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Cardiopulmonary Compensatory Mechanisms In Cyanotic Congenital Heart Disease: A Comprehensive Review

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Abstract
Cyanotic congenital heart disease (CCHD) comprises a diverse group of structural cardiac anomalies characterized by right-to-left shunting and persistent systemic hypoxemia, leading to a complex interaction of cardiopulmonary, hematologic, and metabolic adaptations. This review synthesizes current evidence to clarify the multilayered compensatory mechanisms that maintain oxygen delivery during sustained hypoxia. Traditional physiological models, such as the Fick principle and the Frank–Starling mechanism, explain primary compensatory responses including increased cardiac output and augmented oxygen extraction; however, these frameworks do not fully encompass the cellular and molecular adaptations observed in chronic hypoxemia. At the core of these processes is the hypoxia-inducible factor (HIF) signalling pathway, which coordinates

transcriptional responses that promote erythropoiesis, angiogenesis, and metabolic reprogramming. Prolonged hypoxia induces a metabolic transition from oxidative phosphorylation to glycolysis, accompanied by mitochondrial remodelling and changes in reactive oxygen species dynamics, thereby supporting cellular survival under diminished oxygen conditions. Simultaneously, erythropoietin-driven secondary erythrocytosis enhances oxygen-carrying capacity but increases the risk of hyperviscosity, microcirculatory impairment, and thrombotic events. On an organ level, adaptive responses include pulmonary vascular remodelling, endothelial dysfunction, and right ventricular hypertrophy, which initially help preserve systemic perfusion but eventually contribute to structural deterioration and heart failure. This presents a paradox wherein physiological compensation coexists with multisystem decline. Recent insights into molecular regulators, including HIF isoforms, microRNAs, and metabolic intermediates, underscore potential biomarkers and therapeutic targets. Comprehending the transition from adaptive to maladaptive responses is essential for optimizing clinical management and developing precision therapies aimed at reducing long-term complications in individuals with CCHD.

Keywords: Cyanotic congenital heart disease; cardiopulmonary compensation; chronic hypoxia; hypoxia-inducible factor; erythropoiesis; secondary erythrocytosis; metabolic reprogramming; pulmonary vascular remodeling; cardiac remodeling; endothelial dysfunction.

1. Introduction:

Cyanotic congenital heart disease (CCHD) refers to a diverse group of cardiac malformations caused by structural abnormalities of the heart that lead to systemic arterial desaturation due to right-to-left shunting [1]. Common examples include tetralogy of Fallot (TOF), dextro-transposition of the great arteries, and coarctation of the aorta [2]. The central pathological feature is the mixing of deoxygenated venous blood with oxygenated arterial blood. This mixing may occur at the atrial level (atrial septal defects), ventricular level (ventricular septal defects), or within the vascular system (such as arteriovenous fistulas or a persistent ductus arteriosus), ultimately causing chronic hypoxemia from early life [1]. As a result of prolonged hypoxemia due to venous-arterial mixing, patients develop multiple alterations in hematologic, endothelial, and hemostatic systems, making CCHD a multisystem disorder rather than a condition limited to the heart [3]. Adults with CCHD frequently develop secondary erythrocytosis. Unlike primary erythrocytosis associated with polycythemia vera (PV), the erythrocytosis associated with CCHD arises as a physiological response to chronic tissue hypoxia, leading to elevated serum erythropoietin levels [4].

Hypoxemia remains a persistent feature during infancy and early childhood in patients undergoing staged palliation for congenital heart disease, and many of these individuals now survive into their third or fourth decade of life [3]. In some cases, patients with CCHD remain unoperated for various reasons and experience lifelong hypoxia, which increases the risk of developing heart failure with advancing age. Hypoxia also triggers cellular metabolic adaptations, primarily through the accumulation of hypoxia-inducible factor-1α (HIF-1α) [5].

During chronic hypoxemia, several adaptive survival mechanisms are activated. These include increased erythropoietin (EPO) secretion, which raises red blood cell mass and blood viscosity; enhanced cardiac output to maintain adequate oxygen delivery; increased nitric oxide (NO) release from coronary endothelial cells, promoting vasodilation; elevated tissue levels of 2,3-diphosphoglycerate; and NO-mediated vasodilation of blood vessels [3]. However, these adaptive mechanisms can act as a double-edged sword. Although they are initially protective, they may eventually contribute to harmful consequences such as increased blood viscosity, alterations in the

coagulation profile, and impaired microcirculation. These effects are further aggravated when iron deficiency develops, producing red blood cells that are less deformable than normal RBCs [3].
Therefore, understanding how cells and organs adapt and ultimately fail to adapt to chronic hypoxia is crucial for explaining the paradox of functional compensation coexisting with structural and systemic decline in CCHD. This review presents a comprehensive framework explaining how chronic hypoxemia in CCHD conditions, such as TOF, Transposition of the Great Arteries, and Eisenmenger syndrome, initiates coordinated cardiopulmonary and cellular responses that help sustain life during prolonged oxygen deprivation. It combines traditional physiological models with modern molecular insights, especially hypoxia-inducible factor (HIF) driven oxygen sensing, metabolic changes, erythropoiesis, and vascular adaptation. Moreover, the review explores the paradox of maintained systemic perfusion alongside ongoing structural and multisystem decline. By linking cellular hypoxia signaling to organ-level outcomes, it aims to clarify how adaptive responses eventually become maladaptive, and to identify relevant biomarkers and therapeutic opportunities for precision management.

2. Methodology:

This review involved an extensive online literature survey to identify and synthesize current evidence on systemic and cellular compensatory mechanisms in chronic hypoxia and CCHD. Key search terms incorporated “cyanotic congenital heart disease,” “chronic hypoxia,” “cardiopulmonary adaptation,” “erythrocytosis,” “hypoxia-inducible factor (HIF),” “right ventricular remodeling,” “pulmonary vascular remodeling,” “metabolic adaptation,” “endothelial dysfunction,” “hypoxic pulmonary vasoconstriction,” and “PHD2/HIF-1α pathway.” The electronic databases utilized included PubMed, with a focus on peer-reviewed studies published in English.

