**Global lipid remodeling by hypoxia aggravates migratory potential in pancreatic cancer while maintaining plasma membrane homeostasis**

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**Abstract**

Hypoxia plays an important role in pancreatic cancer progression. It drives various metabolic reprogramming in cells including that of lipids, which in turn, can modify the structure and function of cell membranes. Though homeostatic adaptation of membranes is well-recognized, but how it is regulated in hypoxic pancreatic cancer and its relation to aggressive phenotype and metastasis remains elusive. Here we show hypoxia-induced extensive global lipid remodelling spanning changes in lipid classes, unsaturation levels, glyceryl backbone and acyl chain lengths. No major modulation of membrane biophysical properties interestingly underpins a mutually exclusive regulation of the lipidome and membrane properties under hypoxia. Further, hypoxic conditions the increased migration and invasion were caused by reduced actin volume, cell cortical stiffness and facile tether dynamics. In conclusion, we demonstrate buffering of the lipidome alterations leading to a homeostatic membrane response. These findings will help to understand the hypoxic regulation of pancreatic membrane homeostasis and identify tangible theranostic avenues.

**Keywords:** Pancreatic cancer, hypoxia, cell membranes, lipidomics, membrane biophysics

## Introduction

Pancreatic cancer (PAC) is a highly aggressive malignancy, with a less than 9% five-year survival rate and poor prognosis [1]. The dismal prognosis is due to its rapid progression and highly metastatic potential [2, 3] . PAC involves significant alterations of cellular metabolism including glucose, amino acids, fatty acids (FA), and lipids, indispensable for their growth and survival [4, 5]. Further, multi-omic profiling of pancreatic cancer stem cells revealed extensive reliance on the fatty acid pathway highlighting lipidome rewiring for survival [6]. Another major hallmark of PAC is the presence of oxygen deprivation, i.e., hypoxia, which is correlated strongly to aggressiveness [7–9]. Hypoxia inducible factor-1$\alpha$(HIF-1$\alpha$) mediated hypoxic gene regulation in general is linked with perturbation of many metabolic pathways. Specifically, rewiring of lipid metabolism has revealed a tight regulation of lipid synthesis, lipolysis, and lipid droplets [10]. Extracellular FA flux, TG synthesis, and synthesis of derivative phospholipids increase under hypoxia, while lipid catabolism is suppressed. Notably, the accumulation of cholesterol has also been reported [11]. To obviate lipotoxicity due to an imbalance between synthesis and catabolism, lipid storage in lipid droplets is aptly enhanced [12]. The latter serves as the major source for the production of essential sterol esters and importantly phospholipids for the biogenesis of new membranes.

Modulation of the lipidome foremost affects membranes which are essential for the physiological functioning of mammalian cells. This is rendered by ether by maintaining the structural integrity or via non-structural functional roles in signalling and trafficking [13, 14]. Membranes orchestrate various membrane-associated processes by leveraging biophysical properties such as fluidity, packing, stiffness, curvature, and lateral organization [15]. Changes in these properties alter lipid-protein diffusion, localization, lipid-protein interactions, and finally their activity [16, 17]. These impose an exquisite regulatory control and hence are critically modulated in cancer for survival and proliferation [18]. For instance, membrane fluidity in cancer is altered in multiple ways. In highly metastatic cancer it increases by reduction of cholesterol and saturated lipids for facile movement (deformable membranes), while in drug-resistant cancer, it decreases to restrict permeability to drugs [18]. These suggest non-trivial and complex

regulation of membrane properties and function under stress. Cancer cell membrane mechanics and lateral organization are also linked with their metastatic dissemination.

Because of their central role, effective maintenance of membrane properties is essential in both normal and disease states. However, the correlation between hypoxic stress, lipidome remodeling and associated membrane properties and metastatic potential in pancreatic cancer is not known. Here we evaluate the pancreatic cell membrane response to hypoxia using lipidomics, membrane biophysics and cell biology. Upon hypoxia induction, levels of glycerophospholipids and sphingolipids decreased accompanied by a disproportioned increase of cholesterol esters and triacylglycerides leading to increased lipid storage. Distinct changes in the saturation levels and acyl chain lengths in a lipid class specific fashion was revealed In addition, hypoxia favoured accumulation of acyl lipids compared to their ether-linked counterparts. Next, we revealed decoupling of cell membrane biophysical properties from the lipidome alterations, indicative of a stable homeostatic membrane response under hypoxia. Finally, our data reveals that a homeostatic plasma membrane response may be an essential factor for cellular fitness under hypoxia to maintain high metastatic potential. These findings will drive gaining a deepened understanding of the underlying mechanisms involved in the hypoxic regulation of pancreatic membrane homeostasis. This is a fundamental step towards the development of reliable lipid and membrane biophysical biomarkers as well as membrane-centric therapeutic interventions.

