Getting small blood cells through small gaps; what could go wrong?

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Blood - the ‘liquid’

Getting the blood around the circulation: different properties affect flow in different vessels
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.......... getting small cells through small gaps

Lung

Spleen

Muscle
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It's not just red blood cells

Ulf Bagge, PhD Thesis, Goteborg 1975
Its not just squeezing through vessels ..........

.......... its sticking and crawling out
Circulation of neutrophils

**Arteriole**

- Positive (P)
- Circulation

**Venule**

- Endothelial lining
- Phagocytosis
- Killing
- Remodelling
- Apoptosis

White blood cell recruitment across the vessel wall

- Margination
- Capture/Rolling
- Stabilisation
- Spreading
- Migration

Stimulatory signal

(infection, trauma .....)

Flow
Neutrophils rolling or migrating on ‘inflammed’ endothelium

Low dose

High dose

Tumour necrosis factor
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‘Clinical blood cell rheology’

Red blood cells: mechanics

Cellular mechanical factors affecting deformation

**CELL GEOMETRY**  *Surface area:volume ratio*  →  ability to adapt shape

**MEMBRANE**  (rigidity)

**CYTOPLASM**  *(concentrated haemoglobin solution)*
London, Guys
Membrane elastic modulus

Los Angeles
Membrane viscosity

Surface area/volume

Sickle cell (HbSS) disease
Oxygenated

De-oxygenated
Irreversibly Sickled Cells:
Surface area/volume ↑ x1.25 (Shrunken)
Membrane rigidity ↑ x2
Membrane viscosity ↑ x2.5

Ca^{++}-dependent K^{+} efflux (Gardos effect)
Protection by Ca^{++}-channel blocker Nitrendipine

Endogenous
Induced by cyclical deoxygenation
Decreasing oxygen tension
(HbS polymerisation/sickling)

Rigidity $\uparrow$ x 5-100
Deformation rate $\downarrow$ x 50-200
Plasmodium falciparum malaria

Sequestered in microcirculation
Adhered to endothelium?
Lodged in capillaries?

Adhesive receptors?
Effect of proteins inserted into the red cell membrane revealed by genetic manipulation of the parasite

Glenister F K et al. Blood 2002;99:1060-1063

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Red blood cells: adhesion
Parasitised red cells can mimic ability of white cells to roll and stop on endothelium

Sequestration in blood capillaries key to pathogenesis?

Sickle cells can also adhere to endothelium from flow

Adhesion may delay sickle cells in microvessels
Along with dehydration this allows sickling
Outcome – log-jam of rigid cells causing occlusion
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**White blood cells: mechanics**

[Images of white blood cells]

'S Activated' neutrophils

[Image of activated neutrophils]
Effect of exposure to cigarette smoke

Small vessel inflammation (vasculitis) associated with anti-neutrophil cytoplasm antibodies (ANCA)

Cytoplasmic (c-) ANCA:
- Coarse granular staining
- Specificity for proteinase 3 (PR3)
- Most commonly associated with Wegener’s granulomatosis

Perinuclear (p-) ANCA:
- Staining restricted to sites around the nucleus
- Specificity for myeloperoxidase (MPO)
- Most commonly associated with microscopic polyarteritis
ANCA derived from plasma of patients with vasculitis causes rigidification of neutrophils

Effect of surgical interruption of blood flow (ischaemia and reperfusion)

Healthy control          After repair of aortic aneurysm
Flow resistance of neutrophils after acute myocardial infarction

Peripheral vascular disease - chronic ischaemia of the leg

X-ray - Angiograms
Activation of neutrophils may cause problems systemically as well as in affected ischaemic tissue.

Critical leg ischaemia: Flow resistance of neutrophils

Filtration rate of neutrophils: isolated before and after amputation

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White blood cells: adhesion and migration
(at the wrong time/wrong place)
ANCA causes rolling neutrophils to become to stationary adherent

ANCA causes rolling neutrophils to become to stationary adherent

ANCA also promotes migration across endothelium

ANCA contribution to pathology of vasculitis?
Combined with ............?
Exposure of endothelial cells to hypoxia and re-oxygenation

→ adhesion of flowing neutrophils on return of oxygen

Hypoxia/reoxygenation one driver of neutrophil infiltration

Atherosclerosis - vicious cycle of leukocyte activation?
Clinical blood cell rheology - therapeutic lessons?

Sickle cell disease
Shrinking as a key factor in flow impairment
(deformability, polymerisation, adhesion)

Malaria
Inhibit sequestration to attack the parasite life-cycle

Leukocytes and vascular disease:
Don’t let them get too excited
Quieten them down
Stop them sticking

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