ANGIOGENESIS

- **Angiogenesis is the process of forming new blood vessels.**

- **Angiogenesis is physiological** in the growth and development of the body, the female cycle, pregnancy, and tissue repair; however, **it is pathological when it promotes the worsening of a disease**.

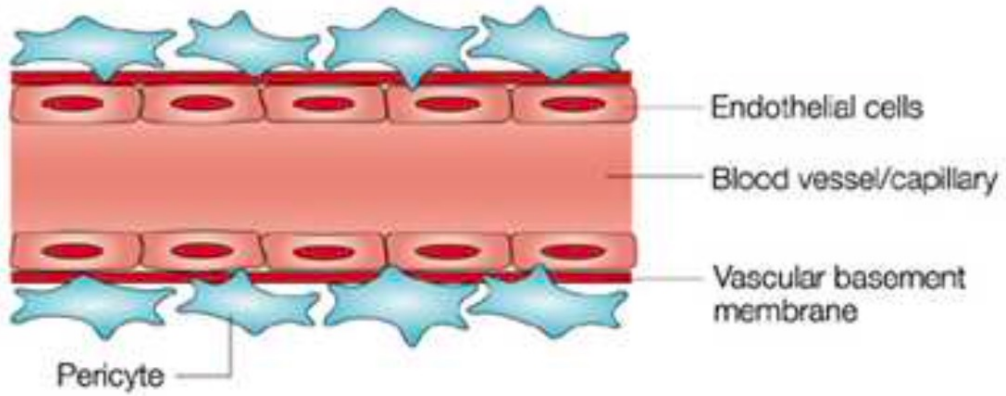
- Through angiogenesis, tumors create a network of vessels useful for gas exchanges, nutrient supply, and elimination of waste substances.

- Blocking the process of tumor angiogenesis can in some cases interfere with the growth of solid tumors.

ENDOTHELIAL CELLS

- one of the most quiescent and genetically stable cells of the body – turnover time is usually hundred of days

- proliferation is inhibited due to the contact with the capillary basement membrane



PRINCIPAL GROWTH FACTORS AND RECEPTORS IN ANGIOGENESIS

VEGF – vascular endothelial growth factors
VEGF-A – *crucial mediator of angiogenesis*

VEGF-R – receptors for vascular endothelial growth factors

Angiopoietins (Ang-1, 2)
Tie- 2 – receptor for Ang-1, -2

FGFs – fibroblast growth factors

PDGF – platelet-derived growth factor

PRO-ANGIOGENIC AND ANTI-ANGIOGENIC SIGNALS: "ANGIOGENIC SWITCH"

It is important to maintain **balance between pro-angiogenic and anti-angiogenic signals, which is known as the "angiogenic switch"**. This steady equilibrium is maintained through the activity of cellular signaling pathways, particularly through the activation of growth factor receptors.

