**Fatal Alliance of Hypoxia-/HIF-1- driven Microenvironmental Traits Promoting Cancer Progression and Resistance to Therapy**

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**Abstract:** Inhospitable microenvironmental conditions are a characteristic feature (“hallmark”) of most solid tumors. Heterogeneously distributed subvolumes of critically low oxygenation (hypoxia) is believed to be the most crucial deficiency, since it has been well documented to play a significant role in malignant progression, in inducing resistance to therapy and in the suppression of antitumor immune responses (1,2). Severe hypoxia is often associated with other detrimental conditions in the tumor microenvironment (TME), e.g. as a consequence of hypoxia-/HIF1-induced metabolic reprogramming. These traits individually or collectively operate towards cancer progression. Alternatively, upregulation of HIF-1 by oncogene activation, mutation of suppressor genes or epigenetics can likely provide a selective growth advantage of cancer cells with subsequent disease progression.

Exemplarily, the following features of the TME as key drivers for tumor progression will be discussed: (a) *hypoxia/HIF-1 pathway proteins*; (b) consequences of *metabolic reprogramming*, e.g., increase in glycolytic flux\* with lactate accumulation up to 40 mM , increased glutaminolysis with elevated ammonia levels up to 5 mM, high uptake/turnover of tryptophan and arginine, and declining nutrient resources; (c) *extracellular acidosis* (pH≤ 6.8) as a consequence of upregulated aerobic glycolysis (“Warburg effect”), ATP hydrolysis, ketogenesis, glutaminolysis and CO2/carbonic acid production; (d) extracellular *accumulation of adenosine* up to 100µM*.*

[***\**** Of note, although aerobic glycolysis yields less ATP than OXPHOS (2 vs. 36-38 molecules), the glycolytic flux allows rapid production of ATP since the speed of ATP generation is approx. 100-times faster than in OXPHOS.]

References: (1) Mayer A, Vaupel P (2013) Hypoxia, lactate accumulation, and acidosis: Siblings or accomplices driving tumor progression and resistance to therapy? Adv. Exp. Med. Biol. *789*: 203 - 209. (2) Vaupel P, Multhoff G. (2018) Hypoxia-/HIF1α driven factors of the tumor microenvironment impeding antitumor immune responses and promoting malignant progression. Adv. Exp. Med. Biol. (in press).

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