## Results and Discussions

*Global lipidomics under hypoxia reveals rewiring of the lipid repertoire in terms of classes, glycerol-backbone and chain lengths*

To investigate hypoxia-induced alterations in the global lipidome of pancreatic cancer, an in-depth quantitative mass spectrometric analysis was performed in PANC-1 cell line. Hypoxia was induced using 200 μM of $CoCl_2$ in absence of serum and confirmed via HIF-1$\alpha$ expression (Fig. S1A-B). Previous studies have shown that induction of hypoxia using $CoCl_2$ is equivalent to having ~1% oxygen level in cellular metabolism [19, 20]. As a control a non-cancerous pancreatic cell line, HPNE was used. In total, 304 and 276 lipids were identified and quantified in PANC-1 and HPNE cells,

respectively. From this pool, around 170 (PANC-1) and 20 (HPNE) lipid molecules were significantly altered under hypoxia compared to normoxic conditions (Fig.1A, Fig.S1C). These lipids belonged to four main categories: glycerophospholipids (GPLs), sphingolipids (SPs), glycerolipids (GLs), and sterol lipids (STs) and covered 12 classes such as phosphatidylcholines (PC), lyso-phosphatidylcholines (LPC), phosphatidylinositol (PI), phosphatidylethanolamine (PE), lyso-phosphatidylethanolamine (LPE), phosphatidylserine (PS), phosphatidylglycerol (PG), sphingomyelin (SM), triacylglyceride (TG), cholesteryl esters (CE), ceramides (CER) and diacylglycerol (DG). TG and CE (belonging to GLs and STs categories, respectively) were significantly upregulated in tumour cell line under hypoxia (Fig.1B). Label free proteomics revealed a higher expression of acyl-coenzyme A (CoA): cholesterol acyltransferase1 (ACAT1, enzyme required for the conversion of cholesterol to cholesterol ester) in PANC-1 under hypoxia, but not in HPNE (Fig.1C) validating the increased abundance of CE in tumorigenic lipidome. Increased abundance of CE and TG also implicate modulation of cellular lipid droplets (LDs) under hypoxia in pancreatic cancer cells as these lipids are major components of LDs [21]. Indeed, we observed a significant accumulation of LDs under HIF-1$\alpha$ upregulation (Fig. 1D). Consistently, differentially expressed proteins involved in LD biogenesis were upregulated in PANC-1 (Fig.1C) only. GPLs, SPs and DG were downregulated under hypoxia (Fig. 1B) in PANC-1 but not in HPNE (Fig. S1D).

