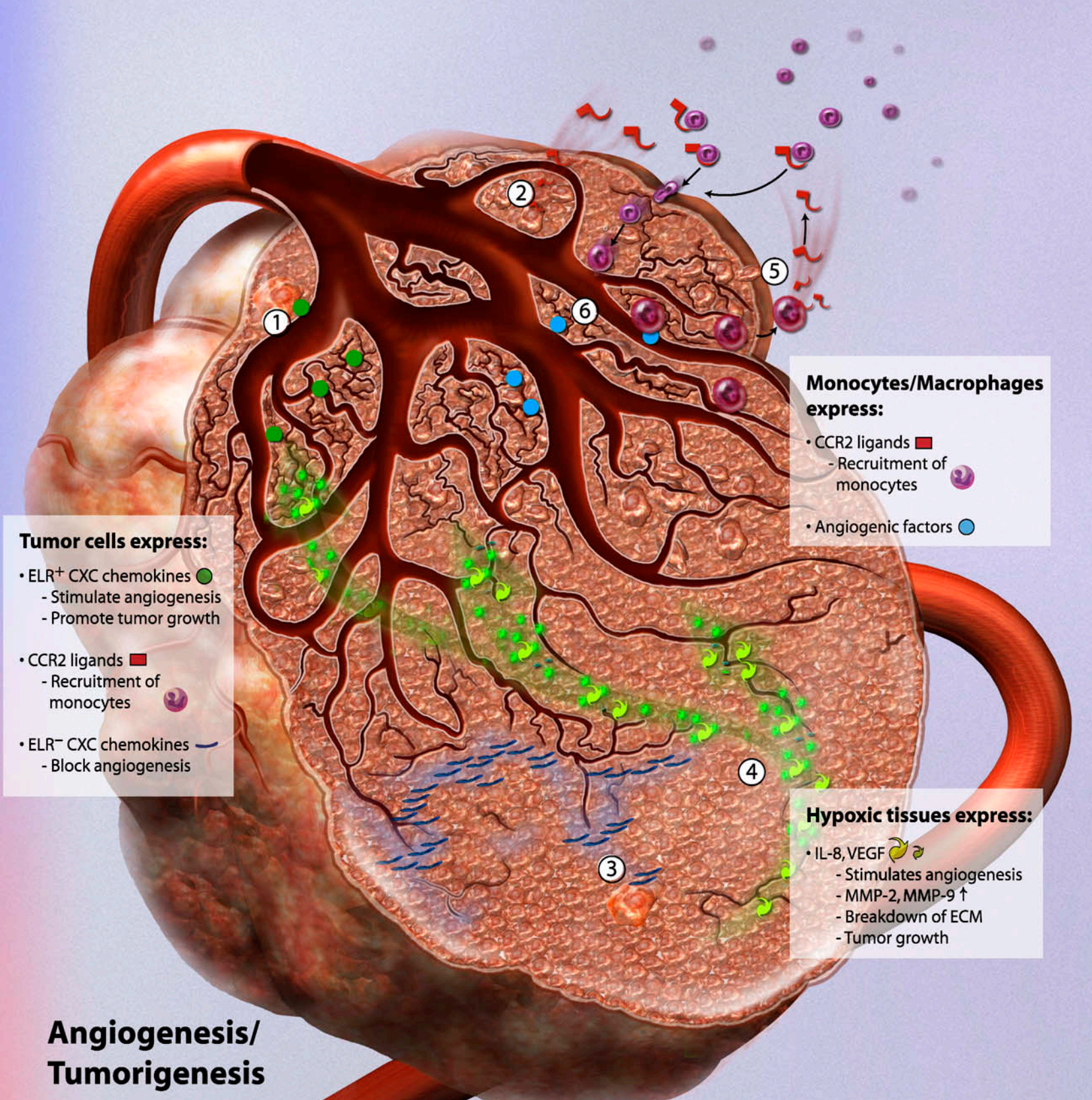


Angiogenic Factors

Anti-angiogenic
Both
Pro-angiogenic

- 6Ckine
- Angiostatin
- BCA-1
- Chondromodulin 1
- Endostatin
- sFGF R
- IFN α
- IFN β
- IFN γ
- IP-10
- IL-1 α
- IL-1 β
- IL-10
- IL-12
- I-TAC
- MIG
- NO
- PEDF
- PAI-1
- PAI-2
- PF-4
- Thrombospondin 1
- Thrombospondin 2
- TIMP-1
- TIMP-2
- TIMP-3
- TIMP-4
- Vasculostatin
- Vasostatin
- VEGI
- GRO β
- TGF- β
- aFGF
- Angiogenin
- Angiopoietin 1
- Angiopoietin 2
- bFGF
- Chymase
- ENA-78
- Eotaxin
- Eph/Ephrins
- EGF
- Fractalkine
- GCP-2
- G-CSF
- GM-CSF
- GRO α
- GRO γ
- HGF
- I-309
- IGF-1
- Integrin α v β 3
- Integrin α v β 5
- IL-1
- IL-4
- IL-6
- IL-8
- IL-13
- Leptin
- MMP-1
- MMP-2
- MMP-9
- Midkine
- MCP-1
- PAF
- PIGF
- Plasminogen Activator
- PBP-2
- PD-ECGF
- PDGF
- Pleiotrophin
- Proliferin
- PGE $_1$
- PGE $_2$
- SDF-1
- Thrombin
- Tie-2
- TGF α
- Tryptase
- TNF α
- VEGF



Angiogenesis/Tumorigenesis

Tumor cells express:

- 1 ELR $^+$ CXC Chemokines: IL-8, GRO α , GRO β , GRO γ , ENA-78, GCP-2, PBP-2. Stimulates angiogenesis.
- 2 CCR2 ligands: MCP-1, MCP-3, MCP-4. Recruitment of monocytes and macrophages.
- 3 ELR $^-$ CXC chemokines: PF-4, IP-10, MIG, I-TAC, 6ckine. Recruitment of T and NK cells which can destroy vasculature. Block angiogenesis.
- 4 IL-8, VEGF. Stimulate angiogenesis by upregulating MMP-2 and MMP-9 which results in destruction of ECM so that blood vessels can infiltrate these areas and grow.