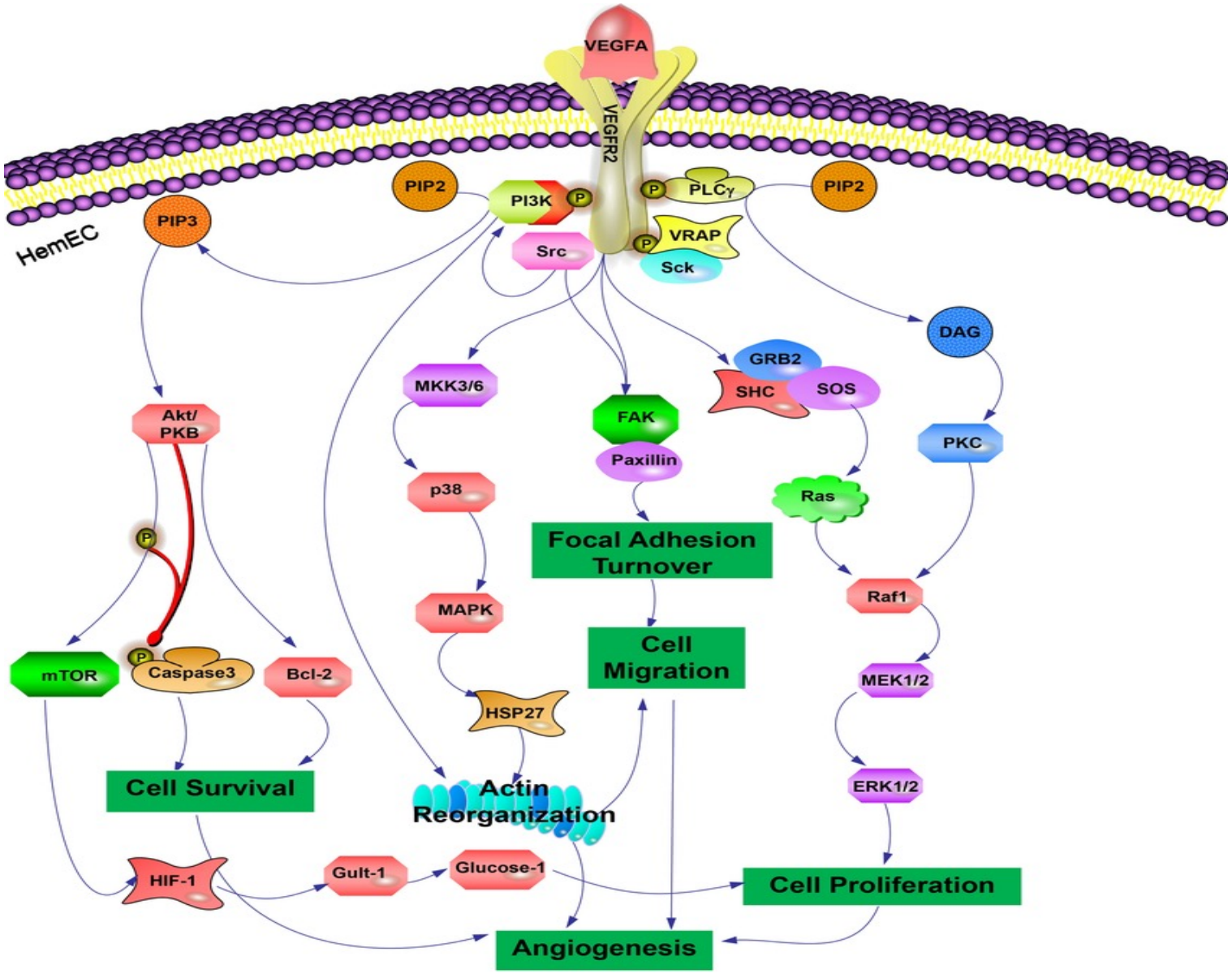
Pro-angiogenic factors include:

- ***VEGFR – vascular endothelial growth factor receptor***
- ***EGFR – endothelial growth factor receptor***
- ***PDGFR – platelet-derived growth factor receptor***
- ***TIE2 – angiopoietin-1 receptor***

Anti-angiogenic factors and endogenous angiogenesis inhibitors include:

