healing process (Davidson and Benn 1996) and of the female reproductive cycle (e.g., during ovulation and gestation) (Yamamoto *et al.,* 1997).

Physiological angiogenesis in adults is a precisely regulated process that is associated with the growth of normal tissues in the body. The angiogenic process under normal conditions is self-limiting, "switching-off" after achieving the appropriate biological end point (e.g., a healed wound). On the other hand, for pathophysiological conditions such as malignancies, the angiogenic process continues unabated and paves the way for aberrant tissue growth (Reynolds and Redmer 1998).

To initiate an angiogenic process, endothelial cells have to break down the basement membrane surrounding them. This process is usually accomplished by the proteolytic activity produced by endothelial cells. Metalloproteinases (MMPs) play a critical role in the degradation of the endothelial basement membrane (O'Reilly *et al.,* 1999, Hiraoka *et al.,* 1998). Therefore, almost all MMP inhibitors including TIMP- 1,2,3 suppress angiogenesis (Zhou *et al.,* 2000). It seems that proteases also contribute to the down-regulation of the process of angiogenesis.

Angiogenesis can occur in a sprouting-dependent or non-sprouting-dependent manner. During sprouting angiogenesis, endothelial cells degrade the vascular basement membrane (VBM), invade into the surrounding tissue and proliferate in response to angiogenic factors. Nonsprouting angiogenesis, also known as intussusception, occurs as a longitudinal division of an existing vessel (Carmeliet and Jain 2000).

Sprouting angiogenesis proceeds via several well-characterized stages. Upon activation by pro-angiogenic stimuli, endothelial cells first begin to release matrix metalloproteinases that degrade the basement membrane to enable migration into the perivascular space and towards angiogenic stimuli. This is followed by the