Effects of low oxygen on human genes.

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The platelet-derived growth factor B (PDGF-B) is a potent growth promoting protein which is involved in the stimulation of blood vessel formation (angiogenesis), wound repair and placental development. PDGF-B is expressed strongly in many types of tumour cells where it is believed to be involved in angiogenesis and promotion of growth, as well as a variety of other roles.

Transcription, an extremely complex process, is the first stage in a series of events in which the genetic code is interpreted and functionally expressed from the gene. In order for transcription to take place, proteins within the cell must interact with a region of the gene known as the promoter. The promoter region of the gene consists of a variety of regulatory sequences attracting proteins which will increase or decrease the activity of the gene. Transcription of the PDGF-B gene is very complicated and varies greatly from one cell type to another. There is very little known about the basic control of transcription of the PDGF-B gene in Neuroblastoma cells (a childhood tumour of the nervous system), so this has been under examination. In order to look at the transcriptional regulation of the PDGF-B gene, several gene constructs were made, having the basic PDGF-B promoter region as well as mutations (i.e. containing changes in the gene sequence). These different constructs were inserted in to Neuroblastoma cells and the activity was examined. By doing this we can distinguish different important promoter regions.

Hypoxia, low oxygen levels, occurs naturally in a variety of living tissues. Hypoxia places cells under severe stress and they must initiate appropriate responses in order to survive this challenge. Various genes will be activated to combat this challenge, such as the PDGF-B gene. Solid tumours contain regions which are severely hypoxic. This selects for cells which are resistant to hypoxia, and these cells have also been found to be resistant to radio-therapy and chemo-therapy. Endothelial cells taken from human umbilical vein (which are used as model for the cells of the veins and arteries) display a two phase response to hypoxia; the PDGF-B gene activity is initially induced by hypoxia, then sharply repressed. The mechanisms controlling the induction are under examination.

Promoter gene constructs inserted into endothelial cells followed by hypoxic treatment showed regions that are responsible for regulating the gene during the first phase of hypoxia. It would be interesting to see if the regions which show decreased activity are responsible for the strong down regulation of the PDGF-B gene activity in the second phase response to hypoxia. The hypoxia experiments also led to the identification of regions which are responsible for the general regulation of the PDGF-B gene in normal conditions in these cells.

Degree project in biology
Examensarbete i biologi, 10p fall 1999
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