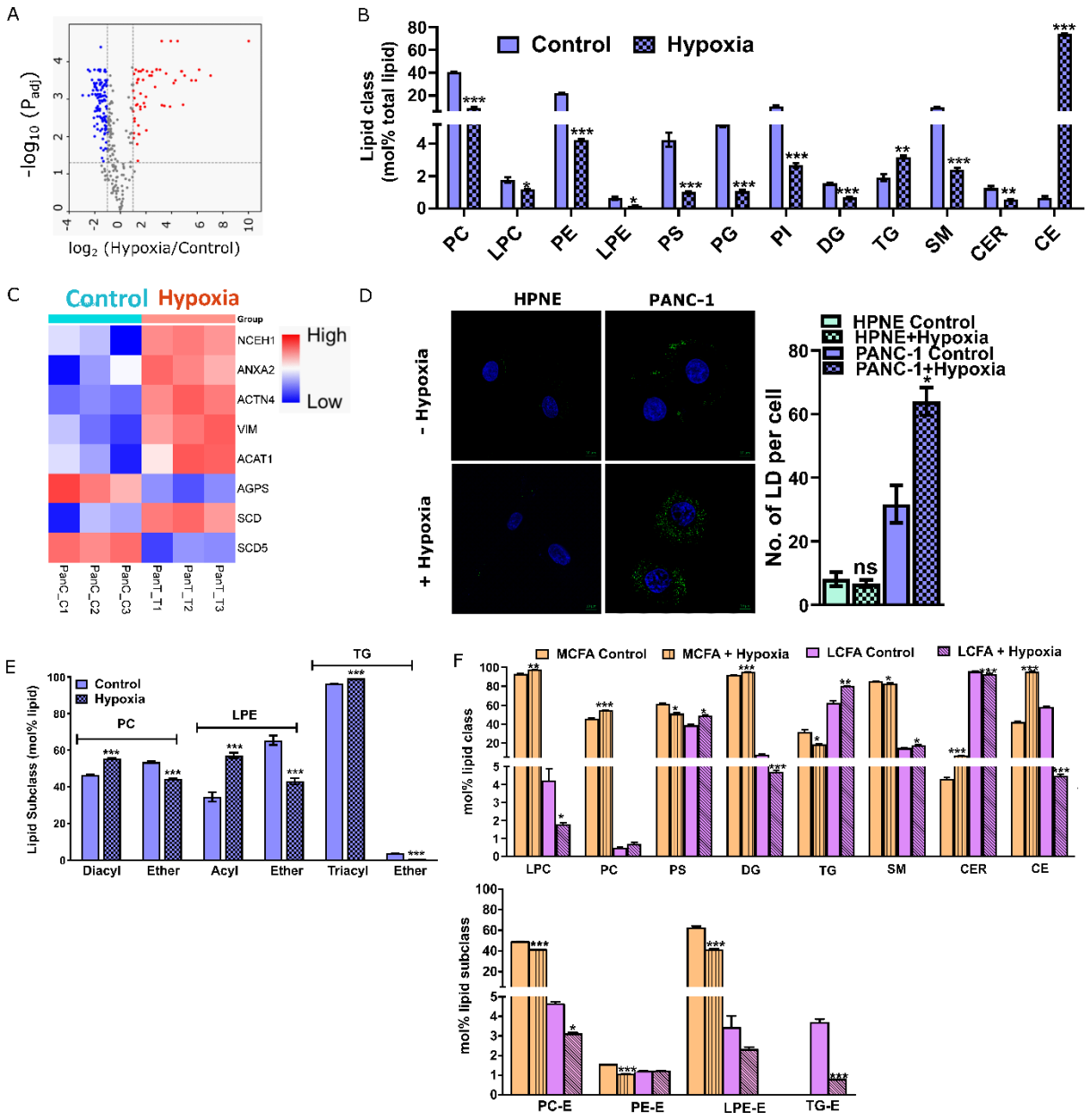


**Figure 1**. (A) Volcano plot depicting the significant fold change of different lipid species in PANC-1 cells cultured in the absence and presence of hypoxia. Lipids with a min. fold change of 2 and adjusted *p-value* < 0.05 are displayed in a color coordinated manner. (B) Mol% total lipid abundance at the lipid class level shows differential distributions. Data represent the average mol% total lipid class abundance ± standard error of the mean of three independent experiments. (C) Heat map showing a distinct pattern in significant protein expression in PANC-1 cells cultured under hypoxia. Proteins with a min. absolute fold change of 1.5 and adjusted *p-value* < 0.05 are displayed. (D) Lipid droplet staining with Bodipy showed a higher number of LDs in the cancer cells in presence of hypoxia compare to normoxia and normal cell line HPNE. Data for LDs are presented as mean ± SEM of two independent experiments. PANC-1 and HPNE are represented by blue and light green colour codes, respectively. Bar plots with patterns represents hypoxic conditions. (E) Mol% individual lipid subclass abundance distribution at the glycerol backbone linkage level. Alkyl ether (O) and plasmalogen (P) were together abbreviated as ether lipids. (F) Mol% total lipid class and subclass abundance to evaluate the distribution of chain lengths with individual lipid class or subclass preferred under hypoxia. In all the cases, bar plots with patterns represents hypoxic conditions. Statistical analysis was determined using student's *t*-test (* *P* value < 0.05, ** *P* value < 0.01, and ****P* value < 0.001).

Lipid metabolism has a high phenotypic plasticity allowing cells to adapt their membrane composition upon different stress conditions. Along these lines, analysing co-regulated lipids can furnish critical hints about the physiological response of the cell to a certain stimulus and the molecular mechanisms underlying it. One such pair is the acyl/ether lipid duo. Replacing the ester-carbonyl group in the sn-1 position of glycero- or glycerophospho-lipids generates ether lipids. We observed modulation of acyl vs. ether lipids in the most abundant lipid classes (Fig. 1D). For the GPLs, these included PC and LPE subclasses , wherein significant increases of diacyl-PC and acyl-LPE were observed under hypoxia with a concomitant reduction of their ether counterparts, PC-E and LPE-E. Likewise, a significant increase of triacylglycerol (TG-acyl) and a corresponding decrease of TG-E was observed in PANC-1. Decreased abundance of ether lipids under hypoxia in PANC-1 was validated by observing a reduced expression of alkylglyceronephosphate synthase (AGPS), a crucial enzyme-involved in the synthesis of ether lipids, including ether glycerophospholipids [22] (Figs.1C). Previously it has been shown that ether-containing ethanolamine phospholipids are significantly reduced in serum of pancreatic cancer patients which also aligns with our data [23]. Also, downregulation of ether lipid has been associated with the upregulation of the equivalent ester phospholipids [24], however the molecular mechanism underlying this co-relation is not fully understood but implicated to drive carcinogenesis. In relevance to this work, whether this has an impact on membrane structure and function needs further clarification but factors such as cross-sectional area of lipids, the melting temperatures, the differences in packing and the interaction with other lipids such as cholesterol between the ester and ether lipids are likely to have a contribution.