- ***Angiostatin***
- ***Endostatin***
- ***Thrombospondin***

VEGF-A/VEGFR-2 SIGNALING PATHWAY PROMOTES ANGIOGENESIS



TYPES OF ANGIOGENESIS

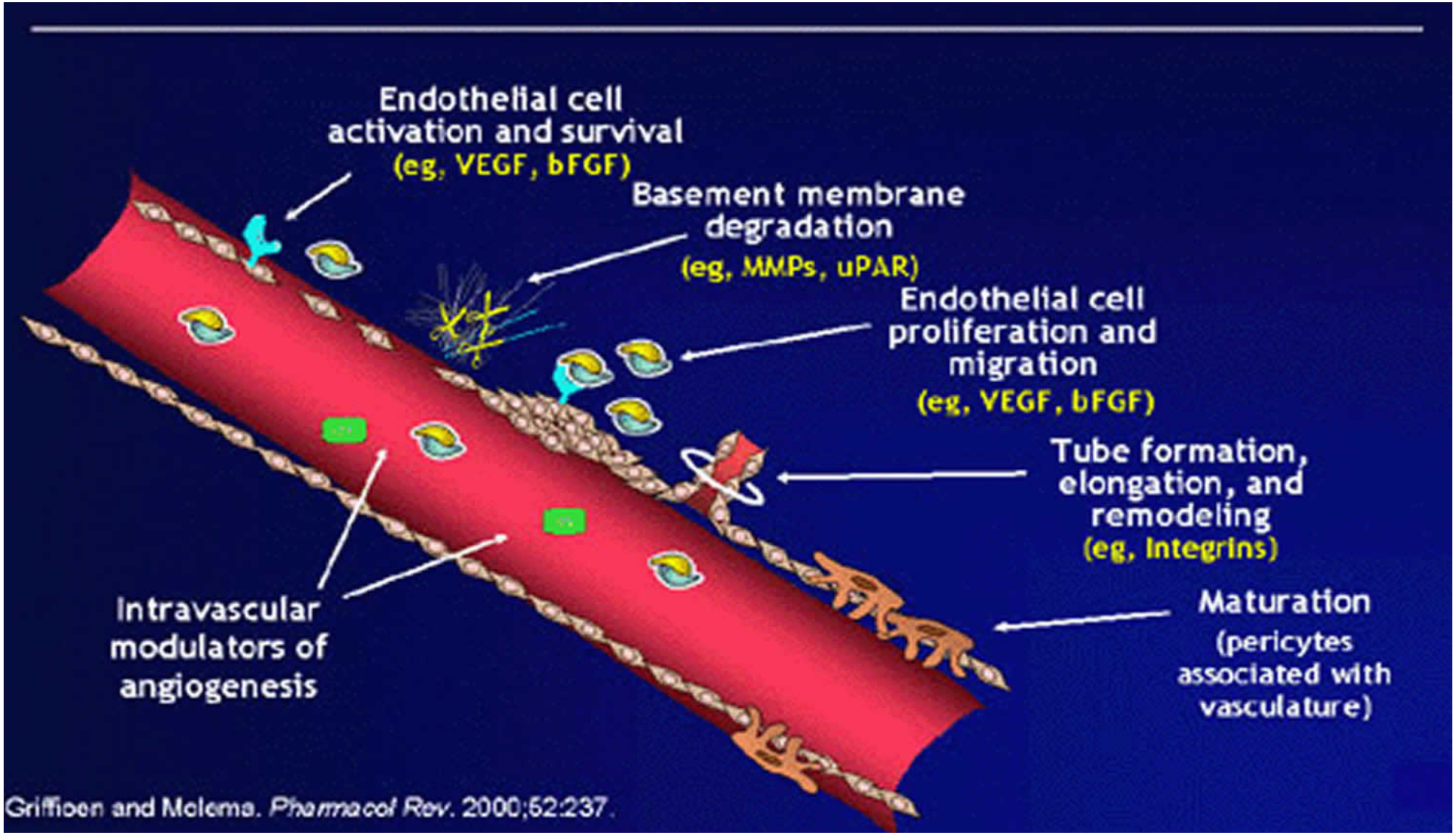
Angiogenesis is split into two main types:

SPROUTING ANGIOGENESIS

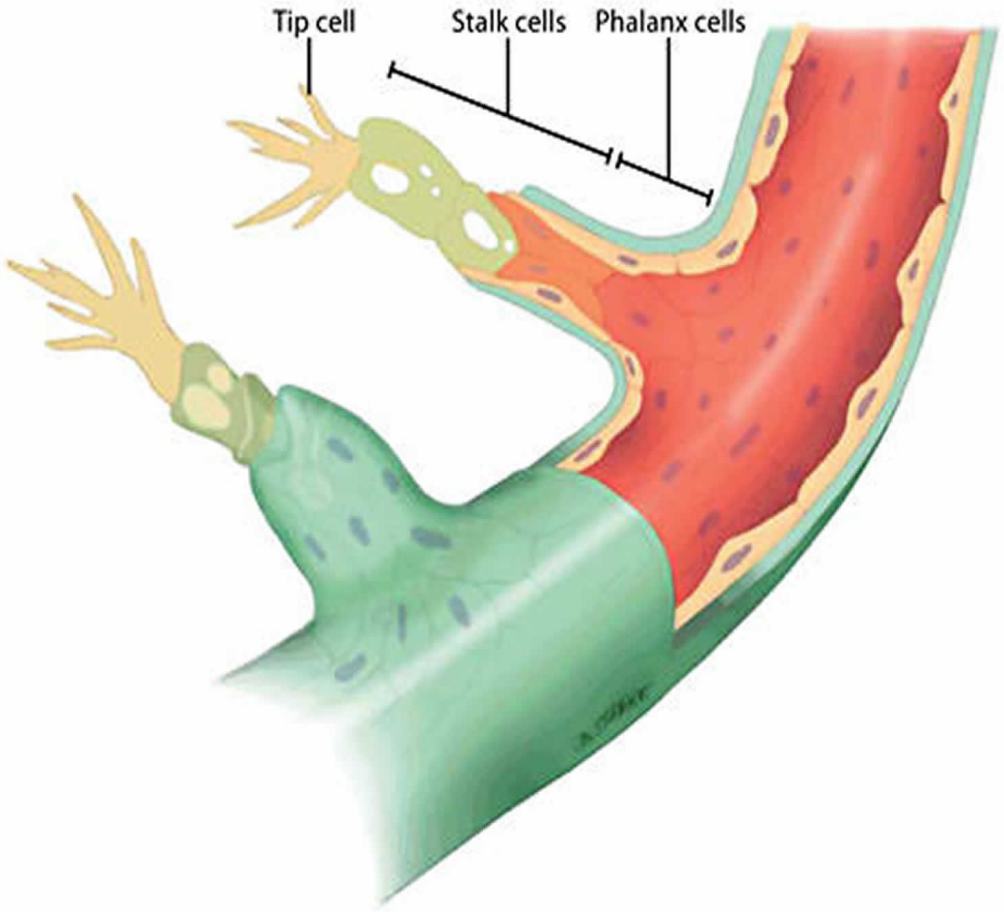
INTUSSUSCEPTIVE ANGIOGENESIS.

