Fluid Shear Stress: a modulator of the vasculo-protective effects of polyphenols?

Laurent-Emmanuel Monfoulet

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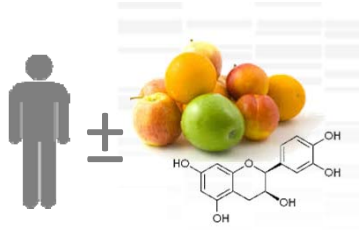
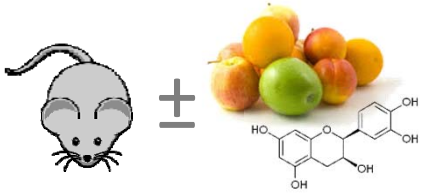


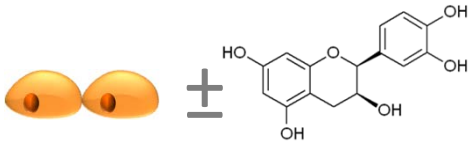
Clinical Trial
Human PBMCs

Morand et al. AJCN 2011; 93:73-80
Milenkovic et al. PLoSOne. 2011;6(11):e26669



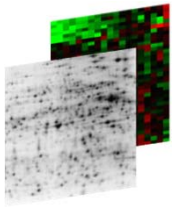
Preclinical studies
Murine Aorta

Mauray et al. 2012 (22):72-80
Coban et al. MNFR 2012, 56: 1270–1281



In vitro studies
Endothelial cells

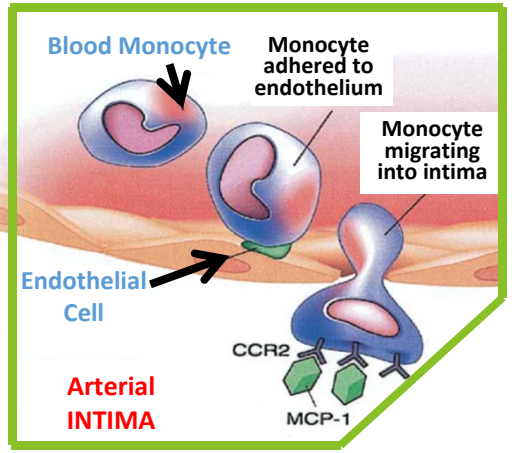
Claude et al. MNFR 2014; 58(5):1016-27
Chanet et al. BJN 2013; 110:587-598



Nutrigenomic approaches:
-Transcriptomic
-Proteomic
-Epigenetic

Hypothesis:

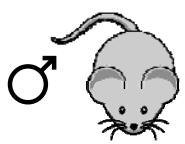
Polyphenols



TransEndothelial Migration (TEM) as a common mode of action of polyphenols on vascular health

Atherosclerotic model:

ApoE$^{-/-}$ Mice
8 week-old



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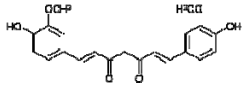
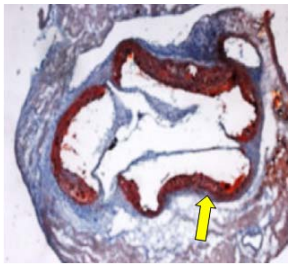


0.2% Curcumin
for 16 weeks

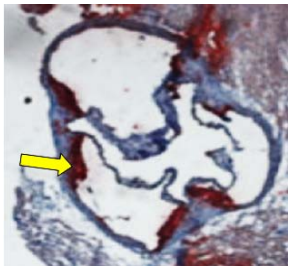
Coban et al. MNFR 2012, 56, 1270–1281

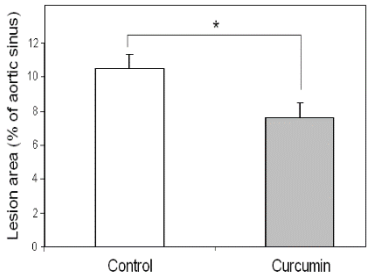
Atherosclerotic lesion (aortic sinus)