Next, lipidomic data revealed that hypoxia-induced an accumulation of medium chain length species within PC (C25-C35), LPC (C16-C20), DG (C30-C39), CE (C16-C20), and CER (C30-C39) in PANC-1. In contrast, for PS (C30-39), SM (C30-C39), and TG (C40-C50) a downregulation of these chain lengths was observed (Fig. 1F). Long-chained species were upregulated within PS (C40-C42), SM (C40-C52), and TG (C51-C60) lipid classes, whereas downregulated within LPC (C22-C28), DG (C40), CE (C22), and CER (C40-C46). Chain length variation at lipid subclass level revealed that in ether-linked PC (C30-C39), PE (C33-C39), and LPE (C16-C20), the medium

chained lipids were downregulated. Additionally, long-chained ether-linked PC (C40-C48) and TG (C53-C56) were lower under hypoxia in PANC-1 (Fig. 1F). No such variations were observed in HPNE except for TG medium (C36-C50) and long chains (C51-C60). This data collectively, suggests a complex remodelling of lipid chain lengths in response to hypoxia in a lipid class/subclass dependent fashion which needs further investigations to elucidate the functional aspect of this remodelling. The upregulation of long chained lipids can be linked with increased expression of elongation of very long-chain fatty acids protein 1 (EVOLV1) in PANC-1 under hypoxia (Figs. S2B).

*Increased unsaturation index at lipid category and class level in response to hypoxia*

To better understand the effect of hypoxia on the unsaturation index of lipids, which are known to impact membrane biophysical properties, we investigated the poly-unsaturation levels in all lipid classes belonging both the cell lines (Fig. 2A, and Fig. S2Ai-iv). Hypoxia modulated multilevel poly-unsaturation within different lipid categories. Specifically, it increased GPLs species with 4 & 6 double bonds; SPs species with >6 double bonds; GLs 3-6 double bonds and STs with 3-4 double bonds in cancer cell (Fig. 2A). Analysis of changes at the lipid class level revealed that the major contributor to the observed changes in GPLs was from PS (Fig. 2B). Furthermore, increase in poly-unsaturation within PS was also accompanied with an increase in corresponding chain lengths (Fig.1E). Similarly, the major contributors for the increase of SPs species with >6 double bonds was mainly from SM; with concomitant increase in its chain lengths as well. For GLs and STs the changes were found to be restricted to TG (along with longer chain lengths) and CE, respectively (Fig. 2B). No such changes were observed in HPNE (Fig. S2A) except for STs with 5 double bonds. Interestingly, the protein expression of many of the desaturases was modulated in PANC-1 cells suggesting a tight balance between saturation vs unsaturation under hypoxia. For example, the expression of stearoyl-CoA Desaturase (SCD) increased, but that of stearoyl-CoA Desaturase 5 (SCD5) decreased (Fig. 1C). At present, it is difficult to predict which enzymes are responsible for the observed changes in the polyunsaturation levels of fatty acids within different lipid classes under hypoxia. In HPNE, following lipidomic profiling, no major changes were observed with these proteins..

