Despite the constant improvement in diagnosis and treatment strategies, cancer remains one of the main causes of death. Every year 14 million new cases and 8 million of cancer-related deaths are reported. There is a constant interest in anticancer strategies development, and miRNA are being considered a very promising novel therapeutic target.

Hypoxia defines conditions in which the tissues are deprived of adequate oxygen supply. Hypoxia is a hallmark of almost all solid tumors. Hypoxic tumors are more resistant to treatment and have greater metastatic potential than non-hypoxic ones.

Oxygen deprivation affects not only cancer itself but also blood vessels within it. Tumor survives and grows only if the first layer of blood vessel, termed endothelium, adapts to hypoxic conditions. However, studies conducted so far were focused mainly on the influence of hypoxia on cancer cells only, not taking endothelial cells into account.

Two main categories of hypoxia occur in tumors and their surroundings: chronic type and cyclic type.
Chronic hypoxia constantly and persistently affects cells which can't get enough oxygen, because they are too far from blood vessels.
Cyclic hypoxia results from abnormal blood flow and is characterized by repeated states of too low oxygen concentration followed by normal oxygenation.
Although the numerous studies shown that the cyclic oxygen deprivation significantly influences cancer therapy resistance and metastatic potential, yet the molecular mechanisms triggered by the cyclic hypoxia are poorly understood.
In particular not much is known about regulation of cyclic hypoxia by small noncoding RNA molecules, termed microRNA (miRNA). miRNA are posttranscriptionally involved in many aspects of the cell functioning, including both carcinogenesis and response to hypoxia. The fact that specific miRNA are crucial for cellular adaptation to chronic hypoxia, makes us think that the other specific miRNA might mediate adaptation to cyclic hypoxia.

Our hypothesis is that cellular adaptation to cyclic hypoxia relays on miRNA, which are specifically affected by repeated periods of too low and normal oxygen levels. During cyclic hypoxia these miRNA could facilitate cell survival. These miRNA would constitute a novel therapeutic target for anticancer treatments.

Hence, the main goal of this application is to determine whether miRNA levels are specifically modulated under cyclic hypoxia in human endothelial cells.

To test this hypothesis, we propose to examine the poorly characterized molecular mechanisms by which the cyclic hypoxia governs miRNA and to identify miRNA characteristic of that process. To achieve that we will determine the changes in the miRNA levels, not only during cyclic hypoxia time course, but also during the chronic hypoxia time course and in normoxia. Next, to assess their therapy usefulness, we will determine their biological roles and significance in cyclic hypoxia response and in other cellular pathways.

The role of miRNA in governing endothelial cells response to cyclic hypoxia has not been examined previously and has potentially far-reaching implications in many types of cancer.
Given that miRNA or their artificial analogs can potentially be used in future therapeutic approaches the studies proposed herein are timely and significant.