Extracellular Matrix Pathology

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William G. Stetler-Stevenson, MD, PhD., Head, Extracellular Matrix Pathology Section
Building 10, Room 6B05
(240) 760-6105

To learn more, visit https://www.irp.nih.gov/pi/william-stetler-stevenson and/or https://scholar.google.com/citations?user=MUtfyW8AAAAJ&hl=en&oi=ao

General Information

Mailing Address:
Extracellular Matrix Pathology Section
Laboratory of Pathology, CCR
National Cancer Institute
Building 10, Room 6B01
10 Center Dr.
Bethesda, MD 20892-1500

Our Science

The Extracellular Matrix (ECM) Pathology Section investigates novel biologic functions of matrix molecules in regulation/modulation of tissue homeostasis, cellular invasion and migration. Specifically, we are focused on the role of Matrix Metalloproteinases (MMPs) and their endogenous inhibitors. Early work in our laboratory identified the molecular and cellular mechanisms of MMP2 activation, and discovery of a new member of the Tissue Inhibitor of MetalloProteinase family, TIMP-2 1-3.

The overarching principle of our research is to utilize highly focused, multifaceted approaches to rigorously study the mechanisms of ECM composition, function and structure in suppression of cell growth, migration, invasion and angiogenesis. Disruption of these pathways contributes to the pathogenesis of chronic diseases, such as cancer progression and metastasis, as well as cardiovascular and neurodegenerative diseases. Our working premise that TIMPs are multifunctional proteins, not just protease inhibitors, was based on our observations that TIMP2 suppression of cell proliferation is dissociable from the MMP inhibitory activity 4,5 (See Figure 1). Continuing investigation led my laboratory to develop a novel TIMP-2 reagent lacking MMP inhibitory activity know as Ala+TIMP-2 6. Utilizing this novel reagent we successfully demonstrate that TIMP-2 inhibition of angiogenesis and primary tumor growth are mediated via MMP-independent mechanism requiring cell surface integrin receptor interactions and protein phosphatase activity 7-10. Our current objective is to translate these basic discoveries of TIMP biology into new effective treatment strategies to prevent disease progression that will result in substantial clinical therapeutic and public health impact.

Ongoing research efforts are directed at elucidating the functional significance of recently discovered post-translational modifications (phosphorylation)11, and co-chaperone role of TIMP2 in regulation of MMP2 activity and cellular functions described above12.