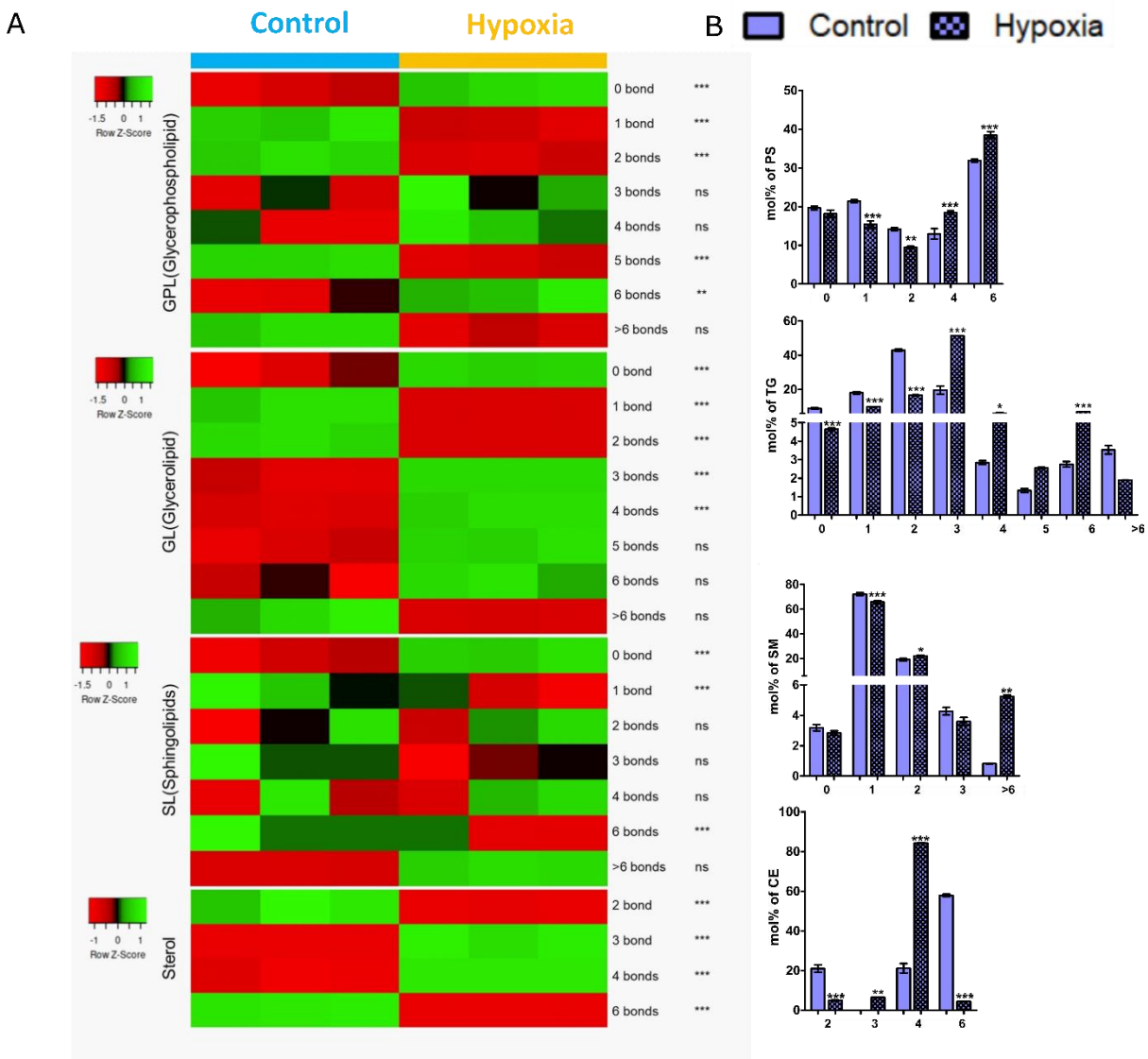


**Figure 2**. Significantly increased unsaturation index is observed at both the lipid category (A) and class level (B) of PANC-1 cells. In all the cases, bar plots with patterns represents hypoxic conditions.

*Homeostatic maintenance of plasma membrane fluidity, order and dynamics under hypoxic stress*

An important objective of this study was to investigate the influence of hypoxia on the membrane biophysical properties. To accomplish that, we analyzed membrane packing in cancerous and non-cancerous live cells using solvatochromic dyes (Laurdan, Di4-ANEPPDHQ) whose spectral characteristics are dependent on membrane properties such as order and hydration [25, 26]. Deconvoluted of the spectra to states with high (longer wavelength) and low hydration (short wavelength) within membrane bilayers provides a ratiometric index called generalized polarization

(GP). GP can take values from +1.0 (high order/low hydration) to -1.0 (low order/high hydration) in lipid membranes. Confocal spectral imaging of Di4-ANEPPDHQ in the live cell membrane was used to construct 2D GP maps of treated and untreated cells (Fig. 3A) and displayed a broad distribution of GP pixels (Fig. S3A) indicative of a heterogeneous plasma membrane organization. No effect on the plasma membrane order/hydration under hypoxia was observed in both cell types (Fig. 3A and S3B). Further, using the Laurdan probe and spectroscopy, similar observation was confirmed (Fig. S3C). Next, we evaluated lipid bilayer depth-dependent plasma membrane fluidity in live cells using fluorescence anisotropy and specific lipid probes. While DPH (diphenylhexatriene) positions itself at the deep hydrophobic acyl chain regions (hydrophobic), its charged counterpart, TMA-DPH (trimethylamino-diphenylhexatriene) is located at the interfacial polar head group region of lipid bilayers [27]. Hypoxia induction did not change any significant level of fluidity in both the cells (Fig.S3D). Membrane dynamics were also unaffected, confirmed by measuring no substantial changes in the lateral lipid diffusion in the plasma membranes of cancer and normal live cells under hypoxic and normoxic conditions (Fig. SF-H). Taken together, the pancreatic cancer plasma cell membranes maintained their hydration, order and dynamics under hypoxic stress.

The decoupling of hypoxia-induced lipidome changes from cell membrane biophysical properties as mentioned above prompted us to explore the lipidome changes specific to plasma membrane itself. Mass analysis of lipids extracted from blebbed giant plasma membrane vesicles in hypoxic and normoxic conditions demonstrated minimal changes in the plasma membrane lipidome (Fig. 3B) compared to global lipidomics. This hints that HIF-1$\alpha$ induced lipid remodelling is organelle specific in hypoxic-aggressive cancers and could preserve plasma cell membrane homeostasis for optimal membrane-associated cellular functions and survival.