3. Theoretical Foundations of Oxygen Homeostasis in CCHD:

Classical models of oxygen homeostasis

The Fick principle states that the rate of oxygen consumption by peripheral tissues is directly proportional to the product of oxygen delivery to the tissues and the arterial-venous oxygen concentration difference [6]. The severity of hypoxemia (arterial desaturation) in CCHD largely depends on the degree of right ventricular outflow tract obstruction or the extent of intracardiac mixing. Chronic arterial hypoxemia stimulates erythropoietin production in the kidneys, which increases red blood cell production. When excessive, this response can lead to polycythemia. Persistent hypoxemia together with polycythemia may further contribute to complications such as coagulation abnormalities and hyperuricemia [7].
The Frank-Starling mechanism plays an important role in compensating for systolic heart failure by helping maintain cardiac output and preserving blood pressure sufficient to perfuse vital organs. In heart failure caused by reduced left ventricular contractility, the left ventricular performance curve shifts downward. Consequently, for any given preload, the stroke volume is lower than normal, resulting in incomplete ventricular emptying. This leads to an increased volume of blood remaining in the left ventricle during diastole. The elevated residual volume stretches myocardial fibers further, which enhances the force of the subsequent contraction and increases stroke volume through the Frank-Starling mechanism. In this way, the dilated ventricle can temporarily improve its pumping efficiency and support cardiac output. However, the compensatory effect of the Frank-Starling mechanism is limited. In severe systolic heart failure, where myocardial contractility is markedly reduced, the ventricular performance curve becomes nearly flat at higher diastolic volumes. As a

result, further increases in end-diastolic volume (EDV) produce minimal improvement in cardiac output. Instead, excessive increases in EDV and left ventricular end-diastolic pressure (LVEDP) can contribute to pulmonary congestion and other related complications [8].
Autonomic and ventilatory adaptations: In a study by Sylvie Legault et al., 55% of patients with asymptomatic left ventricular dysfunction showed features associated with impaired cardiac autonomic control and arrhythmias. Despite this, overall sleep parameters remained normal. The hypoxic ventilatory response, which is known to be highly variable, is typically reduced during sleep. Although oxygen saturation declined further during sleep in five patients, no significant alterations in respiratory parameters or clinically relevant arrhythmias were observed [9]. Assessment of cardiac autonomic function may also provide insight into future disease progression. Myocardial dysfunction is commonly associated with increased sympathetic activity and reduced parasympathetic activity, which may arise from several underlying mechanisms. Enhanced sympathetic stimulation plays a key role in the progression of heart failure and may similarly contribute to the long-term complications observed in congenital heart disease [10].

Limitations of classical frameworks
The Fick principle may be unreliable for cardiac output in ventilation-perfusion mismatch because it assumes normal pulmonary gas exchange. Using mixed venous oxygen from the pulmonary artery ignores lung tissue oxygen use, underestimating total tissue oxygen consumption when pulmonary oxygen demand is high. Its use is limited in neonates and children due to challenges in blood sampling and the effects of shunting and developmental differences. Accurate application needs specialized tools and expertise, which may not be available in resource-limited settings [6].
Increased left ventricular preload surpasses pulmonary venous hydrostatic pressure, resulting in congestion. In systolic heart failure with reduced ejection fraction and pulmonary edema, reducing preload with diuretics (such as furosemide, hydrochlorothiazide) or venous dilators (like nitrates) has little impact on stroke volume because the Frank-Starling curve is flattened and shifted downward at high preload levels. Nevertheless, overly aggressive preload reduction can cause stroke volume to fall too much, leading to hypotension [8].

HIF signaling cascade and temporal switching:

Regulation, hydroxylation, stabilization
Metabolic adaptation to hypoxia is crucial for maintaining ATP generation and preserving cardiac function. Under low-oxygen conditions, the heart shifts its metabolism by reducing fatty acid oxidation and increasing glycolysis, since glycolysis requires less oxygen to produce ATP. Yiwei Liu et al. examined metabolic changes in hypoxic human tissues using multiple approaches, including metabolomics, fluxomic analysis, and in vivo assessment of cardiac fatty acid and glucose uptake. Although enhanced glycolysis is a well-recognized response to chronic hypoxia, the metabolic fate of the glycolytic product pyruvate remains an important consideration. In many hypoxic non-cardiac tissues, PDK1 (pyruvate dehydrogenase kinase 1) is upregulated through HIF-1α-dependent signaling, which inhibits pyruvate dehydrogenase (PDH) and diverts pyruvate away from mitochondrial oxidation toward lactate production, a less energy-efficient pathway. In contrast, the present study found that mitochondrial pyruvate oxidation was increased during hypoxia. This occurred through downregulation of PDK4, regulated by PPARα (peroxisome proliferator-activated receptor α), a mechanism previously described in cardiac tissue. These observations emphasize that understanding hypoxia-induced metabolic changes requires comprehensive metabolic analysis, as

the metabolic responses and HIF-1α-mediated adaptations can vary significantly depending on the cell type [11].

The PHD/HIF pathway is a key oxygen-sensing mechanism that enables tissues to adapt to low-oxygen conditions mainly through regulation of gene transcription. In normoxic conditions, HIF-α is rapidly degraded after specific proline residues undergo hydroxylation. Once hydroxylated, HIF-α is recognized by the von Hippel-Lindau (VHL) tumor suppressor protein, which acts as the substrate-recognition component of an E3 ubiquitin ligase, targeting HIF-α for proteasomal degradation. This oxygen-dependent hydroxylation is mediated by prolyl hydroxylase domain enzymes (PHD1, PHD2, and PHD3) that function as oxygen sensors in the HIF signaling pathway.

Among these enzymes, PHD2, a 2-oxoglutarate (2OG)-dependent dioxygenase, utilizes molecular oxygen to hydroxylate HIF-α and promote its degradation under normoxic conditions. Conversely, inhibition of PHD2 prevents this degradation and leads to activation of the HIF pathway in most cell types [12].

Certain small molecules, including reactive oxygen species, nitric oxide, and the Krebs cycle intermediates succinate and fumarate, can inhibit PHD catalytic activity. This inhibition stabilizes HIF-α and promotes the activation of HIF-dependent transcriptional programs. Under hypoxic conditions, reduced HIF-prolyl hydroxylation prevents HIF-α degradation. As a result, HIF-α accumulates, translocates to the nucleus, heterodimerizes with HIF-β, and initiates transcription of hypoxia-responsive genes. Any decrease in HIF-proline hydroxylation or impairment of VHL function similarly reduces HIF degradation and enhances the expression of HIF target genes [12].