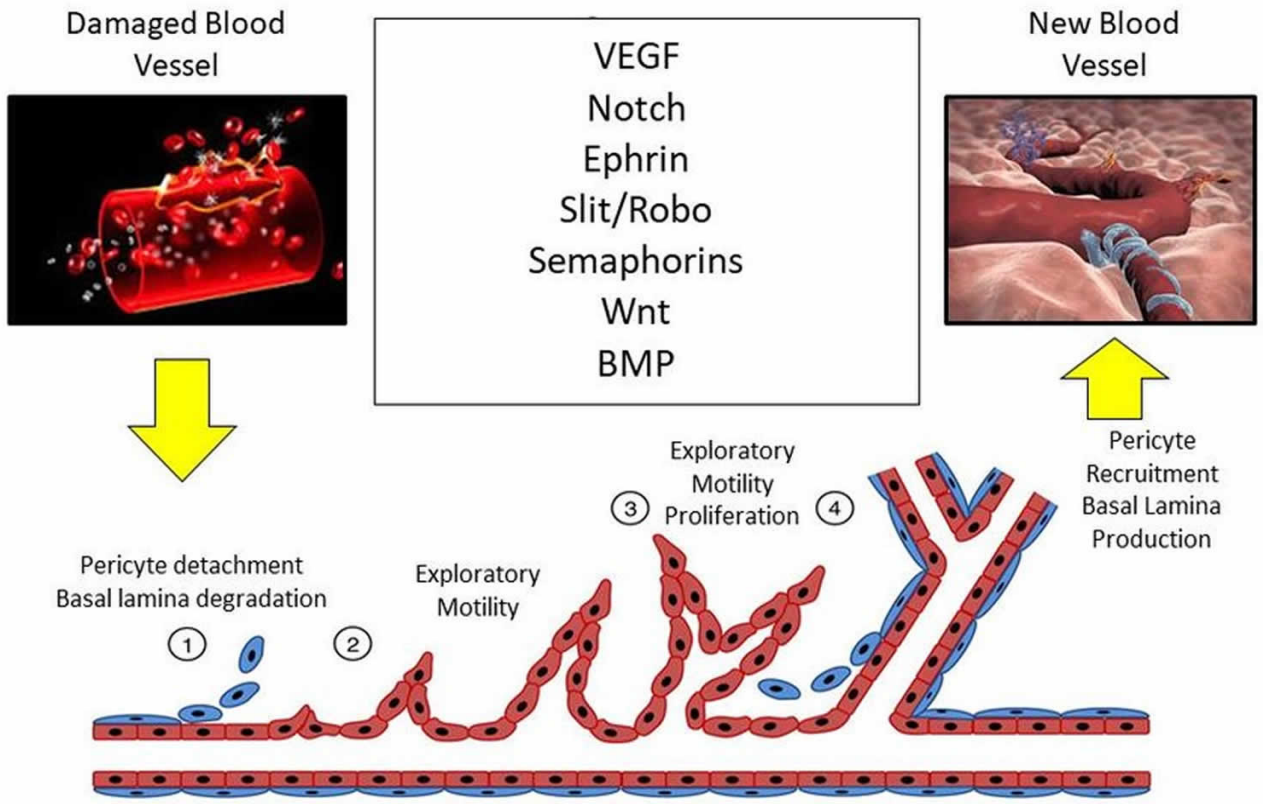
These occur both in adult organisms and *in utero*, taking place in nearly all organs and tissues.

