Current insights of therapeutics against hypoxia-mediated metastasis in cancer cells (Review)

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Introduction: Metastasis of malignant cells is a major challenge in clinical therapy of advanced cancers and the main reason for high patient mortality. Due to migration of cancer cells to adjacent and/or distant locations, conventional modalities such as surgery and chemoradiotherapy would not lead to promising outcomes. From a molecular perspective, different microenvironmental factors influence motility of cancer cells including oxygen level. Due to impaired delivery of oxygen and high rate of its consumption in solid tumors, hypoxia is a common feature of tumor microenvironments. Hence, understanding mechanisms involved in hypoxia-mediated metastasis would introduce potential biomarkers and novel therapeutic targets.

Methods: Published articles including key words cancer cell metastasis, hypoxia and targeted therapy were extracted in databases PubMed, Web of Science and Scopus.

Results: Among different metastasis mediators, hypoxia inducible factors (HIFs) are the one that coordinate cellular responses to low oxygen tension by controlling anaerobic metabolism, angiogenesis, immune evasion and cell proliferation. In this regard, agents that attenuate HIFs level or mechanism of action are at the center of attention, including cetuximab that down-regulates HIF expression, benzophenone-1 that blocks its nuclear localization and bisphenol that mediates HIF degradation. Another interesting approach is the use of hypoxic prodrugs that could exclusively be activated in hypoxic cancer cells. Examples of such agents are apaziquone, evofosfamide and tirapazamine, although results of their clinical trials were disappointing. Meanwhile, combination of HIF inhibition and immunotherapy has been proposed as a powerful anticancer strategy, as HIFs regulates the tumor immune response. Nevertheless, efficacy of this approach needs to be more investigated in the future.

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Keywords: Cancer cell metastasis, Hypoxia, Targeted therapy