1.6 Angiogenesis Inhibitors

Angiogenesis is the process of growth of new capillaries from pre-existing blood vessels, the vasculature remains quiescent in most tissues, except those tissues that undergo transient neovascularization in the female reproductive system and wound repair (Hanahan and Folkman 1996, Folkman 1995). It is now believed that a switch of angiogenic phenotype in a tissue is dependent upon the local balance between angiogenic factors and inhibitors. Although upregulation of angiogenic factors is necessary to stimulate angiogenesis, simultaneous downregulation of angiogenesis inhibitors is also required to sufficiently turn on angiogenesis. The quiescence of the vasculature in a tissue suggests that the tissue either lacks angiogenic stimuli or angiogenesis is suppressed by endogenous inhibitors. For example, in some adult tissues and organs, high levels of expression of angiogenic factors such as vascular endothelial growth factor (VEGF) do not induce new blood vessel growth (Ferrara 1999), suggesting that the production of angiogenesis inhibitors is prominent.

The growth of new blood vessels requires quiescent endothelial cells to degrade the local basement membrane, to change their morphology, to proliferate, to migrate, to invade into the surrounding stromal tissue, to form micro tubes to sprout new capillaries, and to reconstitute new basement membrane (Jain *et al.,* 1997).

Angiogenesis is involved in the development and progression of pathogenic processes of a variety of disorders, including diabetic retinopathy, psoriasis, rheumatoid arthritis, cardiovascular diseases, and tumor growth (Folkman 1995, Folkman 1971).

Since several organs and tissues in the body such as the cartilage and the cornea lack blood vessels, it has been hypothesized that these avascular tissues over-express angiogenesis inhibitors (Moses *et al.,* 1990, Moses and Langer 1991).