



Important pathways regulating HIF-1 $\alpha$  translation. During normoxic conditions *HIF1A* mRNA is translated by cap-dependent mechanisms (green background). Under certain cellular contexts, HIF-1 $\alpha$  translation can be stimulated by growth factors (GFs), oncoproteins or cytokines that activate the PtdIns3K–Akt–mTOR and the MAPK (RAS–MEK–ERK) pathways. Cellular stress such as hypoxia or the absence of nutrients can inhibit cap-dependent translation by two mechanisms. In the first, the ER kinase PERK phosphorylates eIF2- $\alpha$  (2 $\alpha$ ) and prevents its assembly with the ternary complex (TC). In the second, TSC1- and/or TSC2-mediated mTOR inhibition results in 4E-BP hypophosphorylation leading to its interaction with eIF4E (4E) and blocking eIF4F-complex formation and subsequent translation initiation. mTOR inhibition also prevents S6K activation and the regulation of downstream translation components. It has been suggested that during hypoxia HIF-1 $\alpha$  is also translated via a cap-independent mechanism (blue background), possibly through the IRES. The RNA-binding proteins PTB and HuR have been proposed to bind to *HIF1A* mRNA at the 3' UTR and 5' UTR, respectively, and enhance HIF-1 $\alpha$  translation in response to the hypoxia mimetic CoCl<sub>2</sub>. Abbreviations: PI3K, phosphatidylinositol 3-kinase.