1.6.3 The angiogenic switch

Angiogenesis is generally suppressed in healthy adult organisms and is turned on temporarily in settings such as the female reproduction cycle or during tissue repair processes (Folkman and Shing 1992). The “angiogenic switch” (Augustin 2003) is determined by the opposing faces of proangiogenic and anti-angiogenic factors. Depending on the activity on each end of the balance, the “angiogenic switch” is turned “Off”, “On”, or is in a balance. The “angiogenic switch” is likely turned “On” in several diseases such as psoriasis, rheumatoid arthritis, diabetic retinopathy, and cancer (Carmeliet 2003). Switching to an angiogenic phenotype likely requires both up-regulation of angiogenesis activators and downregulation of angiogenesis inhibitors (Nyberg *et al.,* 2005). Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are the most extensively studied angiogenesis inducers (Mesri *et al.,* 2001). Among the various endogenous inhibitors of angiogenesis (O'Reilly *et al.,* 1997) certain factors like Arresten (Colorado *et al.,* 2000), Canstatin (Kamphaus *et al.,* 2000) and Tumstatin (Hamano and Kalluri 2005) are derived from the extracellular matrix (ECM). The ECM is a complex structure composed of many different glycoproteins, proteoglycans and hyaluronic acid.

1.6.4 Advantages of endothelial cells as targets of anti-tumor therapeutics

_ Resistance does not occur as often as it does with drugs that directly target tumor cells. Unlike tumor cells, endothelial cells are genetically stable, diploid and homogenous. Spontaneous mutations are rare and prolonged treatments are possible

_ Tumor endothelial cells divide 50–100 times more rapidly than normal endothelial cells, and activated endothelial cells express markers that quiescent endothelial cells do not express and if they do, expression is much lower