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Cardiovascular disorders remain the leading cause of human morbidity and mortality in developed countries. Many of these disorders are associated with hypoxia or ischemia in different organs and this leads to a decrease in oxygen and nutrient delivery to the tissues. The lowered oxygen tension in the tissues induces a hypoxic adaptive response that enables cells to recover from this cellular insult.

One mechanism for reestablishing cellular and tissue homeostasis is through the induction of angiogenesis and increasing oxygen delivery to the tissues. If the hypoxic conditions persist over extended periods of time, then the cells can undergo programmed cell death.

**While post-ischemic tissue revascularization is crucial in neuronal tissues following stroke, or in the heart following myocardial infarction, activation of angiogenesis is harmful in disorders such as macular degeneration and glaucoma. Understanding the cellular pathways that mediate recovery from hypoxia is therefore critical for developing novel therapeutic approaches for cardiovascular diseases.**

The main protein regulators of these cellular pathways are hypoxia induced factors (HIFs). They are responsible for induction of angiogenesis, as well as for adaptation of metabolism to low oxygen tension.

**To take advantage of regulating the human HIF pathway as a future therapy, the present proposal focuses on the mechanisms by which miRNAs govern human HIF expression**.
MiRNAs are non-coding RNA molecules that specifically reduce protein levels. Hence, modulation of HIF-specific miRNA could allow controlling HIF protein levels, and thus the tissue adaptation to hypoxia.
This application aims to identify such a HIF-specific miRNA, as well as to understand their biological role in human tissues. Furthermore, in human there are three HIF factors: HIF-1, HIF-2 and HIF-3. The cellular function of the latter one is less known, especially in the context of prolonged hypoxia. Analyzing HIF-3 regulation during hypoxia will allow us to better understand human HIF-3 function, being another aim of this project.

**It is clear that understanding the cellular pathways that regulate human tissues adaptation to hypoxia is necessary in order to develop novel treatments for cardiovascular disorders. Although these pathways are extensively studied, there is limited information regarding the role of miRNAs in this process. The possibility that miRNAs or their analogs can be used in future therapeutic approaches to regulate important cellular pathways highlights the importance of the studies proposed here.**