Angiostatin induces intracellular acidosis and anoikis in endothelial cells at a tumor-like low pH.

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Angiostatin inhibits angiogenesis by binding to endothelial cells (ECs) lining the vasculature of growing tumors. These cells are in a dynamic state during angiogenesis and are thus not firmly attached to the extracellular matrix. This makes them more vulnerable to anoikis, a process resulting in cell death initiated by or promoted by loss of attachment. Another potential source of EC vulnerability during tumor angiogenesis is that tumor extracellular pH is typically lower than in normal tissues. This presents an additional challenge to ECs in terms of maintaining ionic homeostasis. We report here that the lethality of angiostatin is significantly enhanced both by reduced matrix attachment during exposure and lowered extracellular pH (pH(e)). Another effect of angiostatin at reduced pH(e) is a decreased intracellular pH (pH(i)). These effects were observed in three model systems: aortic ring sprouts, ECs during tube formation, and ECs in a scratch/migration assay. In these three dynamic assays, angiostatin-induced cell death and intracellular acidification were clearly seen when pH(e) was reduced to 6.7. The intracellular acidification was far greater than that induced by pH(e) reduction alone. In contrast, the effect of angiostatin on pH(i) and on viability were not observed in a subconfluent monolayer in which the cells were allowed to attach to substrate for 48 h prior to exposure to angiostatin. These data suggest that low pH(e) and reduced adhesion to matrix play a role in the specificity of angiostatin for tumor neovasculature in contrast to wound healing and other normal angiogenic processes. The results also implicate roles for both pH(e) and pH(i) regulation in the mechanism of angiostatin action.