BASIC MORPHOLOGICAL EVENTS FOR SPROUTING ANGIOGENESIS



BASIC MORPHOLOGICAL AND MOLECULAR EVENTS FOR SPROUTING ANGIOGENESIS





SPROUTING ANGIOGENESIS: SUMMARY

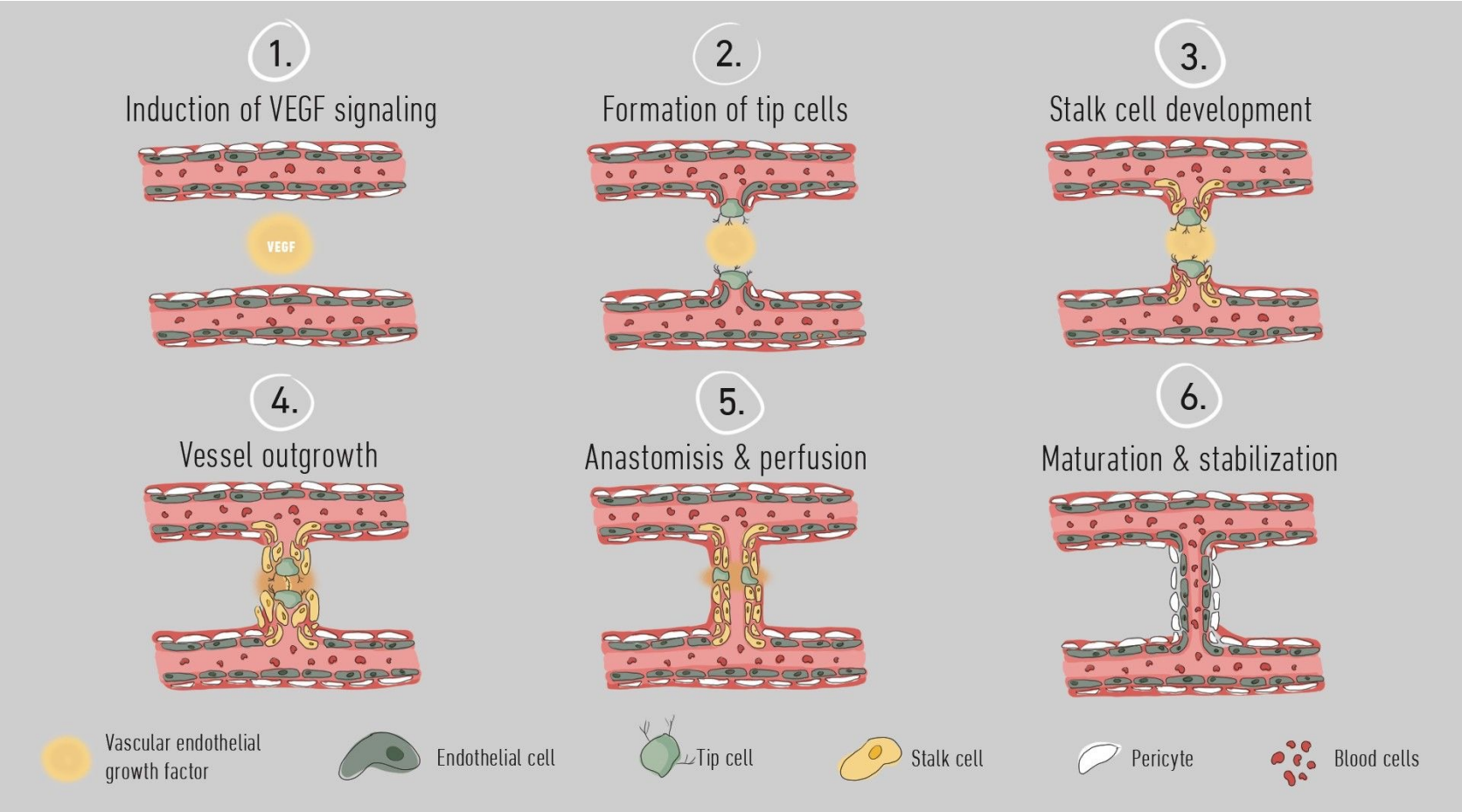
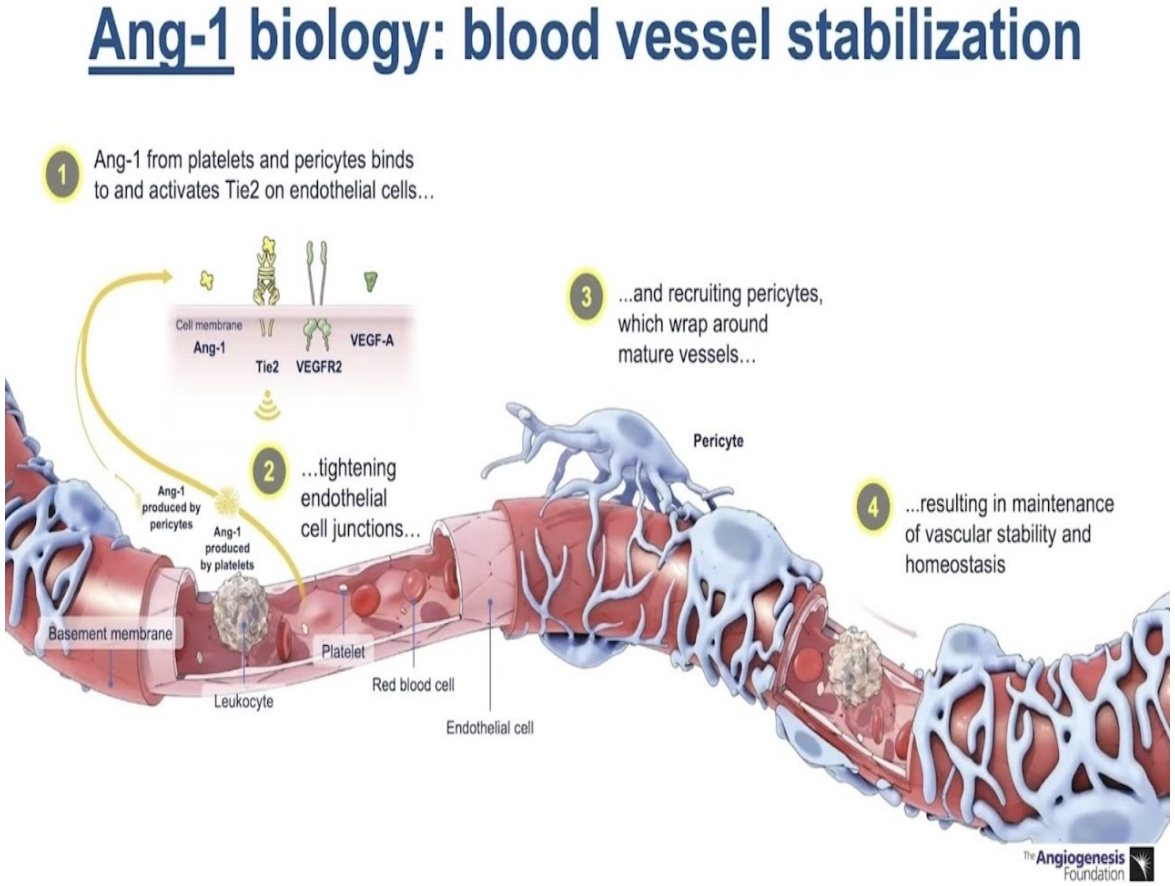
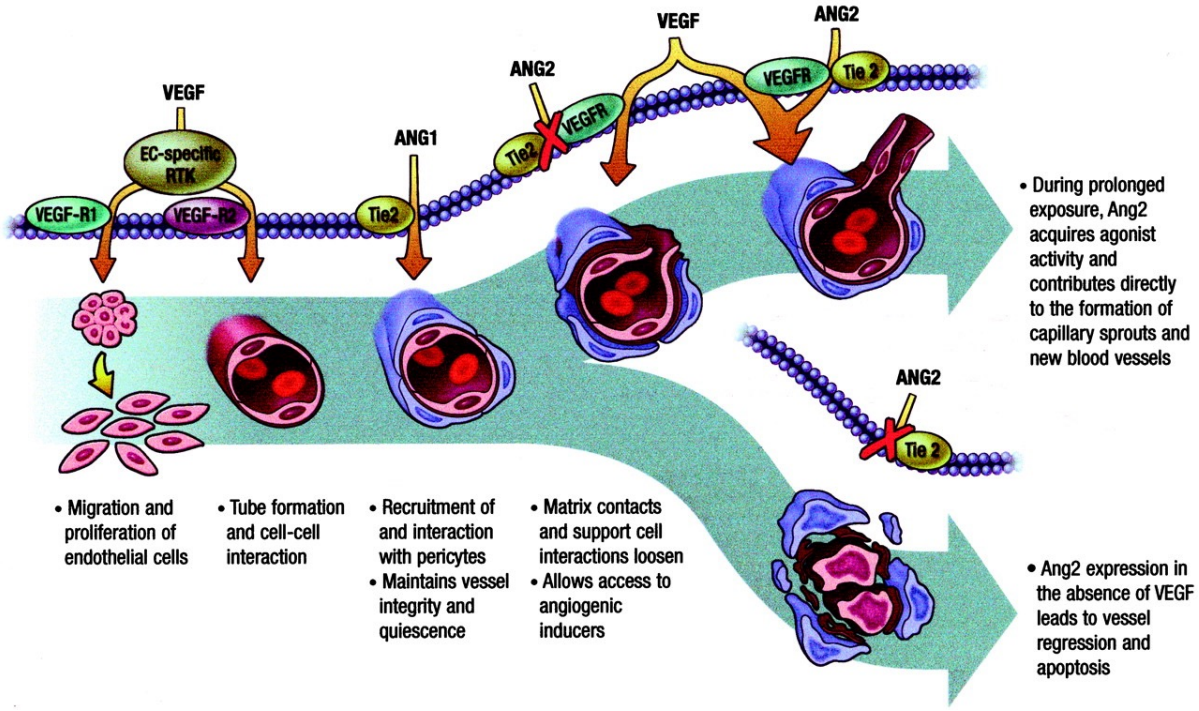