Control



Curcumin



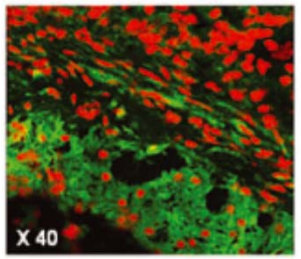


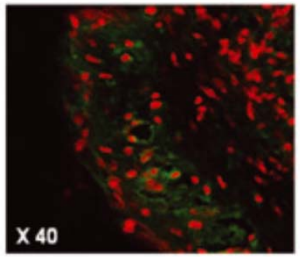
Macrophages within the lesion

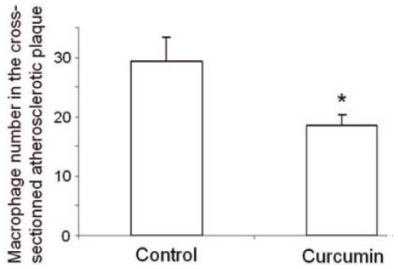
Control

Curcumin

MAC-3
Propidium Iodide





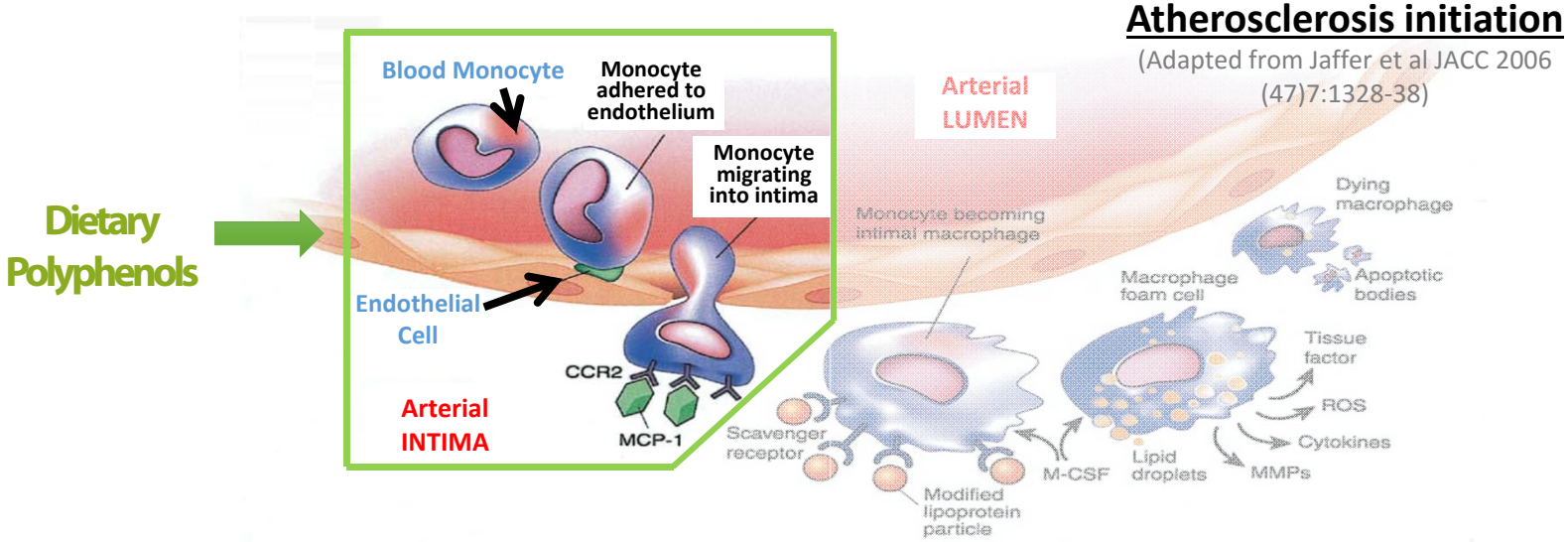


Curcumin intake reduces atherosclerotic lesion development and recruitment of immune cells

Underlying mechanisms of action in *in vitro* studies

Atherosclerosis initiation

(Adapted from Jaffer et al JACC 2006 (47)7:1328-38)



Reproduce conditions as close as possible to the physiology

Polyphenols

- Circulating molecules
- Low plasma concentration (0.1 – 10µM)
- Time of exposure (= resident time in the plasma)

Endothelial cells :

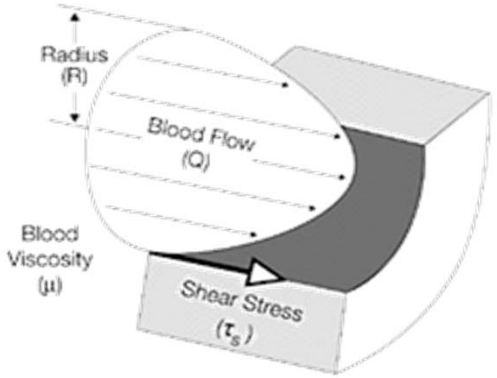
- Hemodynamic conditions

Milenkovic et al. FRBM 2013 (64):40-51

Shear Stress: a vascular and physiological parameter

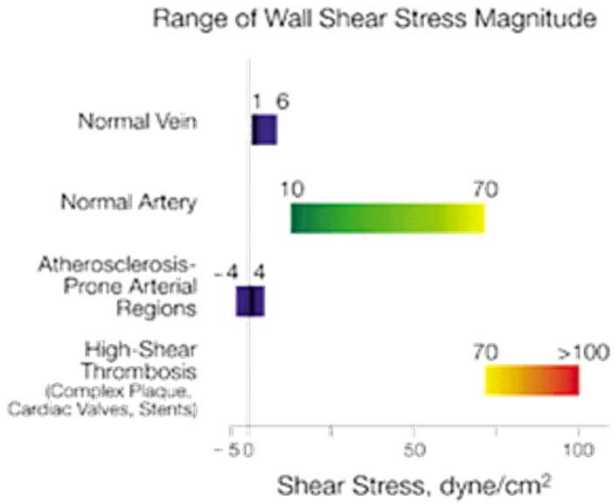
Shear Stress is:

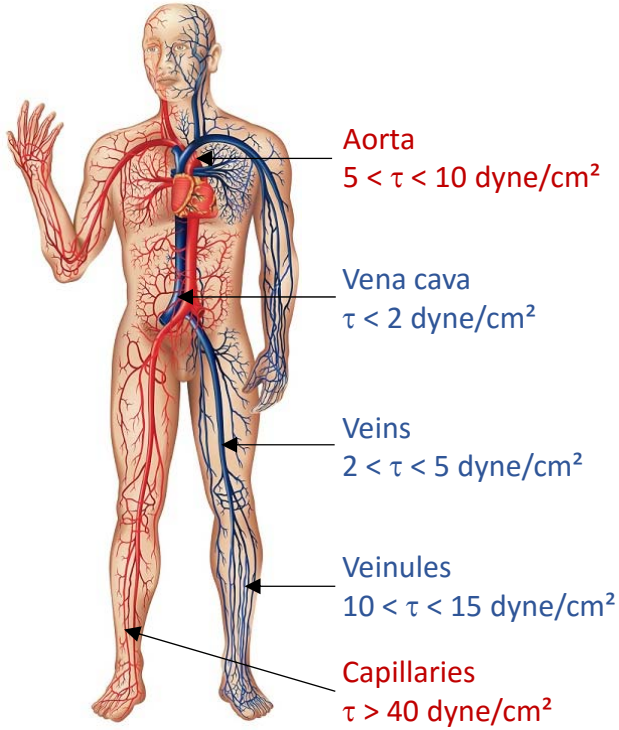
- **A force due to the blow flow**
- **Pulsatile (Heart beats)**
- **Continuous**
- **Laminar and unidirectional**



Poiseuille's law

$$\tau = \frac{4Q\mu}{\pi R^3}$$





Malek et al. JAMA 1999. 282(21):2035-2042
Rocca et al. Cordiologie Conferences 2007. XII (8)

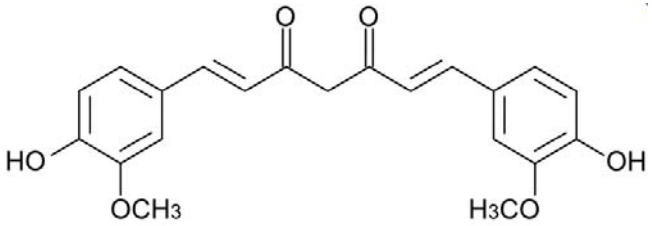
Aims

- **To analyse the response of endothelial cells to physiological relevant concentrations of polyphenols under shear stress conditions**

- **To evaluate how shear stress modulates the response of endothelial cells to polyphenols regarding recruitment, adhesion and TEM of monocytes in comparison to static conditions**