Hypoxia also influences the expression profile of microRNAs (miRNAs) and their regulation of pathways involved in apoptosis and cell proliferation. For example, miR-146b has been shown to contribute to cardiomyocyte adaptation during chronic hypoxia, while its inhibition increases hypoxia-induced apoptosis in these cells. Additionally, miRNA-184 expression is significantly reduced in myocardial samples from patients with CCHD compared with controls. Experimental suppression of miRNA-184 in vitro similarly resulted in reduced cellular proliferation and increased apoptosis, likely mediated through activation of caspase-3 and caspase-9 by oxidized miRNA-184 [13].

Temporal HIF-1 -> HIF-2 -> HIF-3 sequence

The HIF signaling axis plays a crucial role in cardiac development, and variations in fetal oxygen levels and genetic polymorphisms in HIF pathway genes can contribute to CCHD. Key cardiac developmental genes such as Tbx1 and Nkx2.5 are particularly sensitive to hypoxic conditions; disruptions in these genes increase the incidence of cardiac malformations and embryonic lethality. Although HIF-1 primarily mediates the immediate cellular response to hypoxia, HIF-2 appears to regulate longer-term adaptations that help restore oxygen homeostasis. Global deletion of HIF2α has been associated with cardiac hypertrophy, impaired mitochondrial metabolism, and increased production of reactive oxygen species (ROS), likely due to reduced expression of antioxidant enzymes. Conversely, overexpression of HIF2α in cardiomyocytes enhances the transcription of HIF target genes and results in dilated cardiomyopathy, suggesting that HIF-2 plays an important role in chronic hypoxia and mitochondrial regulation. In addition, deletion of VHL in adipocytes can induce cardiac hypertrophy through HIF2-dependent alterations in lipid metabolism and inflammatory signaling [14].

Information regarding HIF-3 function in the heart remains limited. However, in cardiomyocytes suggest that HIF-3 may act similarly to prolyl hydroxylase domain enzymes (PHDs) by suppressing

the expression of typical HIF-1 target genes such as Glut1, Epo, and Glut4. HIF-3 expression has also been reported to increase in response to insulin signaling.

Genetic evidence further indicates that modulation of HIF activity in the cardiovascular system may have therapeutic potential. Several single-nucleotide polymorphisms (SNPs) in the Hif1a gene are associated with altered vascular responses. Similar to HIF-1, multiple HIF-2 (Epas1) knockout models exhibit vascular abnormalities, although the phenotypes vary depending on genetic background and differ from those observed with HIF-1 deletion.

Furthermore, HIF-1 and HIF-2 differ in their sensitivity to oxygen levels and their timing of expression during hypoxia. HIF-1 undergoes greater hydroxylation and turnover at physiological hypoxic conditions and is more prominently expressed during the first 24 hours of hypoxia, while HIF-2 expression becomes dominant after 24 hours, supporting their complementary roles in vascular development. Although research on HIF-3 remains limited, available data suggest it may also influence angiogenesis, with delayed induction in endothelial cells under hypoxic conditions, like HIF-2, and potential roles in the development of the heart, lungs, and vascular system [14].

Metabolic reprogramming in chronic hypoxemia

Shift from Oxidative Phosphorylation to Anaerobic Glycolysis

Patients with CCHD experience a relatively hypoxic physiological state. Because oxygen availability in the myocardium is reduced, mitochondrial oxidative phosphorylation becomes impaired. In these patients, elevated levels of several Krebs cycle metabolites have been observed, suggesting suppression of aerobic energy metabolism and accumulation of metabolic intermediates. At the same time, increased levels of lactic acid and pyruvic acid were detected, indicating enhanced anaerobic respiration and glycolysis in CCHD patients. The limited oxygen supply may also reduce fatty acid oxidation, which in turn stimulates myocardial cells to increase fatty acid uptake as a compensatory mechanism. Further metabolic profiling showed that many intermediates of the Krebs cycle were elevated in individuals with CCHD, reinforcing the idea that aerobic energy metabolism is downregulated under chronic hypoxic conditions. In contrast, higher lactate concentrations in the CCHD group suggest an increased reliance on anaerobic metabolism. Additionally, metabolites associated with glycolysis, including glucose-6-phosphate and pyruvate, were elevated, reflecting alterations in glucose utilization pathways. The concentration of Nicotinamide Adenine Dinucleotide (NAD) in myocardial tissue appears to positively correlate with energy metabolism in CCHD patients. These findings suggest that NAD may function as an endogenous cardioprotective factor, helping the myocardium adapt to prolonged hypoxic stress in CCHD [15].

Lactate Handling, Mitochondrial Remodeling, ROS Dynamics

The increase in anaerobic glycolysis in hematopoietic cells during hypoxia relies on receptor-mediated growth factor signaling. In the absence of growth factor stimulation, these cells fail to express HIF-1 mRNA. Growth factor-deprived cells also do not engage in glucose-dependent anabolic synthesis, and since HIF-1 is not expressed, they do not depend on HIF-1 for survival under hypoxic conditions. In contrast, when hematopoietic cells receive growth factor signals, HIF-1 becomes essential for their survival. Suppression of HIF-1 in these proliferating cells exposed to hypoxia leads to cell death. Growth factor-dependent expression of HIF-1 alters intracellular glucose metabolism by reducing glucose-driven anabolic synthesis and promoting lactate production, thereby shifting metabolism toward glycolysis. This metabolic transition becomes even more pronounced when HIF-1 protein is stabilized under hypoxic conditions [16].

Mitochondrial dysfunction is a well-recognized feature of adult heart failure, and many emerging therapies target pathways related to ROS stress and metabolic regulation. Similarly, mitochondrial dysfunction is a major component of heart disease in patients with CCHD. In the case of CCHD, the presence of cyanosis further exacerbates mitochondrial impairment. Consequently, mitochondrial dysfunction likely plays a critical role in the pathophysiology of CCHD [17].

