TRPM2 channel regulates tumor angiogenesis via interacting with Stat3

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The tumor microenvironment is a complex tissue which is described as the accumulation of various stromal cells, sustaining angiogenesis and redox imbalance. Especially, tumor-associated macrophages (TAMs) are one of the major components of tumor tissues, and they play pivotal roles in prompting the various tumor growths by producing growth factors. Previously, we have reported that Transient receptor potential melastatin 2 (TRPM2), a ROS-sensitive Ca^{2+} channel, is abundantly expressed in macrophages and regulate immune responses by tuning various gene expressions. Here, we found that deletion of TRPM2 gene inhibited tumor growth, and the tumors developing in these conditions were characterized by a high density network of immature vessels, severe haemorrhage and increased hypoxia due to non-productive angiogenesis. In addition, TAMs isolated from TRPM2 knock out mice showed strong expression of proangiogenic factor VEGF according to the enhanced activity of transcription factor Stat3. Importantly, the intratumoral injection of angiostatic soluble VEGFR-1 in tumor-bearing TRPM2 knockout mice led to a rescue of tumor growth. We also found that the activation of TRPM2 channel induced by H_2O_2 suppress the activity of Stat3. TRPM2 protein showed physical interaction with Stat3 protein, and their complex was degraded gradually in the presence of H_2O_2. Together, our results suggest that TRPM2-Stat3 complex promotes functional blood vessel formation by controlling the VEGF levels depending on the environmental oxygen/redox conditions.