CREB Hypoxia and Cancer

Alik Honigman

The Hebrew University- Hadassah Medical School, Jerusalem, Israel

Tumor microenvironment controls the selection of malignant cells capable of surviving in stressful and hypoxic conditions. The transcription factor, cAMP responsive element binding protein (CREB) activated by multiple extracellular signals, modulates cellular response by regulating the expression of a multitude of genes. We have demonstrated that two cystein residues, at the DNA binding domain of CREB, mediate activation of CREB-dependent gene expression at normoxia and hypoxia. The construction of a dominant-positive CREB mutant, insensitive to hypoxia cue (substitution of two cystein residues at position 300 and 310 to serine, in the DNA binding domain) and of a dominant negative CREB mutant (addition of a mutation in serine133) enabled a direct assessment, in-vitro and in-vivo, of the role of CREB in tumor progression. In this work, we demonstrate, that CREB controls hepatocellular carcinoma (HCC) growth both in-vitro and in-vivo, supports angiogenesis and renders resistance to apoptosis. Along with the identification, by DNA array, of at least 77 genes mediated by CREB at hypoxia, we suggest that in parallel to other hypoxia responsive mechanisms, CREB plays an important role in hepatocellular carcinoma (HCC) tumor progression.