Erythropoiesis and red cell adaptations

EPO-driven erythrocytosis and RBC metabolic phenotype

In CCHD, erythrocytosis develops as a physiological response to chronic hypoxemia. This response is primarily mediated by increased renal secretion of EPO triggered by reduced arterial oxygen tension. In many hypoxemic patients, near-normal systemic oxygen transport and tissue oxygen delivery can still be maintained through elevated hemoglobin concentrations and a rightward shift of the oxyhemoglobin dissociation curve, which facilitates oxygen release to tissues [18].

Prolonged hypoxemia and decreased tissue oxygenation in CCHD stimulate continuous EPO production by the kidneys, resulting in secondary erythrocytosis. This process initially acts as an adaptive mechanism to compensate for inadequate oxygen delivery. However, when hypoxemia remains persistent and fixed, such as in the presence of a significant right-to-left cardiac shunt, tissue oxygenation cannot improve beyond a certain limit. Despite this, EPO secretion continues, leading to excessive increases in red blood cell mass and blood viscosity, which can ultimately impair tissue oxygen delivery. Secondary erythrocytosis in CCHD can be classified into two forms: compensated and decompensated. In the compensated state, patients maintain a stable equilibrium with elevated hematocrit levels appropriate for the degree of hypoxemia. Iron stores are adequate, and symptoms related to hyperviscosity are generally absent. In contrast, the decompensated form is characterized by persistent stimulation of EPO secretion without corresponding improvement in tissue oxygenation. Red cell mass continues to increase despite harmful physiological effects, and iron deficiency commonly develops, leading to moderate or severe symptoms of hyperviscosity. Over time, this imbalance can result in negative iron balance and iron-deficient erythropoiesis, reflected by reduced ferritin levels and impaired red blood cell production. Eventually, iron-deficiency anemia may develop. Iron deficiency is particularly significant because erythrocytes produced under these conditions are typically microcytic and less deformable than normal cells. These altered mechanical properties affect blood viscosity within the microcirculation and contribute to many of the clinical manifestations associated with hyperviscosity [3].

CD47 and senescence-signaling in RBC survival

CD47 is a membrane glycoprotein expressed on many cells that acts as a “self” marker on red blood cells (RBCs). Studies have shown that unopsonized murine RBCs lacking CD47 signaling are quickly recognized and removed by splenic red pulp macrophages in normal recipients. Under normal conditions, CD47 on RBCs prevents their clearance by binding to the inhibitory macrophage receptor SIRPα. Evidence also suggests that splenic macrophages possess RBC receptors capable of identifying circulating erythrocytes. [19].

Benefit -risk conflict: oxygen transport vs hyperviscosity

Secondary erythrocytosis in CCHD occurs as a physiological response to tissue hypoxia, leading to increased serum erythropoietin levels, which stimulate bone marrow erythropoiesis and result in elevated red cell mass, hematocrit, and whole blood viscosity. The rise in circulating red blood cells

increases the oxygen-carrying capacity of the blood. However, this benefit is counterbalanced by increased serum viscosity, which reduces blood flow and tissue perfusion and consequently impairs oxygen delivery to tissues. This leads to hyperviscosity symptoms such as headache, visual disturbances, loss of concentration, paresthesia, muscle weakness, and fatigue. The most significant complication of hyperviscosity is thrombosis, which may present as cerebrovascular accident (CVA), myocardial infarction, or other thrombotic events [4].

Patients with CCHD have a higher risk of both bleeding and thrombosis. Bleeding events are attributed to various hemostatic abnormalities, while thromboembolic complications are associated with elevated hematocrit levels [20]. Because patients with increased hematocrit often display a hypocoagulable profile, studies have examined the relationship between elevated hematocrit and hypocoagulability. Thrombelastography (TEG) measurements, particularly those related to clot formation and clot strength, showed a strong negative correlation with hematocrit values, confirming that hemostasis in CCHD patients is impaired by elevated hematocrit itself. Clot formation is largely fibrinogen dependent, and recent studies have demonstrated that increased hematocrit can alter fibrin polymerization [20]. Table no. 1 summarizes the tissue- and cell-specific adaptations observed in CCHD.

Tissue / Cell Type	**Adaptive Response**	**Clinical Outcome / Phenotype**	**Source (first author, year)**
Myocardium (Heart Muscle)	higher NAD levels, elevated BCAAs (such as isoleucine and leucine), and metabolic remodeling featuring impaired fatty acid oxidation, upregulated glycolysis, and reduced aerobic metabolism Chronic hypoxia and RV pressure/volume overload; metabolic switch from fatty acid oxidation to glucose utilization (glycolysis); increase in HIF-1α triggers VEGF for angiogenesis; increase in NAD levels	RV failure (diastolic dysfunction); fibrosis/scarring (ECM remodeling); arrhythmias (scar-related electrical disruption)	[23], [14], [15]
Blood and Vascular System	Polycythemia via EPO-stimulated RBC production; vasodilation (decrease in coronary vascular resistance)	Hyperviscosity syndrome (thrombosis, stroke risk); iron deficiency	[3]
Pulmonary Tissue and Vasculature	Altered alveolar-capillary diffusion, altered ventilation-perfusion ratio, alveolar hypoventilation	Pulmonary atresia	[1]

Tissue / Cell Type	Adaptive Response	Clinical Outcome / Phenotype	Source (first author, year)
Skeletal muscle cells	can easily switch to different substrate utilization without reprogramming metabolism through transcriptional changes	Less muscle harm than the heart; maintains function better	[37]
Vascular endotherm	Grows new vessels via VEGF signals boosted by HIF-1α	Better local oxygen supply; abnormal vessel growth in tissues	[5], [13]

Table 1. Summary of tissue- and cell-specific adaptive responses to chronic hypoxemia in cyanotic congenital heart disease (CCHD), highlighting metabolic, vascular, and structural alterations.
BCAAs (branched-chain amino acids); CCHD (cyanotic congenital heart disease); ECM (extracellular matrix); EPO (erythropoietin); HIF-1α (hypoxia-inducible factor-1 alpha); NAD (nicotinamide adenine dinucleotide); RBC (red blood cells); RV (right ventricle); VEGF (vascular endothelial growth factor).