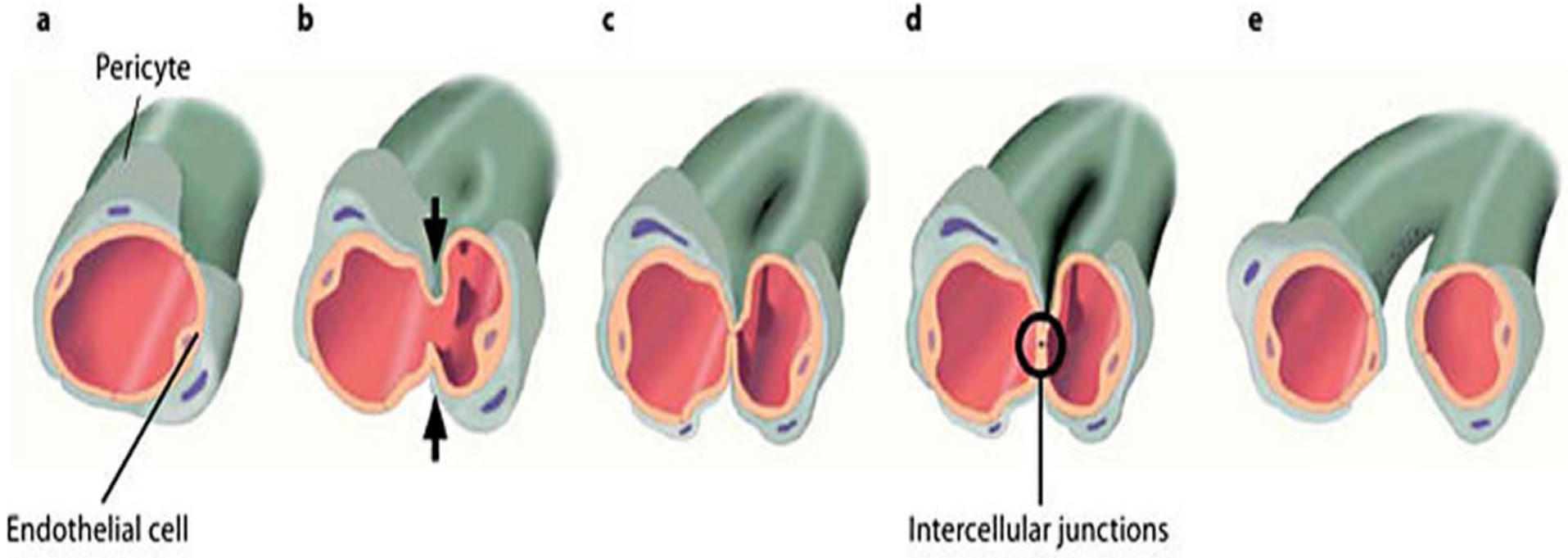
Figure 1: *The stages of sprouting angiogenesis.*

SPROUTING ANGIOGENESIS: SUMMARY





INTUSSUSCEPTIVE ANGIOGENESIS OR "SPLITTING" ANGIOGENESIS



Schematic illustration of a small capillary surrounded by pericytes (a) undergoing intussusceptive angiogenesis. The opposite walls of this capillary start to migrate to each other (b), an intraluminal pillar is formed (c), and the cellular junctions of the opposing endothelial cells are rearranged (d). Subsequently, further growth of the pillar leads to spitting of the blood vessel into two new vessels (e).

