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Substrates and downstream effectors of the Convertases in the malignant phenotype: New anti-cancer therapy approach.

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To attain their biological active forms, a variety of protein precursors are processed by proteases named proprotein convertases (PCs). Our previous studies were the first to demonstrate the importance of the maturation of protein precursors such as matrix metalloproteases, adhesion molecules, and growth factors by these enzymes in carcinogenesis, angiogenesis and metastasis. We found that inhibition of the PCs in various tumor cells inhibit their malignant phenotypes and their ability to mediate tumor growth and angiogenesis. We also identified PDGF-A, PDGF-B, VEGF-C as new PCs substrates. Inhibition of these molecules processing by specific inhibitors or through directed mutagenesis blocks tumor growth and the formation of tumor vascular and lymphatic vessels. Based on these and other findings we postulate that PCs play a key role in the growth, survival and metastatic potential of tumor cells by regulating the activity of their cognate substrates and downstream effectors. Regulation of PCs activities may provide a powerful adjunct approach in cancer therapy. The aim of our research program is to develop and evaluate the effect of small inhibitor molecules of the PCs on the malignant phenotype of tumor cells, tumor progression, angiogenesis and metastasis. The identification of specific and potent small molecule compounds as anti-tumorigenic and angiogenic agents will have the chance to be used alone or in conjunction with standard therapy in clinical settings.

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