A proof of concept

Curcuma longa

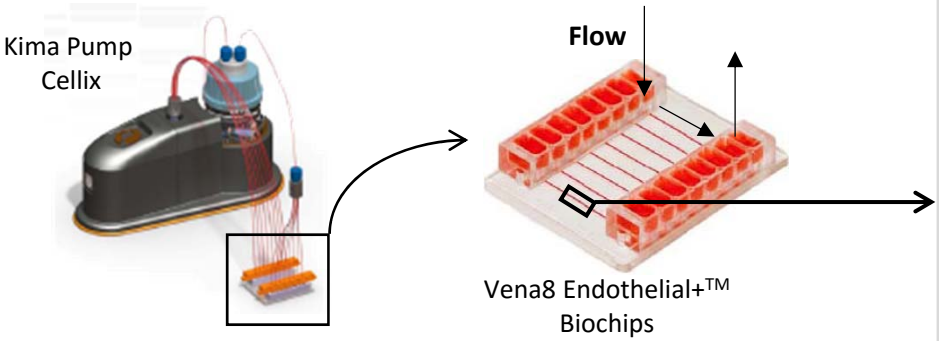


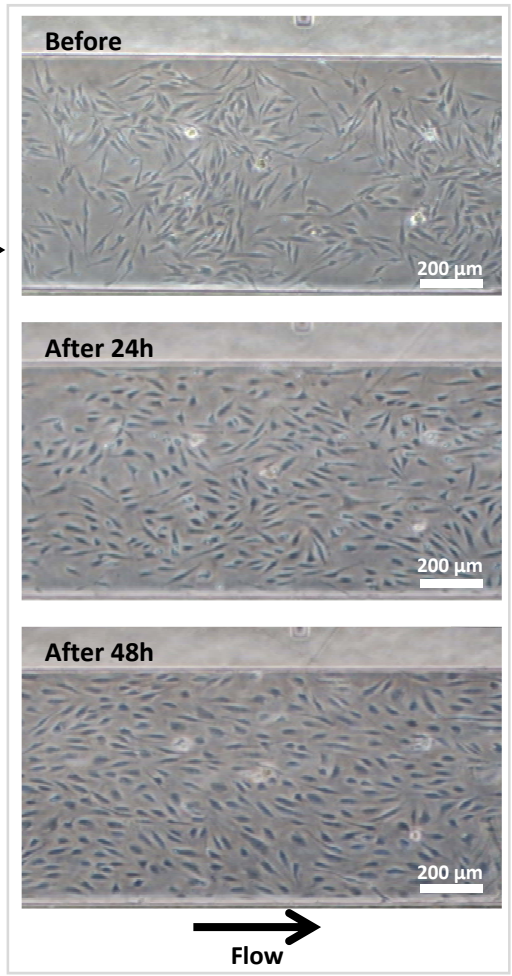
Curcumin

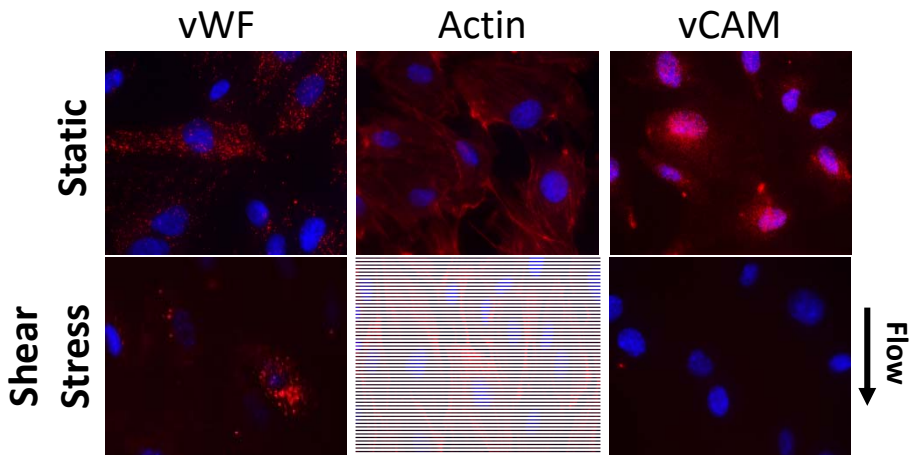
Response of endothelial cells to physiological relevant concentrations of CURCUMIN under shear stress conditions

Imposed shear stress on cultured endothelial cells

Laminar Shear Stress characteristics:
1 Hz pulsatile flow rate
Flow rate: 600µL/min
τ: ~7dyne/cm² (arterial)



