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Melanoma and Hypoxia Melanoma is an Aggressive Skin Tumor

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Short Communication

Melanoma and Hypoxia Melanoma is an aggressive skin tumor, although it is responsible of 5% of all skin cancer, it causes about 70% of all skin cancer death cases [1]. One of the important characteristics of melanoma is rapid metastasis. The rapid metastasis of primary melanoma is mainly through the effect of intercellular hypoxia. Hypoxia changes the expression of several enzymes, those enzymes change tumor cell behavior; the change in the expression of enzymes could be used in the treatment, predicting measures for the metastasis and recurrence. Hypoxia enhances the expression of hypoxia inducible factor -1 (HIF-1). Hypoxia inducible factor 1 (HIF-1) is the main regulator for the shift from aerobic to anaerobic state of the cancer cells. This change is responsible for the activation of vascular endothelial growth factor (VEGF) and angiogenesis [2]. Over Expression of HIF-1 alpha, a regulatory subunit of HIF-1, is significantly higher in melanoma metastasis and cell culture when compared to primary melanomas [3], it also found to be associated with treatment resistance and increase in the severity of tumor grade [4]. By studying the melanoma metastatic cells, the role of HIF is dependent on mRNA binding molecule coding region determinant binding protein (CRD-BP). HIF-1 binds to CRD-BP promoter site. The presence of CRD-BP is important for cell invasion, and its absence makes melanoma cells not responding to hypoxia [5]. Asnaghi et al. [6] studies a different pathway for the invasion in the uveal melanoma. HIF-1 activated canonical Notch singling through activation of Hes1, and Notch pathway is responsible for invasion of the tumor cells to the membrane. Clinically, it has be proved that over expression of the HIF-1 is associated with increased patient mortality, on the other hand, inhibition of HIF-1 activity has a negative effect on the tumor growrth [7]. For the therapeutic implications, the HIF-1 downregulation is done through activation of hydroxylases. Cheli et al. has proved another effect of hypoxia on the differentiation of the melanoma. Hypoxia decrease expression of microphthalmia associated transcription factor (MITF), the main gene for melanocyte regulation. It was proved that HIF-1 is the main down regulator for the expression MITF through Bhlhb2. Also, he proves that over expression of MITF expression significantly decreases the tumor size and metastasis formation [8]. The importance of HIF-1 in the pathway in the invasion and growth of melanoma drives researches for looking for an inhibitory effect on HIF-1 expression. Campbell et al. proves that high ascorbate dietary leads to decrease HIF-1 significantly and decrease the tumor growth 4 times comparing to low ascorbate dietary. Also, ascorbate decrease the other enzymes associated with HIF-1 pathway, like glucose transporter 1, Carbonic anhydrase IX (CA IX) and VEGF. This indicates the ascorbate has an associated with the tumor necrosis and physiology [9]. Tyrosine related protein 2 (TRP-2) involved in melanin synthesis, and melanoma differentiation. Lenggenhager et al. proves that TRP-2 expression level is co related to the degree of differentiation, and there is a significant decrease in the TRP-2 with tumor progression. Also it is found that TRP-2 expression is more prominent in the primary melanomas compared with the metastasis. There is a down regulation of the TRP-2 expression under the effect of hypoxia, and more aggravation of the cells including invasion, and metastasis. From a clinical point of view, the presence of the TRP-2 is a favorable indicator for the use of tumor vaccination and chemotherapy [3]. Hypoxia also has an effect on the cell free microRNA, as microRNA-210 (miR-210) is significantly up regulated in cases a hypoxic state and used a prognostic factor in several cancer [10,11].

In melanoma, miRNA-210 expression level is higher in cases of metastasis (lymph node metastasis and distant organ metastasis), compared with primary tumor. MiR-210 can be used a prognostic factor. It also can predict the disease recurrence, comparing with LDH which cannot predict the disease recurrence [12]. To summarize, Hypoxia at cellular level is the main indicator for the invasion and metastasis. Hypoxia changes the regular picture microRNA and gives predicting idea. Hypoxia also enhances the expression of HIF-1. Studying HIF-1 and its pathway and effects gives us a great idea about the tumor growth, invasion and, metastasis. Those changes give us better chances for the management.

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