Cardiopulmonary Compensatory Mechanisms: System-Level Integration

In chronic CCHD, persistent hypoxia stimulates the kidneys to secrete EPO, resulting in secondary erythrocytosis, characterized by an increase in RBC mass to improve oxygen delivery. Although this adaptation enhances oxygen-carrying capacity, it also increases blood viscosity, which may paradoxically impair tissue oxygenation [3].

CCHD patients show a distinct metabolic profile compared with acyanotic congenital heart disease (ACHD) patients, characterized by decreased protein synthesis and reduced aerobic energy production, while elevated myocardial Nicotinamide Adenine Dinucleotide (NAD) levels may represent a compensatory response to hypoxia [15].

Sex-specific metabolic alterations have also been observed in neonates with CCHD, likely due to chronic hypoxia. Female neonates demonstrate increased fatty acid metabolism and oxidative phosphorylation activity at the transcriptomic and metabolomic levels compared with males. Suppression of mitochondrial oxidative activity is recognized as a cardioprotective response during oxygen deprivation. Interestingly, hypoxic females also exhibit increased expression of hypoxia-related genes and glycolytic activity [21].

White adipose tissue has traditionally been viewed as a storage site for triacylglycerols, but it is now recognized as an endocrine organ that secretes various adipokines involved in energy metabolism, inflammation, and cardiovascular regulation, including TNF-α, IL-1β, IL-6, IL-10, MCP-1, MIF, leptin, resistin, visfatin, and adiponectin. A markedly different metabolic profile has been reported in CCHD patients compared with ACHD patients, including reduced protein synthesis and aerobic energy production, while increased myocardial NAD levels may act as a response mechanism to hypoxia. Adipose tissue hypoxia (ATH) significantly increases the production of inflammation-related adipokines and markedly decreases adiponectin mRNA expression. Hypoxia also activates endoplasmic reticulum (ER) stress markers, and ER stress has been associated with inflammatory responses [22].

The Paradox: Why Structure Deteriorates While Function Compensates

The anatomical complexity of CCHD ranges from simple (mild) to complex (severe). Survival in patients with complex CCHD has improved; however, these patients still experience considerable morbidity and reduced survival compared with the general population. Major advances have occurred in the initial reparative or palliative surgical management of CCHD, particularly in conditions affecting the right ventricle (RV) such as tetralogy of Fallot (TOF) and hypoplastic left heart syndrome (HLHS). The RV tolerates volume overload more effectively than the left ventricle (LV) because of its thin and compliant wall, which allows patients to remain asymptomatic for longer periods while maintaining preserved RV function. CCHD is considered more complex when the RV occupies a subaortic position, when univentricular physiology exists, or when significant residual or progressive lesions are present. The ability of the RV to adapt to stress is influenced by genetic, anatomical, and environmental factors, and this adaptation varies considerably among CCHD patients [23].

In biventricular physiology, interactions between the ventricles are influenced by RV hypertrophy, dilation, and alterations in septal curvature. In TOF, pulmonary regurgitation (PR) and RV dilation are associated with LV deformation and dysfunction, whereas pulmonary valve replacement (PVR) improves left ventricular ejection fraction (LVEF). Comparable ventricular interactions are observed in Ebstein's anomaly and congenitally corrected transposition of the great arteries, where septal displacement negatively affects LV function [23].

In addition, the myocardial interstitium (MI) has recently shifted from being considered an innocent bystander to playing a central role in the development of long-term cardiovascular complications, particularly heart failure. The MI is not a passive structure but a complex and dynamic microenvironment undergoing continuous turnover. It maintains structural integrity of the myocardium, mediates the repair response following injury, enables force transmission during the cardiac cycle, converts cardiomyocyte contraction into effective ventricular pump function, and supports communication between cells. Altered hemodynamic conditions are common in most CCHDs, both before and after palliation or complete surgical repair. Consequently, myocardial fibrosis is expected to represent one of the principal maladaptive mechanisms responsible for the progressive decline in ventricular function in these patients and may serve as a potential therapeutic target. MF may represent part of the reparative response to the loss of contractile myocardial mass, thereby acting as a marker of advanced cardiomyopathy. However, the structural organization of myocardial fibrillar collagen is also essential for systolic function, as it facilitates the transmission of cardiomyocyte contraction. In addition, reduced stretching of myocardial fibers during diastole may impair systolic performance by altering length-dependent cardiac muscle fiber shortening, a mechanism described by the Frank-Starling law [24].

4. Clinical Implications

CCHD should be considered a multisystem disorder, in which chronic hypoxemia leads to significant alterations in hemostatic mechanisms and hematologic and endothelial functions [3]. The hypoxemic syndrome represents a multisystem condition that affects multiple organs and produces severe chronic metabolic disturbances that disrupt normal homeostatic balance. Figure 1 illustrates that chronic hypoxemia ($SaO_2 < 85\%$) triggers coordinated adaptive responses across the hematologic, cardiovascular, pulmonary, and peripheral systems to maintain oxygen delivery and tissue perfusion. These compensatory mechanisms, including erythrocytosis, vascular remodeling, and increased ventilation, initially help sustain physiological function; however, they are often accompanied by

maladaptive consequences such as hyperviscosity, increased afterload, elevated work of breathing, and reduced exercise capacity [1, 40, 41, 44]. As a result, the involved organs and systems operate under a fragile physiological equilibrium in which even minor insults can lead to marked hemodynamic decompensation [1]. Table no. 2 summarizes the clinical implications of these changes, outlining the compensatory mechanisms, their underlying pathophysiology, and the clinical problems experienced by patients.