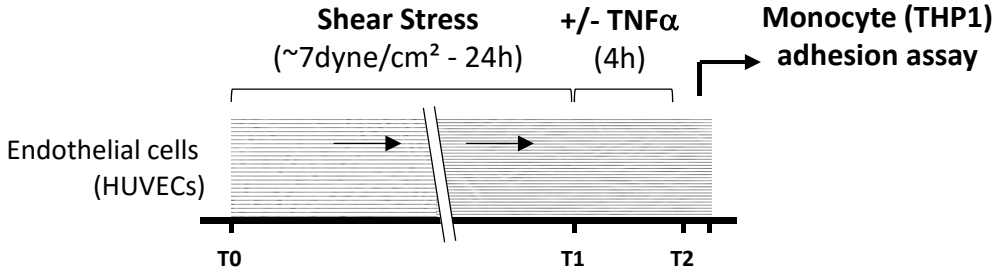


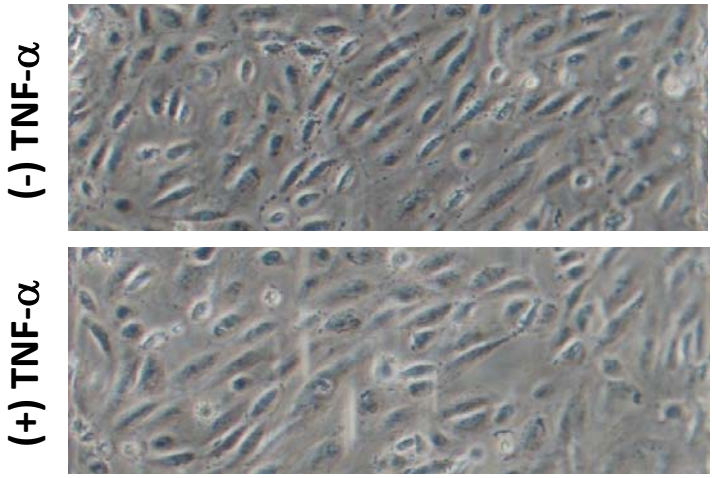


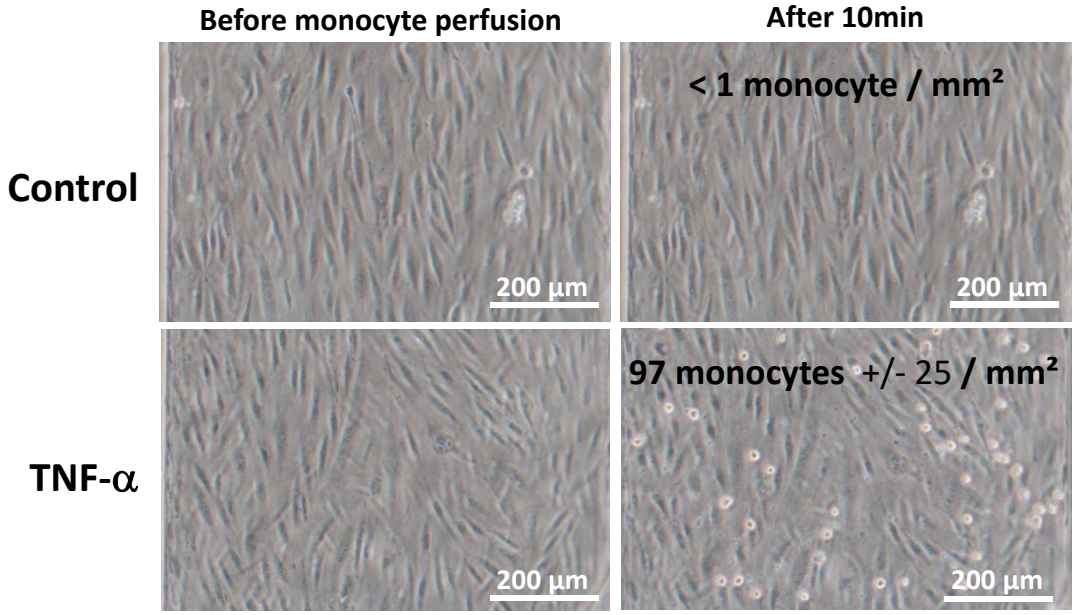
Under shear stress, endothelial cells:

- are firmly spread and aligned in the flow direction.
- have a physiological phenotype (anti-atherogenic).

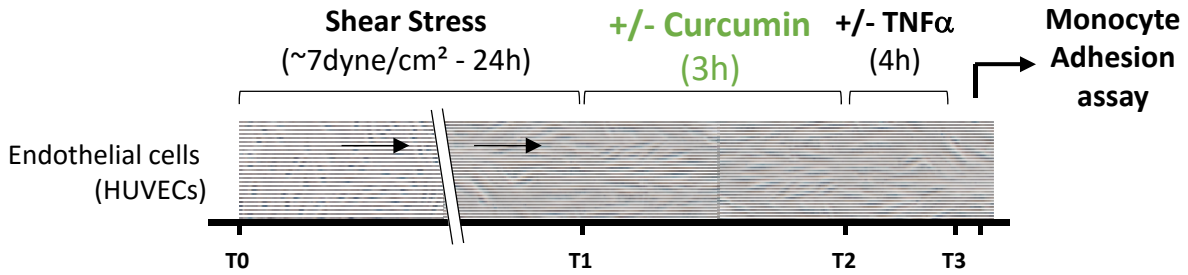
Monocyte adhesion induced by inflammatory stress (TNF-α)

