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The clinical implications of Hypoxia Inducible Factor -A Nobel approach

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The concept of hypoxia began to develop from the second half of the nineteenth century.(1) In 1868,Pfluger reported that hypoxia stimulates breathing(2). Haldane, Fitzgerald, Schneider, Henderson and Douglas has also contributed immensely in understanding Hypoxia (3). It was Otto Warburg, the Nobel prize winner in Physiology or Medicine of 1931, who revealed that oxygen is necessary for the enzymatic conversion of food to energy. Nobel prize in Physiology or Medicine in 1938 was awarded to Corneille Heymans for discovering the mechanism of blood oxygen sensing by the carotid bodies(4). William G. Kaelin Jr, Sir Peter J. Ratcliffe and Gregg L. Semenza were awarded the Nobel prize in Physiology or Medicine 2019 for decoding the mechanisms by which cells sense and adapt to oxygen availability .(4)

Gregg Semenza and Sir Peter Ratcliffe independently studied how varying levels of oxygen regulated erythropoietin gene(EPO) in all the tissues(5). It was Semenza who identified the Hypoxia inducible factor (HIF) which mediated the response to hypoxia(6). William G. Kaelin Jr demonstrated that proteasomal degradation of HIFα requires the Von Hippel Lindau (pVHL) protein and this lead to the solving of the puzzle of hypoxia.(7)

The definition of hypoxia is deficiency of oxygen at the tissue level(8).Hypoxia inducible factor (HIF) is the regulator or the sensor for the detection of hypoxia at tissue level. It also plays a role in transcriptional response to hypoxia which has been present in the organisms throughout the evolution. Thus HIFs are oxygen regulated transcription factors.(6)

HIF is a heterodimer which has an unstable α subunit -HIF1 α and a stable β subunit HIF1β /ARNT 1(Aryl hydrocarbon Receptor Nuclear Translocator).HIF has 1α,2α and 3α subunits whose roles are being studied independently .(9)

When the tissues are well oxygenated ,as shown in fig 1, the HIF1α is hydroxylated by Prolyl Hydroxylase Domain (PHD) /EGLN and binds to von Hippel -Lindau tumour suppressor protein (pVHL) (10). This results in polyubiquitylation and proteasomal degradation of HIF with a half-life of 5 minutes. When there is hypoxia, hydroxylation of HIF fails to occur which leads to accumulation of HIF α. HIF 1α then dimerises with HIF1β. The dimer which is translocated into the nucleus, binds with hypoxia response elements (HRE). This activates

transcription process of around 200 genes. HIF can be regulated by oxygen dependent and independent manners.(11)

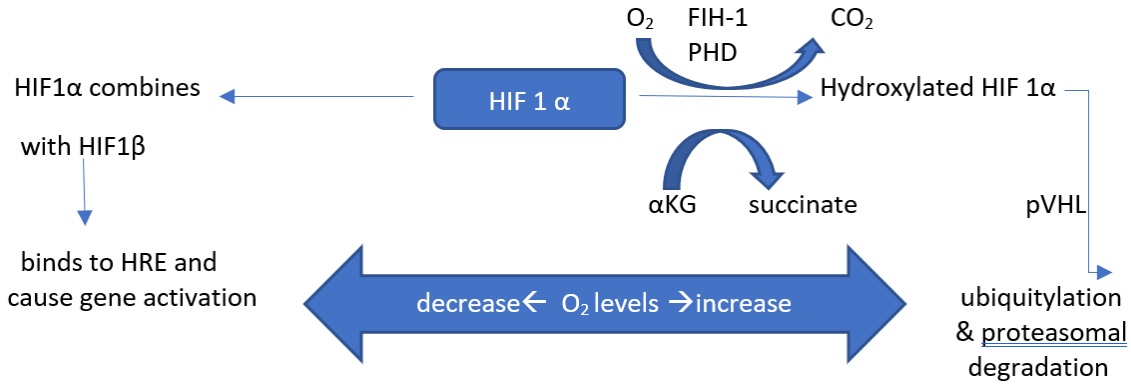

Fig 1:- Original figure showing the HIF activation and degradation.