Compensatory mechanism	Pathophysiology	Clinical problems patients feel	References
Secondary erythrocytosis	EPO-driven increases in RBC mass to improve O_2-carrying capacity in chronic hypoxemia.	Headache, dizziness, fatigue, visual changes, thrombosis, and mucosal bleeding when associated with hyper viscosity and coagulopathy.	[3], [1]
Hyper viscosity and plasma volume contraction	Non-linear increase in viscosity at high hematocrit; relative hypovolemia.	Sluggish circulation, reduced tissue perfusion, worsening cyanosis and exercise intolerance; dehydration and venesection for improved outcomes with respect to iron deficiency anemia.	[38], [3], [1], [39]
Vascular remodeling and endothelial dysfunction	Dilated, tortuous arteries; altered NO pathways; increased microvessel density.	Loss of medial smooth muscle cells, increased collagen and extracellular matrix in the media, disruption of the internal elastic lamina, and intimal fibromuscular dysplasia; Increased acidosis and widened arteriovenous oxygen gradient in exercising skeletal muscles and altered skeletal muscle bioenergetics.	[40], [1]
Ventilatory compensation	Increase in Resting and exercise minute ventilation, abnormal VE/VCO_2 slope, right-to-left shunt preserved.	Exertional dyspnea, limited exercise tolerance, and inability to increase activity beyond low-moderate intensity.	[41], [1], [44]
Myocardial adaptation	Ventricular hypertrophy and remodeling under chronic	Palpitations, arrhythmias, heart-failure symptoms,	[41], [1]

	volume/pressure load and hypoxia.	syncope, further reduction in peak VO_2 over time.	
Neurocognitive impairment	Craniofacial developmental abnormalities and increased risk for OSA (Obstructive Sleep Apnea)	lower IQ; OSA is known to affect the development of the hippocampus, a critical structure for learning and memory, and particularly spatial associative memory tasks such as the Paired Associates Learning test.	[42]
Renal dysfunction	Reduced cardiac output and renal perfusion stimulate activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS).	chronic renal hypoperfusion; neurohormonal activation contributes to progressive renal dysfunction; anemia correlates with reduced exercise tolerance, cyanosis (a multivariable predictor of GFR, implies disease acuity), and fluid-retention (due to hyperviscosity increases efferent glomerular arteriolar resistance, hydraulic pressure, filtration fraction, and oncotic pressure in post glomerular vessels)	[43]

Table 2. Summary of compensatory mechanisms in cyanotic congenital heart disease (CCHD), outlining underlying pathophysiology, associated clinical manifestations, and supporting references. EPO (erythropoietin); GFR (glomerular filtration rate); IQ (intelligence quotient); NO (nitric oxide); OSA (obstructive sleep apnea); RAAS (renin-angiotensin-aldosterone system); RBC (red blood cells); VE/VCO_2 (ventilatory equivalent for carbon dioxide); VO_2 (oxygen consumption).

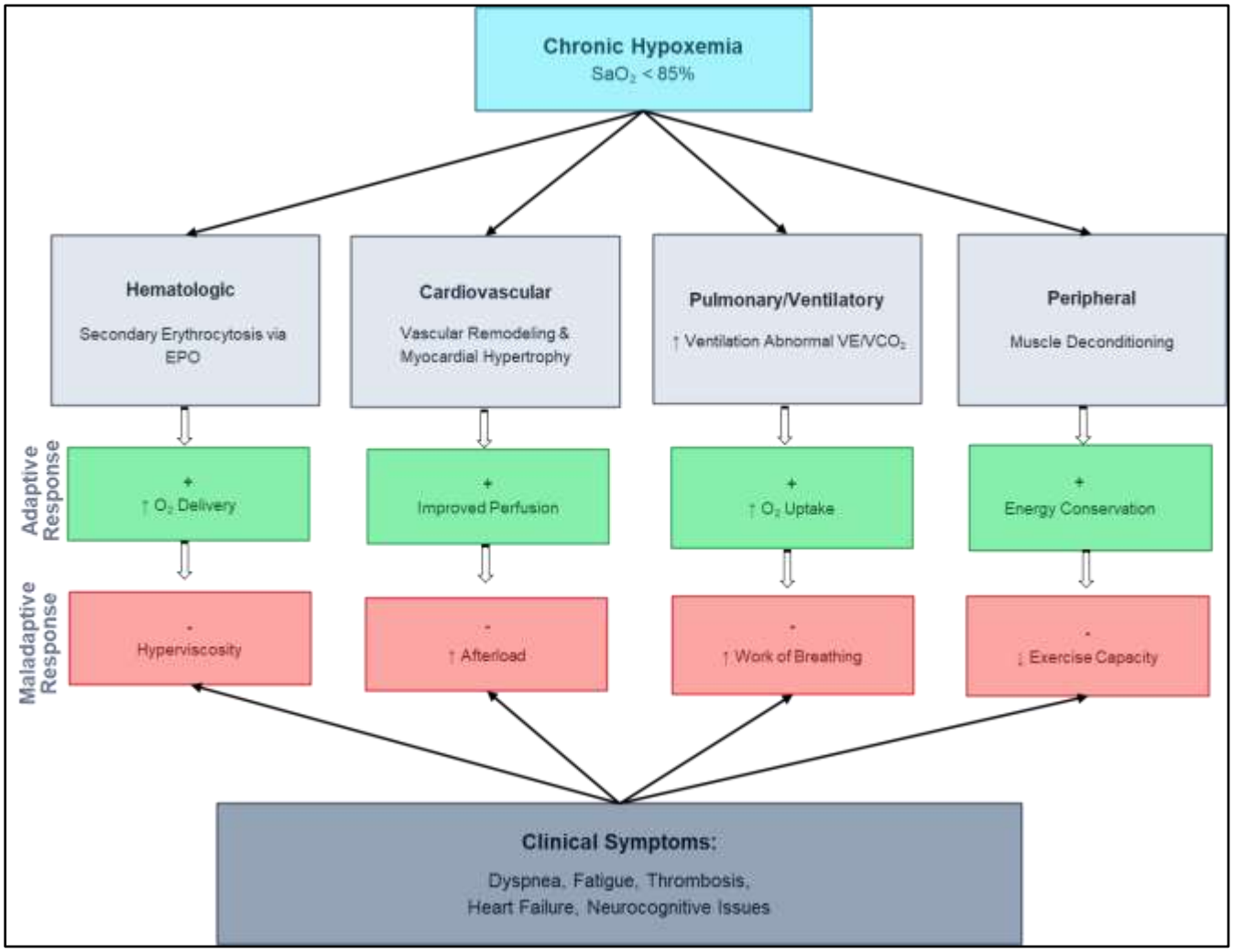

Figure 1. The figure illustrates the nature of compensatory mechanisms in CCHD, from hypoxemia to clinical manifestations.
Cyanotic Congenital Heart Disease (CCHD); Erythropoietin (EPO); Arterial Oxygen Saturation (Sao_2); Ventilatory Equivalent for Carbon Dioxide (VE/VCO_2).

