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Abstract: In contrast to expectations in the past that tumor starvation or unselective inhibition of proteolytic activity would cure cancer, there is accumulating evidence that microenvironmental stress, such as hypoxia or broad-spectrum inhibition of metalloproteinases can promote metastasis. In fact, malignant tumor cells, due to their genetic and epigenetic instability, are predisposed to react to stress by adaptation and, if the stress persists, by escape and formation of metastasis. Recent recognition of the concepts of dynamic evolution as well as population and systems biology is extremely helpful to understand the disappointments of clinical trials with new drugs and may lead to paradigm-shifts in therapy strategies. This must be complemented by an increased understanding of molecular mechanism involved in stress response. Here, we review new roles of Hypoxia-inducible factor-1 (HIF-1), one transcription factor regulating stress response-related gene expression: HIF-1 is crucial for invasion and metastasis, independent from its pro-survival function. In addition, HIF-1 mediates pro-metastatic microenvironmental changes of the proteolytic balance as triggered by high systemic levels of tissue inhibitor of metalloproteinases-1 (TIMP-1), typical for many aggressive cancers, and regulates the metabolic switch to glycolysis, notably via
activation of the microRNA miR-210. There is preliminary evidence that TIMP-1 also induces miR-210. Such positive-regulatory co-operation of HIF-1?, miR-210, and TIMP-1, all described to correlate with bad prognosis of cancer patients, opens new perspectives of gaining insight into molecular mechanisms of metastasis-inducing evasion of tumor cells from stress.

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