HIF affects the physiological process of metabolism, exercise, embryonic development, immune response, altitude adaptation and respiration. It also plays a role in the pathophysiology of anaemia, cancer, stroke, infection, wound healing and myocardial infarction.(9)

HIF and metabolic reprogramming

Glucose metabolism**:** HIF 1α promotes metabolic adaptation during hypoxia. It stimulates glucose entry into cells by upregulation of glucose transporters , GLUT1 and GLUT 3 leading to the Warburg effect of increase in glucose uptake and production of lactate(12–14). It also upregulates glycolytic enzymes like hexokinase and phosphoglycerate kinase 1(15).It inactivates pyruvate dehydrogenase, reducing the conversion of pyruvate to acetyl-CoA(16) .Hence pyruvate gets shunted towards lactate production and due to upregulation of lactate dehydrogenase A ,there is increased NAD^+ regeneration(17). The lactic acidosis in the cells is prevented by increased expression of lactose transporters (18) . This pathway is hundreds of times more active in the hypoxic cancer cells and has been described in thyroid , breast, endometrial ,renal cell carcinoma and malignant melanoma.(12)

Fatty acid metabolism**:** Fatty acid synthesis from carbohydrate derived acetyl CoA (19) and reductive carboxylation of glutamine is upregulated by HIF 1 α(20) .It increases the expression of fatty acid binding proteins(FABPs)(21),decreases oxidation of fatty acids and inhibits acyl - CoA dehydrogenase.HIF1α ,thus leads to lipid accumulations in hypoxic cancer cells(21) .

Amino acid metabolism**:** HIF increases the transport of glutamate and leucine across the cells which is made available for fatty acid synthesis(22).This pathway is found to be active in Renal cell carcinoma(23),neuroblastoma(22) and melanoma

Role of HIF in erythropoiesis

Hypoxia via HIF2α affects erythropoiesis, fig 2, by increasing EPO synthesis and modulating iron metabolism. Erythropoietin (EPO)levels increase in response to systemic hypoxia. The

major EPO production is from peritubular interstitial fibroblasts of kidney and from the hepatocytes around central veins in liver. HIF2α dimerises with HIF β and binds to hypoxia response element (HRE)in the *EPO* gene producing EPO(24). The expression of duodenal cytochrome b (DCYTB), divalent metal transporter -1(DMT1), ferroportin ,Transferrin , ceruloplasmin and Hepicidin which are involved in the iron metabolism , are also regulated by HIF2α.(25–28)

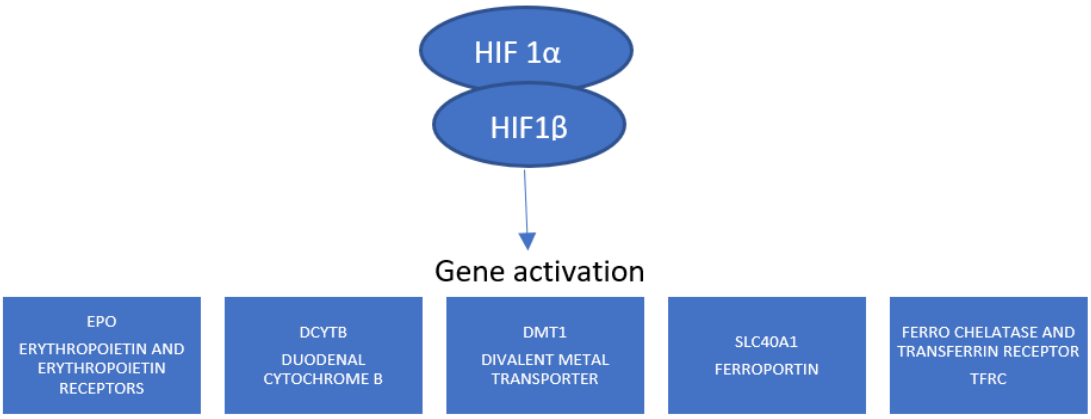

Fig 2: - Genes for erythropoiesis activated in anemia. (Original figure)