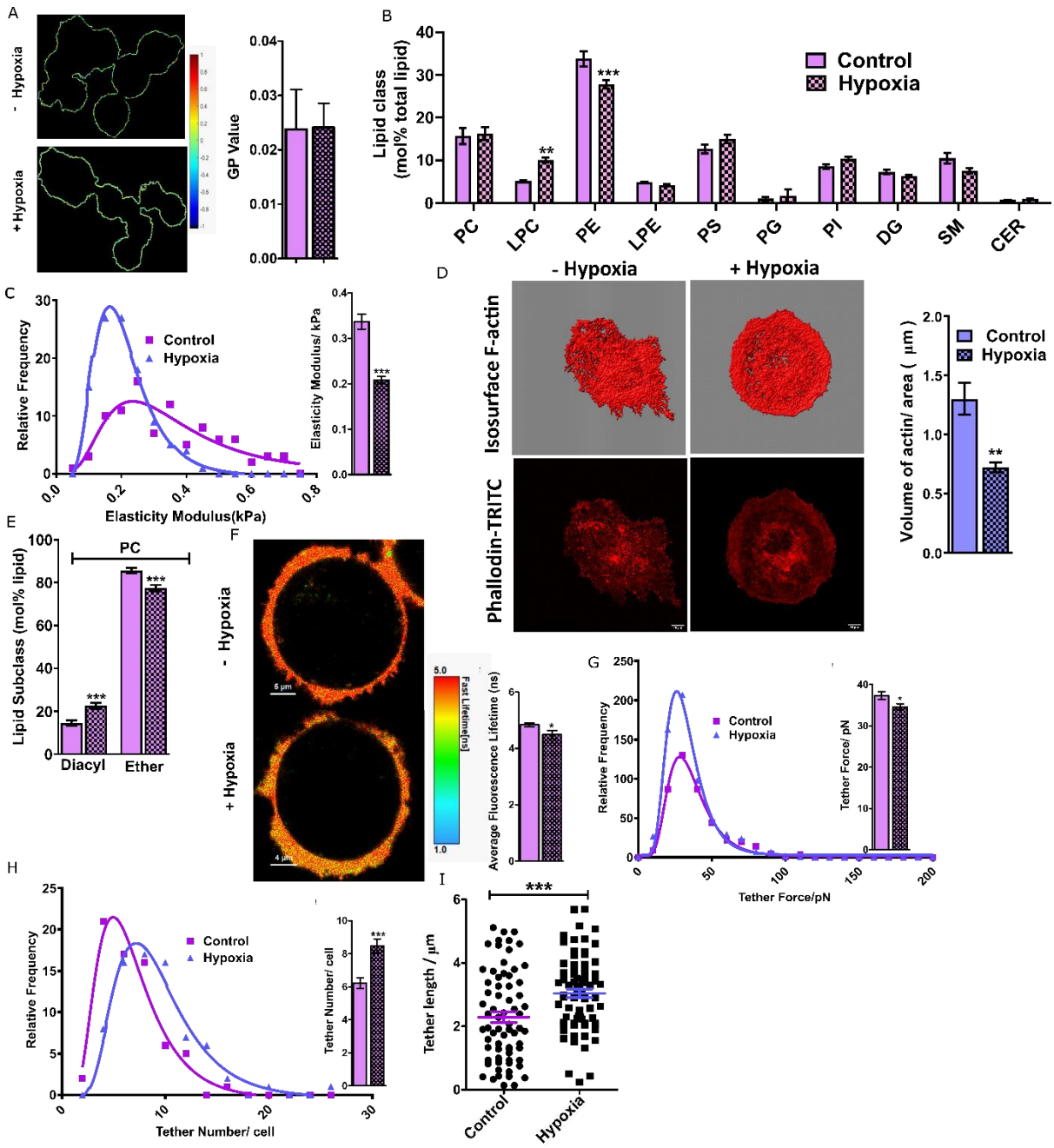


**Figure 3** (A) GP imaging of di-4-ANEPPDHQ-labeled cell membranes of PANC-1 cell line and the corresponding GP values. (B) Mol% total lipid abundance at the lipid class level of plasma membrane (PM) of PANC-1 cells cultured in the absence and presence of hypoxia. (C) Elastic moduli distribution of PANC-1 cells in the presence and absence of hypoxia. (D) Representative isosurface and Phalloidin-TRITC images were used to quantify actin abundance. The bar graph represents the volume of actin per unit area in control and hypoxia-induced cells. Scale bar, 10 µm; 63X oil objective. (E) Mol% PC lipid subclass abundance distribution at the glycerol backbone linkage level of PM extracted lipid. Alkyl ether (O) and plasmalogen (P) were together abbreviated as ether lipids. (F) FLIM imaging of PANC-1 cells with FliptR dye showed a decrease in average fluorescence lifetime after 24 h of hypoxia induction. (G) Relative frequency distributions of membrane tether forces, (H) tether number, and (I) tether length in the presence and absence of hypoxia. The mean values are provided in the bar graph. The significance test was performed using a student's t-test (*$P < 0.01$, two-tailed Student's t-test). In all the cases, bar plots with patterns represents hypoxic conditions and plasma membrane lipidomics data of PANC-1 is given in Magenta colour.

