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Identification by metabolomic analysis of a novel cellular arsenal against inflammation and cancer metastasis

Statement of the Problem: Overexpression of cyclooxygenase-2 (COX-2) and pro-inflammatory (PI) cytokines is a major contributor to human systemic inflammatory disorders and cancer metastasis. Expression of COX-2 and PI cytokines are regulated by transcriptional mechanisms, but it remained unclear whether it is endogenously controlled by small molecules.

Conceptual & Experimental Orientation: We suspected that human cells such as fibroblasts release soluble factors into the extracellular milieu which act in a paracrine manner to control COX-2 and PI cytokine expression. Soluble factors isolated from normal cells inhibit COX-2 overexpression in inflammatory and cancer cells. NMR analysis suggests that the soluble factors contain indole moiety. We named the factors cytoguardins. We subsequently found that cancer cells do not release cytoguardins. Comparative metabolomics analysis coupled with molecular genetics and biochemical studies identify 5-methoxytryptophan (5-MTP) as a cytoguardin. Endothelial cells (ECs) produce abundant 5-MTP which accounts for a high human serum level of 5-MTP. 5-MTP is a powerful innate factor defending against systemic inflammation and cancer cell metastasis. Compromised 5-MTP production due to insulting agents such as LPS results in COX-2 and cytokine storm, organ failure and death in animal models. Administration of 5-MTP attenuates cytokine storm and prevents organ failure and death. 5-MTP inhibits cancer cell migration and EMT *in vitro* and cancer metastasis in murine xenograft tumor model. 5-MTP exerts its biological actions in part by blocking p38 MAPK, p300 HAT and NF-kB activation.

Conclusion & Significance: Human cells such as fibroblasts and endothelial cells produce and release 5-MTP to maintain inflammatory homeostasis and control cancer metastasis by inhibiting the expression of COX-2 and PI genes. It represents a new class of protective molecules and a valuable lead compound for developing new drugs against systemic inflammatory disorders and cancer metastasis.

Biography

Kenneth K Wu has received his MD from National Taiwan University, Taipei, Taiwan, MS from Yale University New Haven, CT, USA and PhD in Pharmacology from University of London, UK. He was the Huffington Chair and Director of Hematology Division at University of Texas Health Science Center at Houston and Distinguished Investigator and Former President of National Health Research Institutes (NHRI), Taiwan. He is currently a Distinguished Professor and Director of Metabolomic Medicine Research Center at CMU, Taiwan. He holds Ho Jin Dui Chair at NTHU and Distinguished Chair at National Taiwan University, Taiwan. His research interests have centered on thrombosis, vascular biology and prostaglandin synthesis and regulation. He is a Member of several distinguished academic societies and has received international recognitions and awards.

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