Congenital polycythemia or hereditary erythrocytosis occurs due to mutations of EPO receptor. It can also occur due to mutations of *VHL,PHD2, HIF2α. VHL* or *EPAS1*.It has been found that mutations with hereditary erythrocytosis have been associated with pulmonary hypertension. (29)

HIF and angiogenesis

Local hypoxia in the tissues stimulates angiogenesis. The angiogenic factors stimulated by HIF pathway include Vascular endothelial growth factors(VEGF), Angiopoietin, Adrenomedullin(ADM),fibroblast growth factor(FGF),Placenta growth factor(PLGF),Platelet derived growth factor(PDGF),Stem cell factor(SCF), Osteopontin, Plasminogen activator inhibitor(PAI-1),Matrix metalloproteinases(MMP),Tissue inhibitor of metalloproteinases (TIMP), Nitric oxide synthase(NOS),Cyclooxygenase 2(COX-2), Endoglin, adrenergic receptor.Endothelin-1,Semaphorin 4D, Integrins, Endosialin, Adenosine A2A receptor, Oxygen regulated protein -150,Stromal derived growth factor (SDF-1) and Interleukins. The anti-angiogenic factors induced by HIF are DLLI-4, Vasoinhibin-1,Thrombospondin-1,Carbonic anhydrase -9,Regulator of G protein signalling 5,Angiostatin, Endostatin, Canstatin and Interferons.(30)

Induction of these factors by local hypoxia causes endothelial cell proliferation, migration sprouting assembly , vasodilation ,vascular permeability, stabilisation, extracellular matrix degradation , plasma protein extravasation, pericyte and smooth muscle recruitment , vessel maturation, maintenance, differentiation and remodelling.(30)

HIF 1 has been implicated in the production of atherosclerotic lesions by promoting angiogenesis in addition to increased lipid synthesis and accumulation of inflammatory

cells(31). HIF1α mutations has been found in humans to cause critical coronary artery stenosis.(32,33)Chronic continuous hypoxia in mice has shown to result in pulmonary hypertension via activation of HIF 1α.(34)

Transverse aortic constriction mouse models has shown HIF1α induced initial angiogenesis maintaining myocardial oxygenation in right ventricle ,but chronic overload caused HIF1α inhibition resulting in myocardial hypoxia and cardiac failure.(35)

HIF1α provides cardio protection in ischemic preconditioning by inducing adenosine production in endothelial cells increasing the chances of endothelial cell and myocyte survival.(36) It also protects against cardiac failure due to pressure overload ,evident from the accelerated failure in HIF1α knockout mice and in digoxin administration, which inhibits HIF1α accumulation.(36)

HIF1α is a potential target for the treatment of diabetic retinopathy and retinopathy of prematurity(37)

Role in wound healing

HIF1α is required for tissue vascularisation, perfusion and healing of wounds. Wound healing in burns is impaired in HIF1α knockout mice(38) and is improved with desferrioxamine administration which is a HIF1α inducer.(39)

HIF and embryogenesis

HIF is required for the normal placental development which is in response to the hypoxic environment where the embryo develops. It is required for the normal development of heart and endochondrial bone formation. But non physiological hypoxia will adversely affect embryogenesis.(40)

HIF and Respiration

It was Fernado de Castro, Jean-Francois Heymans and Corneille Heymans and later, von Euler who identified the carotid bodies as the chemoreceptors sensing arterial oxygen level.(41,42)The mechanism of carotid body stimulation by hypoxia has become clearly evident with the discovery of HIF.