*Nanomechanical characterization of membranes under hypoxia*

Malignancy is associated with changes in cell mechanics and hence we were interested to evaluate pancreatic cancer membrane mechanics under oxygen deprivation using atomic force microscopy. Hypoxia-induced cell membrane softening was observed in PANC-1 with no change in control healthy cells (Fig. 3C and S3I). PC ether-linked lipids, which are known to modulate lipid raft domains in the plasma membrane displayed a downregulation in PANC-1 and hence may account for disrupted raft membrane regions and hence softness (Fig. 3E). However, as we did not observe any major changes in the order, fluidity and packing of plasma membrane, a softer cell membrane strongly implies contribution from other factors. One such factor is modulation of actin cytoskeleton which is underneath the plasma membrane and impacts measurements of cell elasticity. We observed decreased actin volume per area per cell in PANC-1 induced by HIF-1$\alpha$ underlying the decreased elastic modulus (Fig. 3D). Next, as membrane elasticity is linked with membrane tension, we also analyzed membrane tension in live cell membrane under normoxic and hypoxic induction using fluorescence lifetime imaging of a mechanosensitive FliptR probe [28]. Upon hypoxia induction the average lifetime of the probe slightly decreased in PANC-1 cells with no change in HPNE cells (Fig. 3F and Fig. S3K). Decreased lifetime indicates either a reduction in lipid phase separation, local plasma membrane composition becoming more homogenous or changes in membrane curvature; the latter being independently probed through tether analysis [29].

We then investigated the impact of hypoxia on tether dynamics in pancreatic cancer. Membrane tethers are membrane nanotubes regulating cellular communication, adhesion, and immune responses [30]. Tether force, total extension of the tethers per cell, and tether numbers indicate alterations in the membrane reservoir and curvature. Tether force is associated with membrane stiffness and bending rigidity and tether length and number indicate membrane resistance to bending or curving. The accumulation of specific lipids can affect membrane tethers by inducing curvature and signals the plausible role of lipid sorting (induced by hypoxia during lipid remodeling) toward the formation of such curved regions at the site of insertion [31] . Hypoxia significantly reduced the median tether force in PANC-1 compared to normoxic conditions, whereas no change in HPNE cells was observed (Fig. 3G and S3L). These

findings support the elastic modulus's analysis and suggest that hypoxia induction reduces the force required for the tethers to be extended, reducing surface tension and bending rigidity/elastic modulus in a cell-line-dependent fashion. (39). The tether number/cell increased in hypoxic conditions along with an increase in the total extension of the last tether (i.e. tether length) in PANC-1 compared to HPNE (Fig. 3H-I and S3M-N). These collectively support facile tether dynamics, which could be crucial for cancer progression under hypoxic states. Finally, the formation of the membrane tethers are associated with the positively and negatively curved membrane at the tether circumference and base, respectively. Thus a tempting hypothesis emerges that hypoxia-induced lipidome rewiring might affect lipid sorting leading to selective enrichment of inverted cone-shape lipids, that may foster the formation of highly curved regions at the site of cell membrane insertion, eventually leading to more frequent membrane nanotube generation.

*Hypoxia aggravates the migratory and invasive potential in pancreatic cancer*

The aggressiveness of cancer cells is determined by their capacity to invade through the epithelial basement membrane. Hypoxia has been shown to promote cell migration and invasion in many cancers [32]. In the purview of membrane biophysics, the understanding of key factors underlying tumor dissemination is limited, but changes in cell mechanics which are associated with lipidome/membrane remodelling are integral to metastatic dissemination. This  inturn governs cellular extensive deformation to migrate through tissues and enter blood vessels [33, 34]. In accordance, recent studies have shown a strong correlation between decreasing cell stiffness and increasing invasive and metastatic efficiency [35–37]; the former was seen in our hypoxic perturbation of cortical stiffness in PANC-1.