FORM OF INTUSSUSCEPTIVE ANGIOGENESIS

Three forms of intussusceptive angiogenesis are recognized, depending on the outcome or phenotype of these forms

- intussusceptive microvascular growth (intussusceptive microvascular growth),
- intussusceptive arborization (intussusceptive arborization),
- intussusceptive branching remodeling (intussusceptive branching remodeling)

TUMOR ANGIOGENESIS

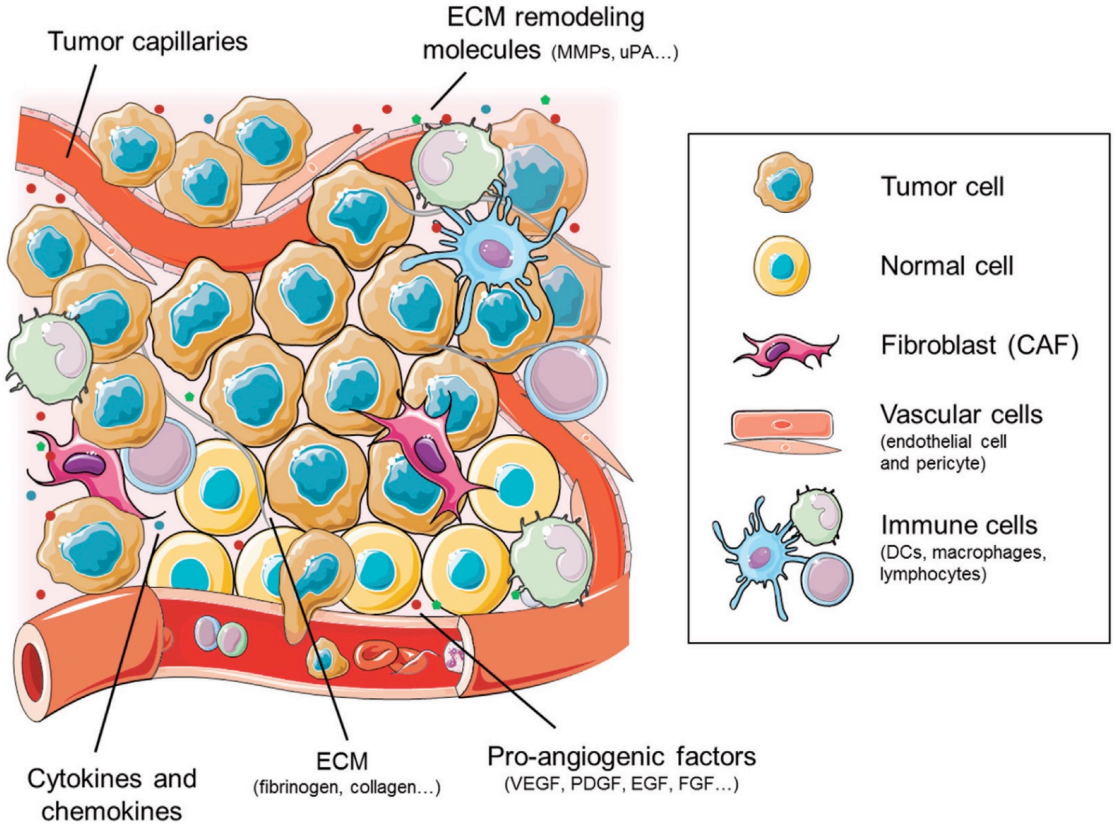


Fig 1 | Cellular and molecular components of the tumor ecosystem that shape the tumor angiogenic landscape. The cellular components primarily consist of tumor and normal cells, together with the vascular endothelial and pericyte cells and the stromal fibroblasts [cancer-associated fibroblasts (CAFs)]. The immune cell compartment comprises mainly tumor-infiltrating macrophages, dendritic cells (DCs), and lymphocytes.

Zuazo-Gaztelu I and Casanovas O (2018) Unraveling the Role of Angiogenesis in Cancer Ecosystems. Front. Oncol. 8:248. doi: 10.3389/fonc.2018.00248

TUMOR ANGIOGENESIS