Monocyte phenotyping: a sensitive biomarker for predicting adverse vascular events?

Selecting patients for vascular intervention

John P Fletcher, MBBS, MD, FRACS, FRCS (Engl.), DDU
VEITH Symposium, New York; November 17-21, 2015

Conflict of Interest Disclosure
No potential conflict of interest

Factors affecting carotid plaque stability

1. plaque echolucency / echogenicity
2. inflammatory markers
   - matrix metalloproteinases (MMPs)
   - CD40L & TGF-β
3. fibrous cap thickness, vessel wall tensile stress

Fibrous cap formation:
Cells from vessel wall or bone marrow derived?

Adventitial myofibroblast
Medial Smooth Muscle Cell derived

Monocytes contribute to the core and cap

Foam cells
Cap
Core

18 week old Macgreen / Apo E−
9 month old Macgreen / Apo E−

Monocyte and monocyte derived cells fluoresce green
Monocytes / Macrophages - M1/M2 phenotypes

Classically activated M1
- LPS & IFNγ
- IL-12, IFNγ
- T cell help
- TH1 cytokines
- M1 macrophages: inversely correlate to cap thickness

Alternatively activated M2
- IL-4, immune complexes, IL-10
- T cell help
- TH2 cytokines
- M2 macrophages: associated with more stable plaque morphology

Monocyte / macrophage phenotypes, ↑ vascular risk

- in healthy controls, a minor population of monocytes is M1-like
- in controls with ↑ vascular risk, a major population of monocytes becomes more M1-like
- in atherosclerotic patients, an even greater population of monocytes becomes more M1-like

CD86/163 (M1/M2) – predictor of atherosclerosis and ↑ vascular risk

Compared to current biomarkers, e.g. total cholesterol/HDL, LDL, ApoB/A, WBC count, monocyte count – CD86/163 (M1/M2) was the most sensitive with highest Odds Ratio

Conclusion

- atherosclerotic plaque rupture
  - more likely with
  - thin fibrous cap, large fatty core
  - plaque stability may be promoted by modulation of monocyte / macrophage transformation (M1 → M2)
  - thicker cap, smaller core

- CD86/163 (ratio of M1/M2 monocytes / macrophages)
  - marker of vascular risk
  - biomarker for selection of patients for intervention

Monocytes / Macrophages - M1/M2 phenotypes

Classically activated M1
- LPS & IFNγ
- IL-12, IFNγ
- T cell help
- TH1 cytokines
- M1 macrophages: inversely correlate to cap thickness

Alternatively activated M2
- IL-4, immune complexes, IL-10
- T cell help
- TH2 cytokines
- M2 macrophages: associated with more stable plaque morphology

Plaque instability? Vascular event protective?

Carotid endarterectomy specimens

M1 macrophages associated with unstable plaque morphology
- thin cap, large core

M2 macrophages associated with more stable plaque morphology
- thicker cap, smaller core
  - co-localisation with TGF, associated with new collagen deposition

Trend for ↑ plaque stability with M2 phenotype:
- asymptomatic patients, symptomatic patients with symptoms > 4 weeks prior to surgery

Acknowledgements

Westmead Vascular Biology Research Centre

VIRGINIA JAMES, Pathologist
HELEN WILLIAMS, Scientist
NAJWA MARMASH, Scientist
MAURO VICARETTI, Vascular Surgeon
HEATHER MEDBURY, Chief Scientist

University of Sydney
Department of Surgery

Westmead Hospital
Division of Surgery