The intermittent hypoxia in carotid body ,fig 3, increase the HIF 1α dependent NADPH oxidase 2 synthesis, which is a prooxidant and decrease HIF 2 α dependent Superoxide dismutase 2 synthesis which is an antioxidant.(43,44)The reactive oxygen species(ROS) hence generated during hypoxia leads to inhibition of heme oxygenase2(HO2) in carotid body, which normally converts heme to carbon monoxide (CO)(45,46).The CO normally inhibits the soluble Guanyl cyclase (sGC). Hence, less amount of CO produced during hypoxia, causes less production of cGMP. cGMP normally inhibits protein kinase G(PKG), required for cystathionine -ϒ-lyase activity converting homocysteine to Hydrogen sulfide(H_2S)(47).Thus hypoxia leads to

decreased production of CO and increased production of H_2S within the carotid body.

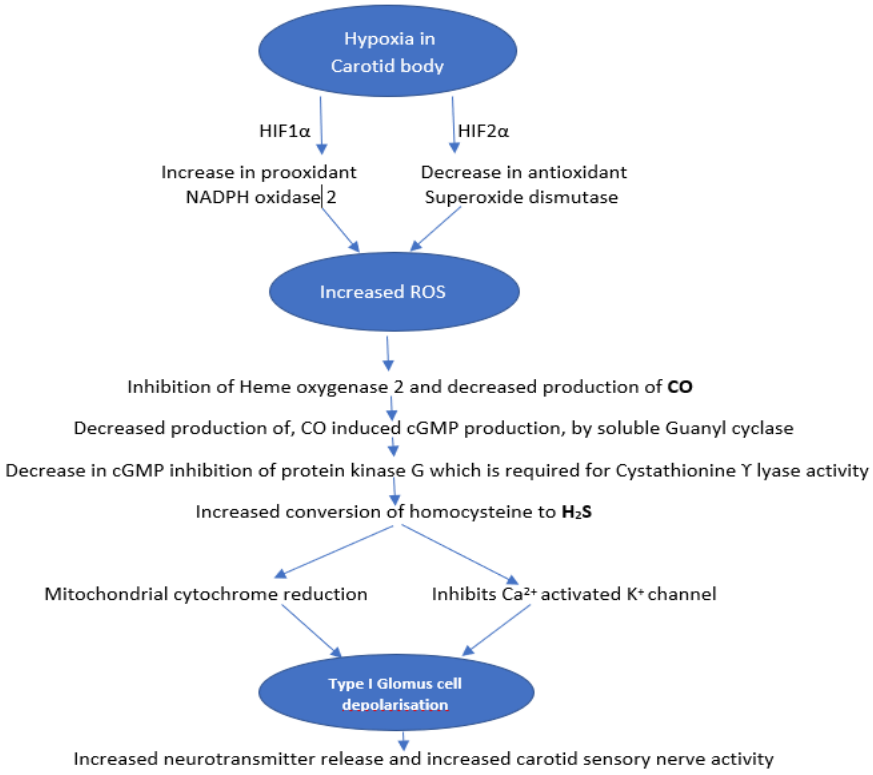

Fig 3:Carotid body activation by hypoxia (original figure)

The increased levels of H_2S inhibits Ca^{2+} activated K^+ channel, causing depolarisation of type 1 glomus cells. It may also get depolarised by mitochondrial cytochrome reduction ,which leads to mitochondrial depolarisation(48) .The depolarisation releases excitatory neurotransmitters and there is increased activity in carotid sensory nerves ,bringing out the effects of chemoreceptor stimulation.(47).HIF, thus affects the gasotransmitter production and the signalling from carotid bodies.

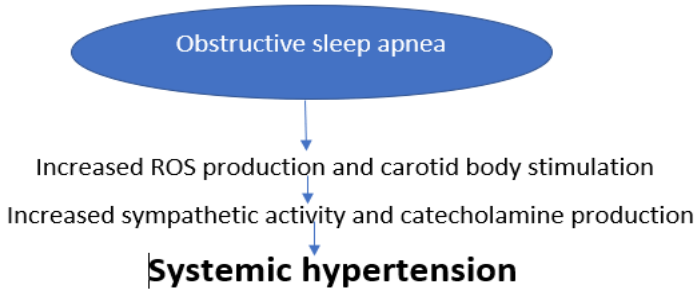

Fig 4: - Chronic intermittent hypoxia in Obstructive sleep apnea causing systemic hypertension (original figure)

This pathway has been implicated in pathophysiology of obstructive sleep apnea induced systemic hypertension, fig 5, and neurogenic hypertension.(48,49)

HIF and Immunity

HIF1α deficient mice showed decreased motility ,aggregation and bacterial killing by macrophages, increased activation of $CD4^+$ cells by dendritic cells, decreased survival and glycolysis by neutrophils, increased protection against sepsis and autoimmune neuroinflammation by T cells, decreased normal B cell development and decreased IL-10 producing B cells (50).

