

TITLE

SIGNALING MECHANISMS OF ENDOGENOUS ANTI- CANCER MOLECULES DERIVED FROM EXTRA CELLULAR MATRIX TYPE IV COLLAGEN

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Cancer is currently one of the most prevalent causes of human deaths in the world. Current therapeutic options aim only to slow the progression of cancer disease. Therefore, a renewed effort must be made to identify relevant endogenous cancer inhibitors that could be exploited as therapeutic drugs. We identified several endogenous anti-cancer molecules, which are released from extracellular matrix (ECM) into the circulating blood of cancer patients. Several of these endogenous circulating molecules were cloned in the laboratory and identified them as angioinhibitors of solid tumor growth. These endogenous angioinhibitory proteins binding to cell surface integrins and transduce the signalling mechanisms in regulating angioinhibitory activity. Thus, integrins serve as transmembrane linkers between the ECM and cytoskeleton for outside-in signalling. One such endogenous circulating molecule, tumstatin, a 28-kDa protein from the C-terminal non-collagenous (NC1) domain of alpha3 type IV collagen was earlier identified by us as an inhibitor of angiogenesis (Science 2002; PNAS 2003). Tumstatin interacting with alphaVbeta3 integrin and inhibits activation of focal adhesion kinase (FAK), phosphatidylinositol 3-kinase (PI-3K), serine/threonine kinase (Akt/protein kinase B), mammalian target of rapamycin (mTOR) and prevents dissociation of eukaryotic translation initiation factor 4E (eIF4E) from 4E binding protein (4E-BP1) leading to the inhibition of Cap-dependent translation in proliferating endothelial cells. Recently, we also discovered that tumstatin inhibits hypoxia induced pro-inflammatory cyclooxygenase-2 (COX-2) expression via FAK/Akt/NFkB pathway, leading to decreased tumor angiogenesis and tumor growth in an alpha3beta1 integrin dependent manner (Blood 2007; J Canc Sci Ther 2009). At present my laboratory is studying to understand four such endogenous angioinhibitors derived from type IV collagen that include tumstatin, arresten, combostatin and malignostatin which are involved in cell signalling and the way these proteins control adhesion and migration of endothelial cells in pathological processes involved tumor angiogenesis.