1.6.2 Hypoxia-Driven angiogenesis

Hypoxia is believed to be an important driving force behind tumor-promoted angiogenesis (for reviews, see (Ferrara 1997, Royds *et al.*, 1998). Tumors are thought to become hypoxic when their growth rate exceeds that of neovascularization or when their fragile, poorly organized vasculature partially collapses under interstitial pressures (Helmlinger *et al.*, 1997).

Areas of central necrosis arise from excess VEGF production, which in turn leads to increased permeability of immature tumor vessels and interstitial edema restricting tumor circulation. Nevertheless, all solid tumors experience gradients of oxygen, pH, and nutrients stemming from the differential perfusion of blood into tumor tissues (Scott *et al.,* 1998). Cells near the center of the tumor or furthest away from the supporting vasculature become necrotic, which stimulates the production of angiogenic growth factors. Most notably, the pro-angiogenic growth factor VEGF has been shown to be up-regulated in the vicinity of necrotic tumor areas (Brekken *et al.,* 1998, McCarthy *et al.*, 1998, Rofstad and Danielsen 1998).

The production of VEGF in breast cancer cell lines in response to several stimuli (hypoxia, pH, hypoglycemia, hormones, and vitamin D), hypoxia was found to be the most potent inducer of VEGF expression (Scott *et al.,* 1998).

Tumors subjected to transient hypoxia in vitro have shown increased metastatic potential and increased resistance to chemotherapy (Brown, 1998) and radiotherapy (Guichard *et al.*, 1998).