The rodent based studies based on HIF1α has shown promising results in lung transplantation (51)and renal transplantation(52).

HIF1α induced immune response is affected in Rheumatoid arthritis, Inflammatory Bowel Disease, Sepsis and Cancer. (50)

HIF and Cell cycle

When the tissues become hypoxic, cell cycle is arrested by HIF1α by direct inhibition of DNA replication. But endothelial cells proliferate in hypoxia which is brought about by the differential action of cyclin dependent kinase 1 and 2.(53)

Increased expression of HIF1α as well as HIF2α in tumour tissues of bladder, brain, breast, colon, oesophagus, liver, lung, pancreas, skin, stomach and uterus was associated with increased mortality. It has also been associated with acute lymphocytic and myeloid leukemia.(54)The mechanisms of cancer induction due to hypoxia include, cell immortalisation by activation of telomerase production, activated transcription of *EPO,VEGF,IGF2, SDF1, TGFA and KITL* genes, metabolic reprogramming, vascularisation, immune evasion and accelerated invasion and metastasis.(55)

Pharmacologic targeting of HIF.

As discussed, Hypoxia and HIF play a major role in the pathophysiology of many diseases. Hence the role of HIF stabilisers and inhibitors in the treatment of diseases is under trial.

HIF stabilisers

Anemia in Chronic Kidney Disease (CKD) due to EPO deficiency can be treated with HIF stabilisers like Daprodustat, Molidustat, Roxadustat, Vadadustat, DS-1093, FG-2216. JTZ-951. They act by inhibiting PHD which cause HIF degradation. This treatment would be better than expensive recombinant EPO and repeated blood transfusion. But long term follow up studies are required to ensure the safety due to the long array of genes activated by HIFs.(56)

The treatment of Inflammatory bowel disease with HIF stabilisers in mice shows a promising future. Liquid emulsions and intraperitoneal injections of HIF stabilisers has been studied in mice with colitis.(56)

Injection of AdCA5, an adenovirus which carries oxygen dependent degradation resistant HIF 1α in young mice with limb ischaemia has shown promising results.(56)

HIF Inhibitors

HIF Inhibitors have been found to have a beneficial role in rodent models of ischaemic retinopathy by intravitreal injection of HIF inhibitors. They are found to be effective in pulmonary hypertension as well.

HIF inhibitors show a promising future as anticancer drug by inhibiting tumour growth, vascularisation, and metastases. It acts by decreasing HIF protein expression, increasing HIF degradation, decreasing HIF synthesis or by decreasing HIF transcriptional activity.(56)

Some of the HIF inhibitors being used in anticancer research are Acriflavine, Apigenein, AmphotericinB, Ascorbate, Berberine, Curcumin, Daunorubicin, Digoxin, Doxorubicin, Echinomycin, Ganetespib, Geldanamycin, Ibuprofen, Metformin, Nelfinavir and Radicicol.(56)

Conclusions and Future perspectives.

Since the Nobel winning discovery of Hypoxia Inducible Factors by Semenza, a pathway was paved for discovering the pathophysiology of diseases like Anemia in CKD, Polycythemia, Hypertension in obstructive sleep apnea, Pulmonary hypertension, Coronary artery disease, Inflammatory Bowel Disease and Cancers.

This also led to the discovery of various drugs targeting HIF which includes HIF inhibitors and stabilisers. These drugs give a promising future, especially in the treatment of cancer in the coming decade. The question that remains is about the of consequences of hypoxia survivors from covid pandemic.

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