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Hypoxia and inflammation activate a sequential pathway leading to tumor progression

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HIF1α and NFkB are two transcription factors involved in tumor growth and progression. HIF1α and NFkB regulate transcription of over a thousand genes that, in turn, control adaptation to hypoxia, metabolic reprogramming, inflammatory-reparative response, extracellular matrix digestion, etc. Interestingly, hypoxia and inflammation have been sequentially bridged in tumors by the discovery that alarmin receptors genes such as RAGE, P2X7 and some TLRs, are controlled by HIF1α; and that, in turn, alarmin receptors are activated by alarmins (DAMPs) released by necrotic tumor cells. The signaling of alarmin receptors converges to activate NFkB and proinflammatory gene expression, in surviving tumor cells, evidencing all the hallmarks of the malignant phenotype. Although many pieces of the puzzle have been rightly placed into this hypothetical framework, a number of questions are still waiting to be answered. What is the precise role of the individual HIF-dependent genes? What is the role of the NFkB-dependent gene families in generating the malignant phenotype? What tumor cells (stem cells?) are best responding to the hypoxia adaptation and to the proinflammatory gene expression? How metastasis are generated and conditioned to the final site? How is determined the metastatic pattern in the individual patient? Can inhibitors of HIF and/or NFkB pathway change substantially tumor progression? Recently, drugs have been identified that inhibit one or both transcription factors. Many of these molecules are natural compounds or off-label drugs already used to cure other pathologies and some of them are undergoing clinical trials either alone or in combination with standard anti-tumoral with the primary end-points of a better quality of life and a net increase in survival.

Biography

Matteo A Russo is full Professor of General Pathophysiology at School of Medicine, University of Rome Sapienza, Rome, Italy. He graduated in Medicine and Surgery (1969). Specialized in Cardiology, Oncology and General Pathology, is a Fulbright Scholar (1974-1976) in Philadelphia, at University of Pennsylvania and Temple University, Adjunct Professor of Pathology and Pharmacology (1980-1990) at Temple University and Member of the Research Committee of Italian Ministry of Health (2000-2007). At present, he is Director of the Research Doctorate in Human Pathology of University of Rome, Sapienza; Member of Scientific Committee of Fondazione San Raffele, Milan; Member of Scientific Committee of IRCCS San Raffaele Pisana, Rome. He has published more than 150 papers in reputed journals and serving as an editorial board member of 7 journals.Some research interest: a) Mechanisms of cell volume control independent from ATP-ase Na/K-dependent, b) Ca^{++} and cytoskeleton in the pathogenesis of necrosis and apoptosis and c) Proinflammatory genes expression in different human diseases (brain and tumors).

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