Development and management strategies for preoperative optimization should focus on minimizing perioperative risk and improving postprocedural outcomes

Patients with cyanosis, complex congenital heart disease, frailty, heart failure, pulmonary hypertension, and those undergoing operations involving the respiratory or nervous systems have an increased risk of perioperative morbidity and mortality. The risk is further elevated in urgent or emergency procedures. Preoperative assessment should therefore consider arrhythmias, abnormal venous or arterial anatomy affecting access and blood pressure monitoring, adjustment of anticoagulant volume for blood work in cyanotic patients, developmental disability, differential dependence on preload and afterload influencing ventilation or insufflation strategies, endocarditis prophylaxis, erythrocytosis, monitoring renal and liver function, meticulous line care with air filters to prevent paradoxical embolism in right-to-left shunts, periprocedural anticoagulation, persistent

shunts, prevention of venous thrombosis, pulmonary vascular disease, valvular disease, and ventricular function [25].

Patients with CCHD require careful clinical management to prevent complications and improve functional outcomes. They should undergo annual screening and treatment for iron deficiency to improve exercise capacity and functional status. Patients presenting with persistent, new, or worsening neurologic deficits should receive urgent brain imaging to exclude cerebral abscess or stroke. In those with symptoms of hyperviscosity, rehydration with oral or intravenous fluids should be performed to relieve symptoms and reduce the risk of vascular complications. Pregnant patients with CCHD and cyanosis should be closely monitored throughout pregnancy by a multidisciplinary cardio-obstetrics team, including specialists in maternal-fetal medicine, CCHD, and obstetric anesthesia, to reduce cardiovascular and obstetric risks. In addition, patients of childbearing age should receive comprehensive family planning counseling, including guidance on safe and reliable contraceptive methods, from a multidisciplinary team experienced in CCHD care [25].

Exercise

As the population ages and survives complications of CCHD, individuals remain exposed to traditional cardiovascular risk factors such as hypertension, high cholesterol, prolonged smoking, obesity, and physical inactivity. Therefore, greater emphasis on managing these risk factors is essential. Preventive strategies are crucial, and early promotion of physical activity plays an important role. Even a modest level of physical activity provides both physical and mental health benefits [26].

Evidence strongly indicates that exercise is generally safe for individuals with structural heart disease. Research has shown that most sudden cardiac deaths in adults with congenital heart disease occur during periods of rest rather than physical activity. Additionally, participation in structured exercise programs, such as adult cardiac rehabilitation, has been shown to enhance cardiorespiratory fitness, muscular strength, flexibility, and metabolic function. It also contributes to reduced morbidity and mortality, fewer hospitalizations, and an overall improvement in quality of life [27].

The cardiovascular responses to these two types differ significantly. Dynamic exercise involving large muscle groups leads to a marked increase in oxygen consumption, cardiac output, heart rate, stroke volume, and systolic blood pressure, along with a moderate rise in mean arterial pressure. Diastolic pressure decreases, resulting in reduced total peripheral resistance. On the other hand, static exercise causes only a slight increase in oxygen consumption, cardiac output, and heart rate, with no change in stroke volume. However, it leads to a significant rise in systolic, diastolic, and mean arterial pressure, with little change in peripheral resistance. Overall, dynamic exercise imposes a volume load on the left ventricle, whereas static exercise creates a pressure load. With repeated training, dynamic exercise leads to increased left ventricular mass along with chamber enlargement, while static exercise increases left ventricular mass without enlarging the chamber [27].

To achieve health benefits, it is recommended to engage in 3 to 4.5 hours of physical activity per week, with each session lasting at least 30 minutes. For individuals starting from a deconditioned state, exercise intensity should be increased gradually, with regular reassessment and follow-up [26].

Biomarkers and Diagnostics

In a pilot study conducted at the John Araujo Hunter Hospital, Newcastle, Australia, levels of novel biomarkers were investigated in a diverse group of patients with adult congenital heart disease (ACHD). The key finding was that plasma S100B levels were detectable only in patients with moderate and severe ACHD complexity, with the highest concentrations observed in individuals

who had previously undergone atrial switch surgery for transposition of the great arteries and in those with Fontan palliation for complex congenital heart disease, which may indicate cumulative neurological injury. Increased Vascular Endothelial Growth Factor A (VEGF-A) levels were also identified across patients with moderate and severe ACHD, while ADMA concentrations were highest in patients who had undergone aortic coarctation repair. Besides serving as a biomarker of cerebral injury, S100B is also elevated in brain malignancies and neurodegenerative diseases, suggesting its potential usefulness as a biomarker in different neurological disorders. ADMA, an endogenous inhibitor of nitric oxide synthase, regulates nitric oxide bioavailability, and elevated ADMA levels are linked with impaired endothelial function. Higher ADMA concentrations are also associated with an increased risk of cardiovascular mortality and overall mortality in various patient populations. VEGF-A plays a role in promoting angiogenesis, and increased levels are observed in cardiac failure as a response to tissue hypoxemia. Moreover, elevated VEGF-A levels have been reported in pediatric patients with heart failure and cardiomegaly, with concentrations generally higher in cyanotic patients, again reflecting a response to tissue hypoxia [28].

The discriminatory metabolites were further evaluated using the area under the receiver operating characteristic (AUROC) curve, which identified five metabolic compounds (valine, glucose, glutamine, creatinine, and Polyunsaturated Fatty Acids (PUFA)) capable of distinguishing CCHD cases from controls with higher specificity. Overall, the untargeted metabolomic approach was useful in identifying and differentiating disease-related metabolites in cyanotic patients compared with healthy individuals. Five metabolic biomarkers were strongly associated with the cyanotic group, showing improved specificity and sensitivity. These metabolites included valine, glutamine, creatinine, glucose, and PUFA [29].

