Overexpression of hyaluronan synthase-2 enhances angiogenesis and stroma reaction in neu-induced mammary tumors.

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Tumor angiogenesis, referred to the formation of new blood vessels toward and within the tumor, is accompanied with the remodeling of extracellular environment in tumor tissues. Here we investigated the roles of hyaluronan-rich extracellular matrix in tumor angiogenesis using MMTV-Neu mammary tumor model. Transgenic mice that allow expression of mouse hyaluronan synthase 2 (Has2) in a manner dependent on Cre-mediated recombination were generated and crossed with the MMTV-Neu mice. By expressing Cre recombinase under the control of MMTV promoter, the bigenic mice bearing Has2 and neu transgenes exhibited a deposition of hyaluronan matrix and aggressive growth of Neu-initiated mammary tumors. Immunohistochemical staining with an antibody specific for CD31 endothelial cell marker revealed that neovascularization in the tumors proceeded in normal fashion with a ring of endothelial cells surrounding by hyaluronan-rich matrix, but the number of tumor microvessels was significantly increased in the tumors of Has2 overexpressing mice as compared with those of the control mice. Notably, the forced expression of Has2 enhanced the infiltration of stromal cells into mammary tumor compared to the control mice. This was consistent with the increased deposition of fibronectin and collagen type I in tumor-associated stroma. These results suggest that hyaluronan enhances tumor angiogenesis and stroma reaction in neu-induced mammary tumors.