

## Human Carbonic Anhydrase Inhibitors (hCAIs) a Druggable Target for Cancer Therapy

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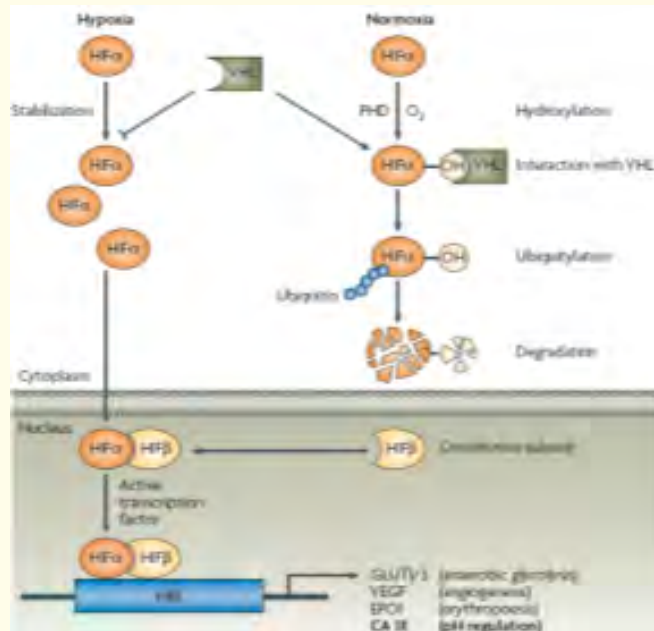
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Carbonic anhydrases (CA, EC 4.2.1.1) are ubiquitous metalloenzymes present in prokaryotes and eukaryotes that are encoded by four evolutionarily unrelated gene families. These are the  $\alpha$ -CAs (present in vertebrates, bacteria, algae and cytoplasm of green plants); the  $\beta$ -CAs (predominantly in bacteria, algae and chloroplasts of monocotyledons and dicotyledons); the  $\gamma$ -CAs (mainly in archaea and some bacteria); and the  $\delta$ -CAs and  $\zeta$ -CAs (present in some marine diatoms). In mammals, 16  $\alpha$ -CA isozymes or CA-related proteins with different catalytic activity, subcellular localization and tissue distribution are there. CAs catalyse a simple physiological reaction the conversion of  $\text{CO}_2$  to the bicarbonate ion and protons. The active site of most CAs contains a zinc ion ( $\text{Zn}^{2+}$ ), which is essential for catalysis. The CA reaction is involved in many physiological and pathological processes, including respiration and transport of  $\text{CO}_2$  and bicarbonate between metabolizing tissues and lungs; pH and  $\text{CO}_2$  homeostasis; electrolyte secretion in various tissues and organs; biosynthetic reactions (such as gluconeogenesis, lipogenesis and ureagenesis); bone resorption; calcification; and tumorigenicity [1-3].

Human carbonic anhydrase IX (hCA IX) has recently been found to be a druggable target for imaging and treatment of hypoxic tumors overexpressing this protein. hCA IX is the most strongly overexpressed gene in response to hypoxia in human cancer cells. This enzyme is a multidomain protein with the CA subdomain situated outside the cell and possessing a very high  $\text{CO}_2$  hydrase catalytic activity, making it a key player in the regulation of tumor pH. hCA IX expression is strongly increased in many types of solid tumors, such as gliomas/ependymomas, mesotheliomas, and papillary/follicular carcinomas; carcinomas of the bladder, uterine cervix, kidneys, esophagus, lungs, head and neck, breast, brain, and vulva; and squamous/basal cell carcinomas. Furthermore, such hypoxic tumors do not generally respond to the classic chemo- and radiotherapy [1-7].

At normal oxygen levels (normoxia), prolyl-4-hydroxylase (PHD) hydroxylates the P564 on hypoxia inducible factor- $\alpha$  (HIF $\alpha$ ) (Figure). The von Hippel-Lindau protein (VHL) binds hydroxylated HIF $\alpha$  and targets it for degradation by the ubiquitin-proteasome system. Under hypoxia, HIF $\alpha$  is not hydroxylated, because PHD is inactive in the absence of dioxygen. Non-hydroxylated HIF $\alpha$  is not recognized by the VHL protein, it is stabilized and accumulates. After translocation to the nucleus, HIF $\alpha$  dimerizes with the HIF $\beta$  constitutive subunit to form an active transcription factor. The HIF transcription factor then binds the hypoxia response element (HRE) in target genes and activates their transcription. Target genes include glucose transporters (GLUT1 and GLUT3) that participate in glucose metabolism, vascular endothelial growth factor (VEGF) that triggers neoangiogenesis, erythropoietin (EPO1) involved in erythropoiesis, CA IX involved in pH regulation and tumorigenesis, and additional genes with functions in cell survival, proliferation, metabolism and other processes [1-2].

Primary sulphonamides, sulphamates and sulphamides act as carbonic anhydrase inhibitors (CAIs) by binding to the catalytic  $\text{Zn}^{2+}$  ion in the active site of the enzyme and blocking its function. Some of these compounds inhibit both CA IX and CA XII. Studies in mice have shown that inhibition of CA IX has a strong anticancer effect on both the primary tumour and metastases, and in Phase III clinical trials in patients with RCC, girentuximab showed promising results [8]. Many such compounds were specifically designed for targeting these tumour-associated isoforms of CA. Recently, novel interesting chemotypes, in addition to the sulfonamide and sulfamate were discovered, many of which are based on natural products, such as phenols/polyphenols, phenolic acids, coumarins, and thiocoumarins [1,2,9,10]. The development of isoform selective hCAIs represents the key approach for the successful development of druggable molecules.



**Figure:** Mechanism of hypoxia-induced gene expression mediated by the HIF transcription factor (Retrieved from *Nature Reviews Drug Discovery* 7 (2008): 168-181).

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