli, however, their relative contribution remains to be determined. Thus, improvement beyond the current understanding requires in silico models that can predict both cellular and microvillus deformation and experiments that allow measurement of forces acting on individual microvilli and tethers.

Biophysical Journal 100:1697-1707 (2011)

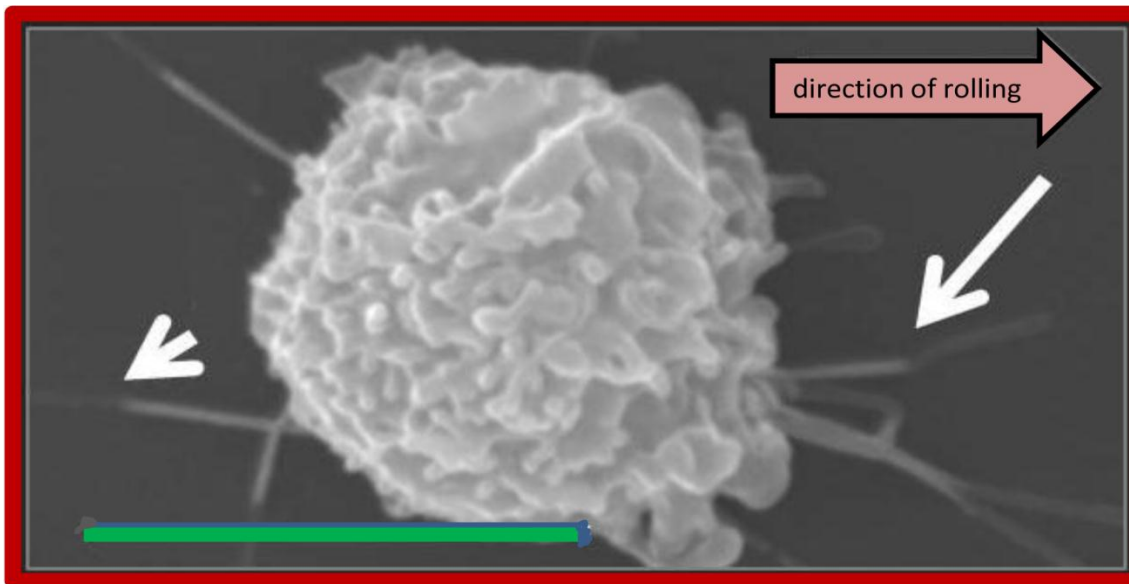
Cell protrusions and tethers: a unified approach

Maria K. Pospieszalska¹, Irena Lasiecka² & Klaus Ley¹

¹Division of Inflammation Biology, La Jolla Institute for Allergy and Immunology, La Jolla, California, USA

²Department of Mathematics, University of Virginia, Charlottesville, Virginia, USA

Abstract: Low pulling forces applied locally to cell surface membranes produce viscoelastic cell surface protrusions. As the force increases, the membrane can locally separate from the cytoskeleton and a tether forms. Tethers can grow to great lengths exceeding the cell diameter. The protrusion-to-tether transition is known as the crossover. Here we propose a unified approach to protrusions and tethers providing, to our knowledge, new insights into their biomechanics. We derive a necessary and sufficient condition for a crossover to occur, a formula for predicting the crossover time, conditions for a tether to establish a dynamic equilibrium (characterized by constant nonzero pulling force and tether extension rate), a general formula for the tether material after crossover, and a general modeling method for tether pulling experiments. We introduce two general protrusion parameters, the spring constant and effective viscosity, valid before and after crossover. Their first estimates for neutrophils are $50 \text{ pN } \mu\text{m}^{-1}$ and $9 \text{ pN s } \mu\text{m}^{-1}$, respectively. The tether elongation after crossover is described as elongation of a viscoelastic-like material with a nonlinearly decaying spring (NLDs-viscoelastic material). Our model correctly describes the results of the published protrusion and tether pulling experiments, suggesting that it is universally applicable to such experiments.



Nature 488: 399-403.
Scanning electron micrograph of a rolling neutrophil showing tethers at the rear (white arrowhead) and slings in the front (white arrow). Scale bar $5 \mu\text{m}$.

Nature Methods 7: 821-824 (2010)

Quantitative dynamic footprinting microscopy reveals mechanisms of neutrophil rolling

Prithu Sundd¹, Edgar Gutierrez², Maria K Pospieszalska¹, Hong Zhang¹, Alexander Groisman² & Klaus Ley¹

¹Division of Inflammation Biology, La Jolla Institute for Allergy and Immunology, La Jolla, California, USA

²Department of Physics, University of California San Diego, La Jolla, California, USA

Abstract: We introduce quantitative dynamic footprinting microscopy to resolve neutrophil rolling on P-selectin. We observed that the footprint of a rolling neutrophil was fourfold larger than previously thought, and that P-selectin-PSGL-1 bonds were relaxed at the leading edge of the rolling cell, compressed under the cell center, and stretched at the trailing edge. Each rolling neutrophil formed three to four long tethers that extended up to $16 \mu\text{m}$ behind the rolling cell.