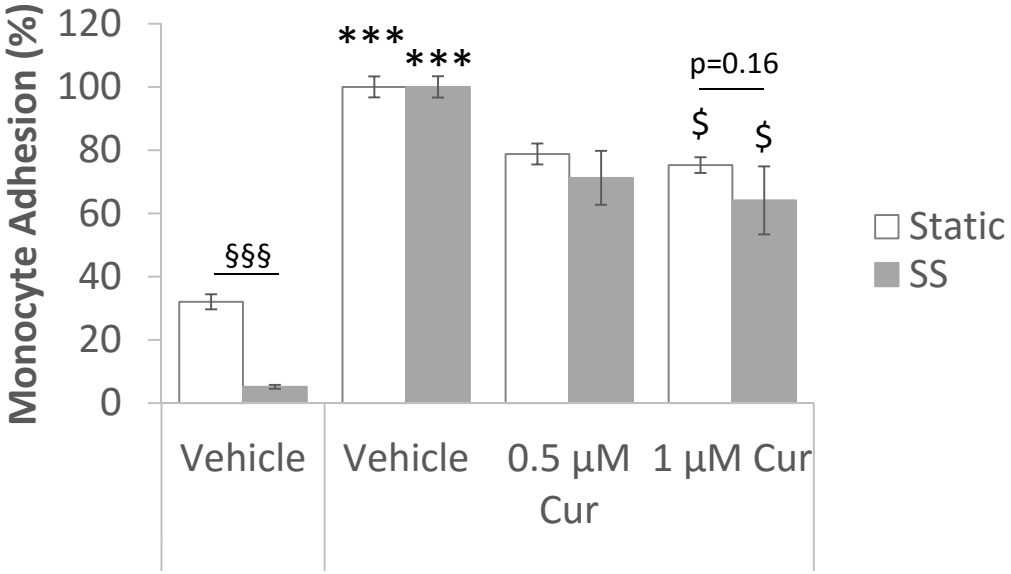






Impact of curcumin on monocyte adhesion





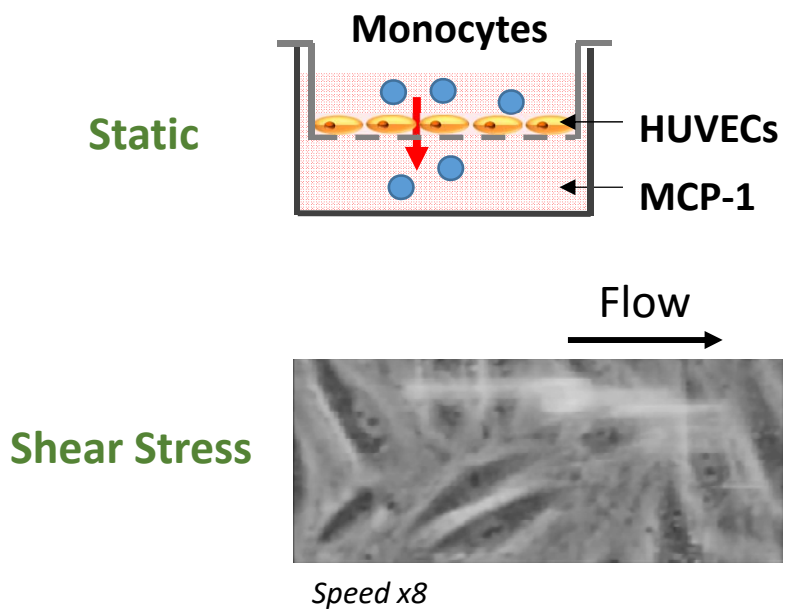
***p<0.001 compared to Vehicle (-) TNF-α

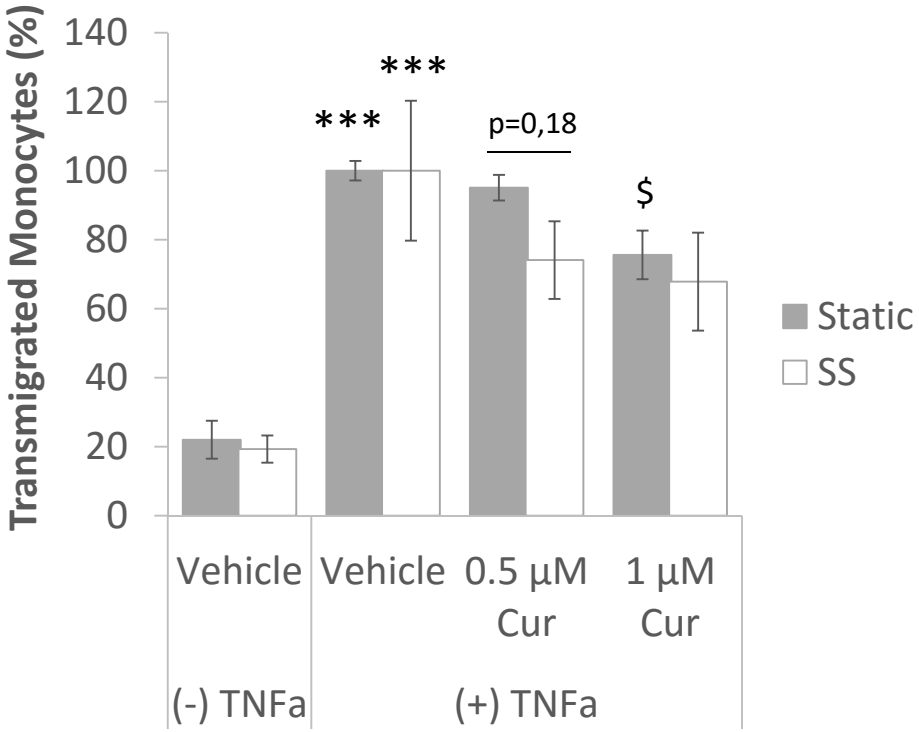
$ p<0.05 compared to Vehicle + TNF-α

The reduction of monocyte adhesion by curcumin is slightly enhanced in shear stress conditions