Monocytes/Macrophages express:

- 5 CCR2 ligands. Positive feedback loop for recruitment of monocytes and macrophages.
- 6 Angiogenic factors: bFGF, VEGF, ECM modulators, Proteases. Stimulate angiogenesis.
- TNF α , IL-1 α . Enhance the production of IL-8, bFGF, and VEGF, which promote angiogenesis and tumor growth.

ECM = Extracellular matrix

Inflammatory Factors

Anti-inflammatory
Both
Pro-inflammatory

- CTLA-4
- IL-1 receptor antagonist
- IL-4
- IL-10
- IL-11
- IL-13
- Somatostatin
- TCR α
- TCR β
- TIMP-1
- TIMP-2
- TNF RI
- TGF- β 1
- IL-7
- IL-9
- IFN α
- IFN β
- 4-1 BB
- CD27 Ligand
- CD30 Ligand
- CD40 Ligand
- COX-2
- Fas Ligand
- GM-CSF
- IFN γ
- IL-1 α
- IL-1 β
- IL-2
- IL-6
- IL-8
- IL-12
- IL-15
- IL-17
- IL-18
- LIF
- LIGHT
- LT β
- LTB4
- MCP-1
- M-CSF
- MIF
- MMP-1
- MMP-3
- NOS
- OPN
- OSM
- OX40 Ligand
- Substance P
- TNF α
- TNF β



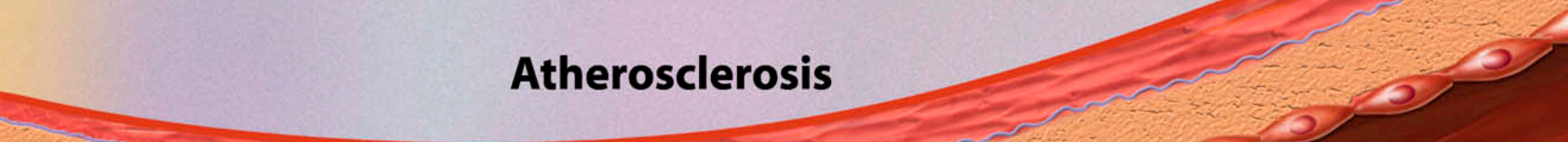
Normal Capillary

Hyperglycemic Conditions Leading to Hypoxia

- 1 VEGF \uparrow , TGF- β \uparrow . Thickened basement membrane.
- 2 NO \downarrow , PG12 \downarrow , ET-1 \uparrow . Vessel constriction, Loss of endothelial cells, Loss of Pericyte cells.
- 3 PKC \uparrow , PAF \uparrow . Coagulation cascade, Platelet aggregation.
- 4 PAF \uparrow , LTB4 \uparrow , β 2 integrins \uparrow , ICAM-1 \uparrow . Leukocyte activation and adherence.

Neovascularization

- VEGF \uparrow , VEGF R1 \uparrow , VEGF R2 \uparrow . Stimulates endothelial cells to degrade ECM, migrate, proliferate and form tubes.
- IGF-1 \uparrow , IGFBRs \uparrow . Endothelial cell proliferation, Migration, Basement membrane degradation.
- bFGF \uparrow . Induces mitogenesis in endothelial cells, Upregulate VEGF.
- HGF \uparrow . Promotes epithelial and endothelial cell motility, Regulates tube morphogenesis and tube branching.
- PDGF \uparrow , PIGF \uparrow . Tissue injury repair, Enhances effect of VEGF.
- Ang1 \uparrow . Induces sprouting and chemotaxis in endothelial cells.
- Ang2 \uparrow , Tie2 \uparrow . Vascular remodeling, Vascular maturation.
- PEDF \downarrow . An anti-angiogenic factor.



Normal Artery

Inflammation

- 1 Retention of LDL in intima.
- 2 Minimally oxidized LDL stimulates overlying endothelial cells to produce: Adhesion molecules: ICAM-1, P-Selectin, E-Selectin, VCAM-1. Monocyte chemoattractant protein (MCP-1), Macrophage colony stimulating factor (M-CSF).
- 3 These proteins and factors lead to: Recruitment of monocytes to vessel wall and entry, NO $_2$, vasorelaxation \uparrow , permeability \uparrow , Endothelial-leukocyte adhesion molecules, Leukocyte adhesion, Monocyte proliferation and differentiation into macrophages.
- 4 TNF α and IFN γ cause macrophages to uptake highly oxidized LDL, leading to foam cell formation.
- 5 Death of foam cells leads to growing mass of extracellular lipids and cell debris.

Fibrous Plaque

- 6 Angiotensin I \uparrow , Angiotensin II \uparrow , ACE \uparrow , Homocystein \uparrow . Stimulate migration and proliferation of smooth muscle cells (SMC).
- 7 CD40 and CD40L interaction stimulates T Cells and macrophages to express cytokines (IFN γ) that can influence inflammation, smooth muscle cell growth, and matrix accumulation.
- 8 SMCs in the intima secrete extracellular matrix and give rise to a fibrous cap.
- 9 Infection, increased tissue factor and decreased plasminogen activator (PA) lead to degradation of the matrix of the fibrous cap by collagenases, gelatinases, stromelysin, and cathepsins.
- 10 Formation of thrombus results from plaque rupture, exposing tissue factor in the necrotic core.

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