The HIF proteins belong to the family of basic helix-loop-helix transcription factors. The HIF complex functions as a heterodimer composed of a regulated α subunit and a constitutively expressed β subunit. Under normoxic conditions, hydroxylation occurs at specific proline residues on the α subunit, marking it for ubiquitination by proteins such as Von Hippel-Lindau (VHL), which leads to its subsequent degradation via the proteasome. There are two transcriptionally active α subunits- HIF-1α and HIF-2α-along with a third variant, HIF-3α, which lacks the DNA-binding domain and appears to inhibit HIF signaling by competing with HIF-1α and HIF-2α for β subunit association. The HIF-1α/HIF-1β heterodimer binds to hypoxia response elements within the regulatory regions of numerous target genes, including VEGF, plasminogen activator inhibitor (PAI-1), inducible nitric oxide synthase (iNOS), erythropoietin, BCL2/Adenovirus E1B 19 kDa Interacting Protein 3 (BNIP3), heme oxygenase-1, and glucose transporter-1 (GLUT-1). Beyond hypoxic regulation, the HIF pathway can also be influenced by reactive species, nitric oxide, metals, cytokines, and growth factor signaling cascades mediated through the phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways [30].

Future Research and Therapeutic Opportunities:

Degradation of the HIF-1α protein using the chemical compound YC-1 was found to disrupt the "memory" response associated with the induction of HIF-1α, VEGF, BNIP3, PAI-1, and iNOS. Moreover, reducing cellular reactive species using a general antioxidant or by inhibiting xanthine oxidoreductase similarly disrupted the "memory" of GLUT-1 induction. Interestingly, levels of ubiquitylated HIF-1α were found to decrease under conditions of chronic, mild hypoxia and showed only partial recovery once normoxic conditions were restored. Based on these observations, it is proposed that persistent HIF signaling may contribute to endothelial dysfunction and could represent a potential therapeutic target beyond strategies aimed solely at oxygen normalization [30].

Chronic hypoxia can modify the oxidative capacity of mitochondria. These functional alterations in cardiac mitochondria must be interpreted alongside shifts in cardiac energy substrate utilization [31]. Citrate synthase activity serves as a common surrogate marker for estimating mitochondrial mass in various studies. Under sustained hypoxic conditions, an elevated mitochondrial count is generally adaptive, as it enhances oxygen delivery efficiency through a greater mitochondrial surface-to-volume ratio [32, 33].

Recently, miRNAs have offered new understanding into the molecular mechanisms underlying CCHDs. This narrative review examines the evidence connecting RNA expression with CHDs and discusses the potential of RNA expression regulation as a promising approach for the development of therapeutic biomarkers. Regulation of mRNA expression appears to play an important role in the pathogenesis of CCHD and may facilitate the identification of novel molecular biomarkers. Changes in transcriptional profiles may provide innovative and highly specific methods for risk stratification and clinical monitoring of patients [34].

A miR-219-5p inhibitor has been shown to protect against spinal cord injury through regulation of the LRH-1/Wnt/β-catenin signaling pathway, while miR-219-5p has also been reported to promote the growth and metastasis of hepatocellular carcinoma through downregulation of cadherin-1 [35].

Several studies have reported deregulated miRNAs in CCHDs (Table 3) [36]. Understanding the molecular mechanisms underlying congenital heart disease remains essential for improving early diagnosis and the development of targeted therapies. In this context, regulation of mRNA expression is recognized as a key factor in disease pathogenesis and may assist in identifying novel molecular biomarkers. Changes in transcriptional profiles may provide innovative and highly specific tools for risk stratification and patient monitoring. Although additional studies are required to validate their clinical usefulness, mRNA-based strategies represent a promising direction for precision medicine in CCHDs [34].

Conclusion:

In CCHD, chronic hypoxia triggers HIF-centered cellular adaptations that sustain survival beyond classical hemodynamic models like Fick's principle and Starling's law. These include HIF stabilization under low oxygen, driving metabolic shifts to glycolysis, erythropoiesis via EPO, and tissue-specific responses such as RV remodeling and vascular changes, enabling preferential perfusion to vital organs. While these mechanisms maintain cardiac output and oxygen delivery, they impose long-term multi-system costs, including hyperviscosity, thrombosis, pulmonary hypertension, growth retardation, and myocardial fibrosis. The paradox arises as energy reallocation preserves function but leads to structural decline, evident in preserved perfusion alongside osteopenia and neurocognitive deficits.

Bridging physiology and cellular biology through biomarkers like HIF isoforms, VEGF, and RBC profiling is crucial for future management. Therapeutic opportunities lie in HIF-PHD inhibitors, miRNA modulation, metabolic therapies, and timed interventions to mitigate maladaptations, advancing precision care in CCHD.

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Abbreviations:

Cyanotic Congenital Heart Disease (CCHD); Polycythemia Vera (PV); Hypoxia-Inducible Factor-1α (HIF-1α); Erythropoietin (EPO); Nitric Oxide (NO); Hypoxia-Inducible Factor (HIF); End-Diastolic Volume (EDV); Left Ventricular End-Diastolic Pressure (LVEDP); Pyruvate Dehydrogenase Kinase 1 (PDK1); Pyruvate Dehydrogenase (PDH); Peroxisome Proliferator–Activated Receptor A (PPARα); Von Hippel-Lindau (VHL); 2-Oxoglutarate (2OG); MicroRNAs (miRNAs); Reactive Oxygen Species (ROS); Single-Nucleotide Polymorphisms (SNPs); Nicotinamide Adenine Dinucleotide (NAD); Red Blood Cells (RBC); Cerebrovascular Accident (CVA); Thrombelastography (TEG); Acyanotic Congenital Heart Disease (ACHD); Nicotinamide Adenine Dinucleotide (NAD); Adipose Tissue Hypoxia (ATH); Endoplasmic Reticulum (ER);

Right Ventricle (RV); Tetralogy Of Fallot (TOF); Hypoplastic Left Heart Syndrome (HLHS); Left Ventricle (LV); Pulmonary Regurgitation (PR); Pulmonary Valve Replacement (PVR); Left Ventricular Ejection Fraction (LVEF); Myocardial Interstitium (MI); Adult Congenital Heart Disease (ACHD); Vascular Endothelial Growth Factor A (VEGF-A); Polyunsaturated Fatty Acids (PUFA); Von Hippel-Lindau (VHL); Plasminogen Activator Inhibitor (PAI-1); Nitric Oxide Synthase (iNOS); BCL2/Adenovirus E1B 19 KDa Interacting Protein 3 (BNIP3); Glucose Transporter-1 (GLUT-1); Phosphatidylinositol 3-Kinase (PI3K); Mitogen-Activated Protein Kinase (MAPK).