Impact of curcumin on monocyte TransEndothelial Migration

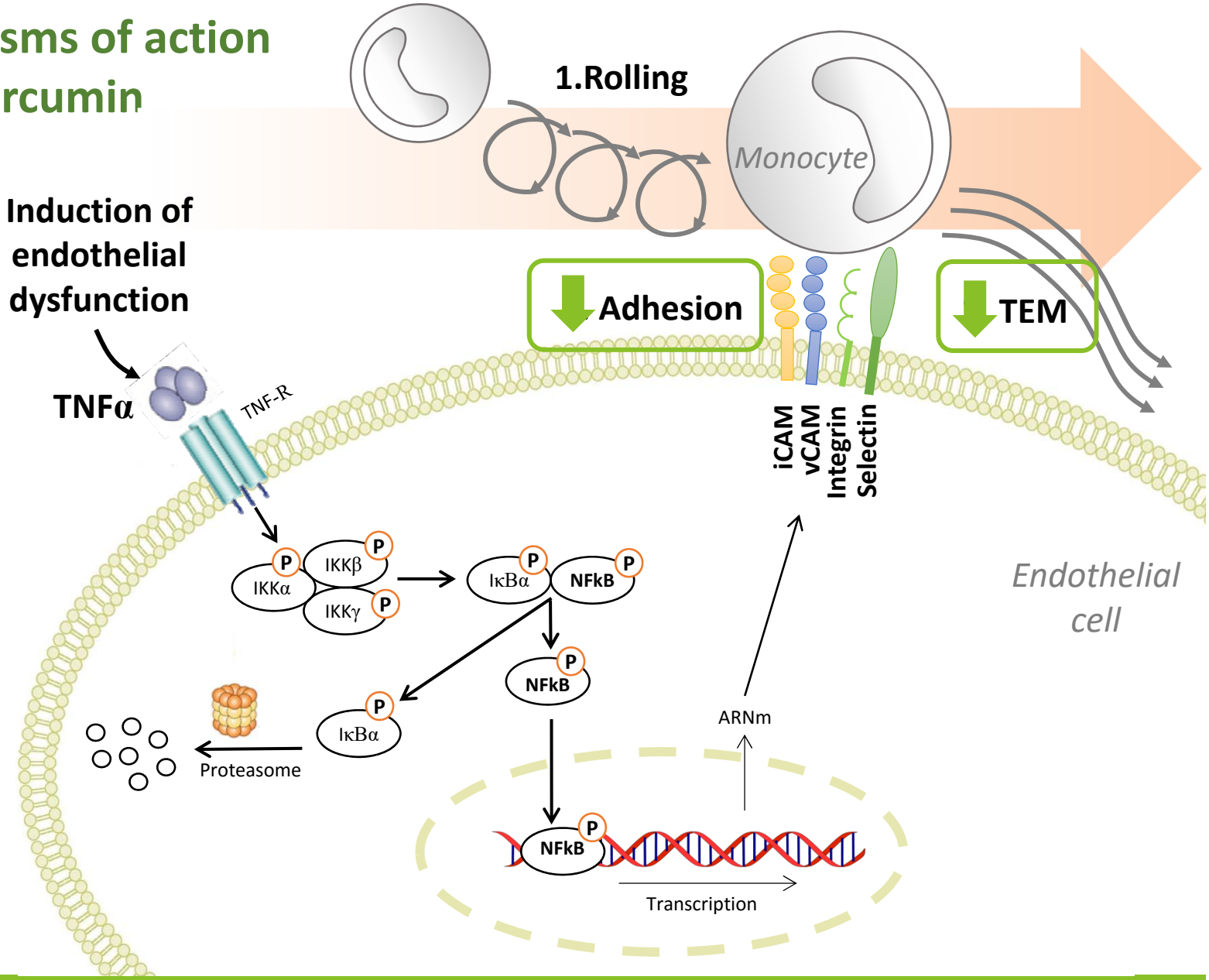
Preliminary results



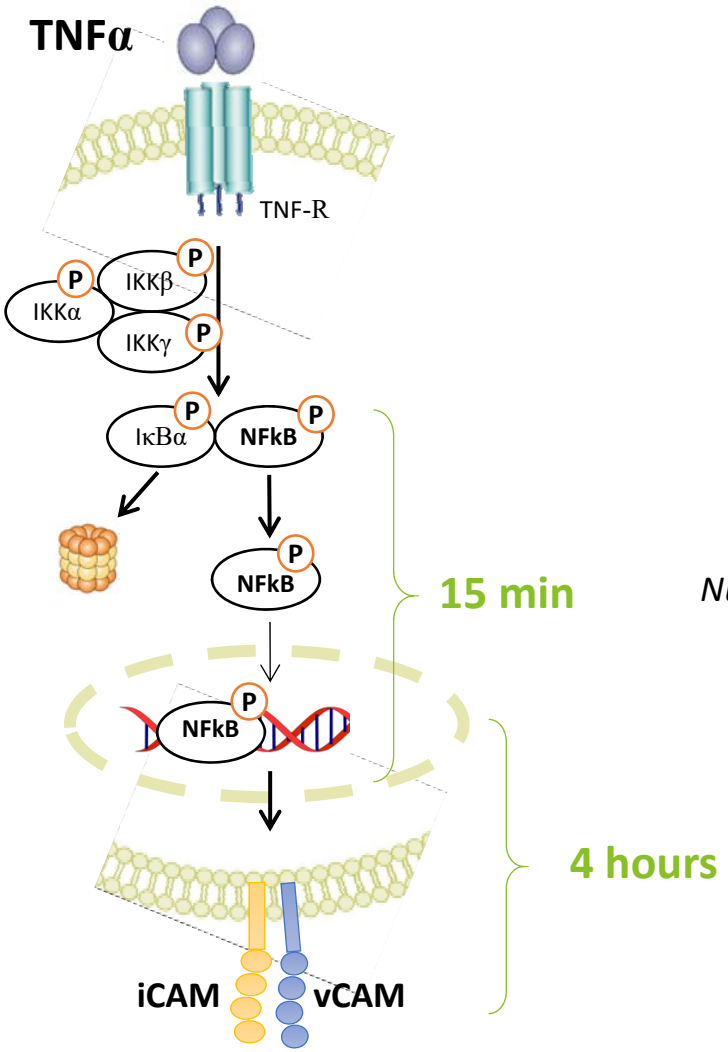


The reduction of TEM by curcumin is heightened in shear stress conditions

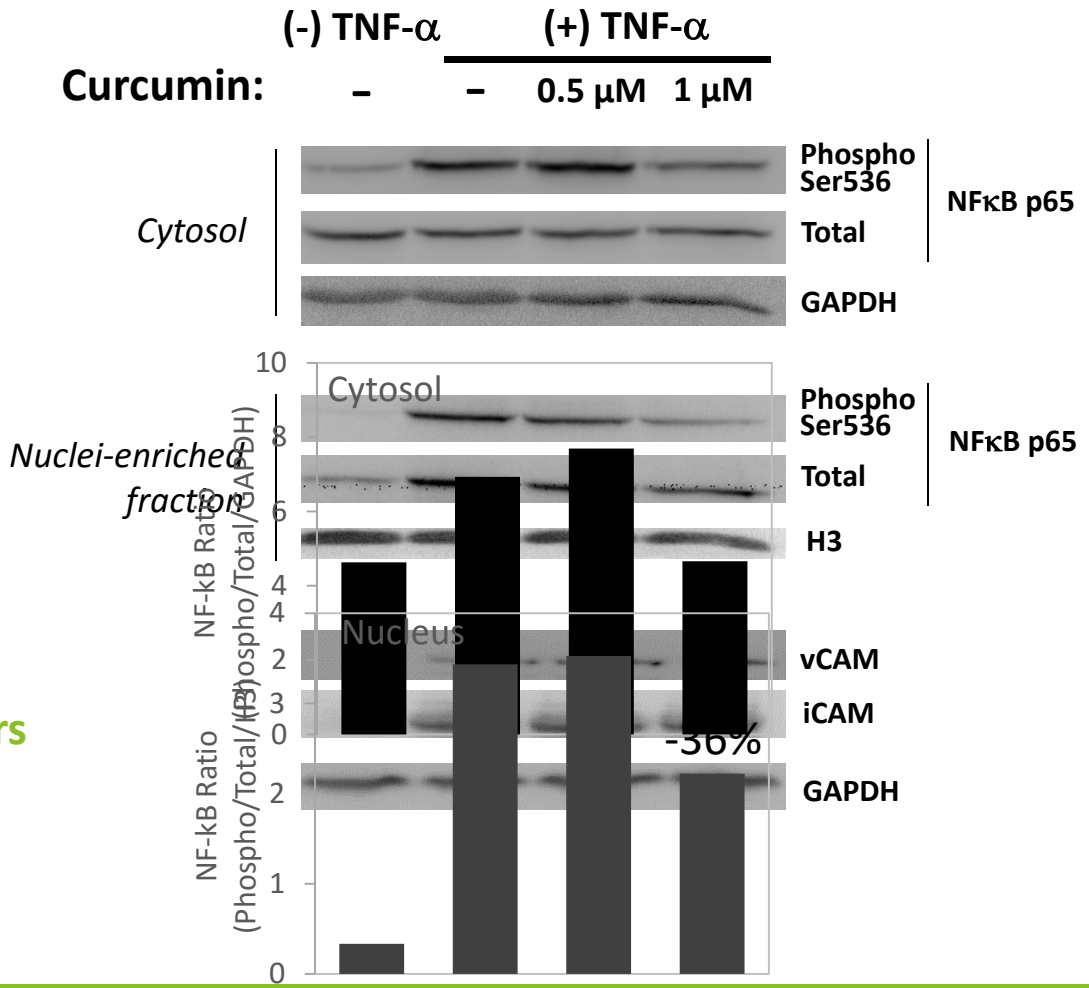
Mechanisms of action of the curcumin



Mechanisms of action of the curcumin



Static



Conclusion

- We showed that a pre-exposition of endothelial cells to **curcumin significantly reduces the adhesion of monocytes to endothelial cells and their TEM**.

- The reduction of both adhesion and TEM by curcumin are **enhanced under physiological shear stress.**

- In static conditions, **curcumin modulates the TNF-R pathway** (NF-κB phosphorylation and its nuclear translocation), but does not affect the expression of adhesion molecules.

- Other cellular process can be modulated by curcumin that could explain their inhibitory effect on monocyte infiltration (cytoskeleton & cell junction dynamic?)

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