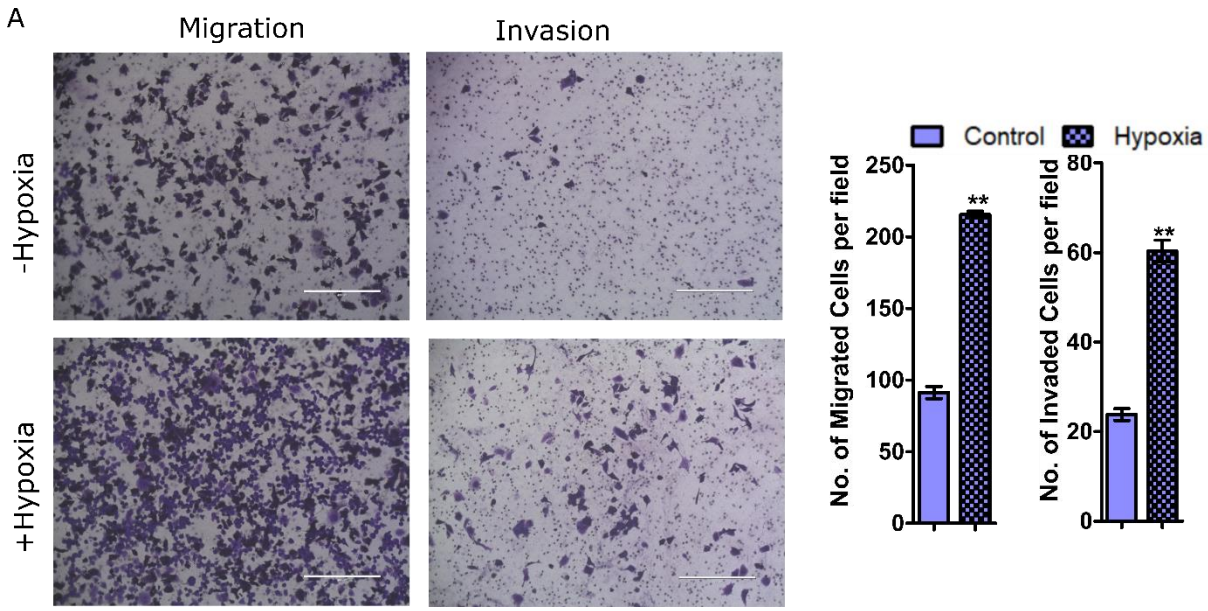


**Figure 4**. (A) Transwell migration assay based on the visualization and quantification of the number of migratory cells compare to control cells. (B) Transwell matrigel invasion assay to show invasive potential of hypoxia-treated PANC-1 cells. The significance test was performed using a student's *t*-test (**P* < 0.01, two-tailed Student's t-test).In all the cases, bar plots with patterns represents hypoxic conditions.

Using transwell migration and invasion assay, we observed that hypoxic pancreatic cancer cell exhibit enhanced migration and invasion compared to when in normoxic conditions (Fig. 4A). No change was seen in healthy pancreatic cells (Fig. S4A). Accumulation of unsaturated fatty acids including PUFAs has been positively correlated with higher migration and invasion [38]; a higher increase of these species was seen in PANC-1 (Fig. 2A, B). Similarly, an increased abundance of cholesterol and cholesterol esters (CE) aggravates the metastatic potential in many cancers such as renal cell carcinoma, prostate, breast, and pancreatic cancer [39–42]. The accumulation of these also corroborates a higher migratory and invasion potential in PANC-1 cells induced under hypoxia. Finally, decreased cell stiffness in PANC-1 also correlates well with these observations. Surprisingly, enhanced metastasis index in endometrial cancer progresses through the coordinated action of the EMT pathway and higher cell membrane fluidity [38]. Our data suggest the interplay of additional factors in hypoxic pancreatic cancer cells without the involvement of cell membrane fluidity. Furthermore, the PM tension in PANC-1 was attenuated under hypoxia and supports a higher migratory potential, as increased PM tension is associated with inhibited cancer cell migration and invasion by modulating membrane curvature formation mediated by both lipids and membrane proteins [29].

## Conclusion

Hypoxia plays an active role in promoting tumor survival, progression, and invasion and is a common phenomenon in most malignant tumors, especially in pancreatic cancer [7, 43, 44].Thus, studying the effect and response of hypoxic microenvironment in pancreatic cancer is gaining attention as an important therapeutic target. To adapt to the severe hypoxic environment, in general, cancer cells change their metabolic phenotypes to maintain their survival and proliferation [45]. Among them, aberrant metabolism of fatty acids, and lipids are some of the well decorated hallmarks [46]. The foremost impact of altered lipid metabolism is on the biophysical properties of cellular membranes, including plasma membrane [47]. Cell membranes orchestrate various physiological functions where the membrane biophysical properties such as membrane order, hydration, fluidity, curvature, tension etc all have specific roles. By regulating the sorting, structure, diffusion and interactions with other partners, membrane modulate functions of imbedded or associated biomolecules. Thus, a optimal response of cell membranes is crucial in both normal and disease states and led us to explore the lipidome and biophysical properties of PANC-1 cell membranes under hypoxic stress compared to non-malignant cells.

Lipidomic analysis of hypoxic pancreatic cancer cells revealed enhanced accumulation of TG and CE, while downregulation of GPLs and SPs. Increased abundance of CE and TG underlined a significant induction of lipid droplets. Lipid species with longer acyl chains lengths and increased desaturation levels showed a significant increase under hypoxia. Furthermore, typical acyl-containing species were upregulated, and alkyl- and alkenyl-containing ether PC, LPE and TG lipid species were downregulated, which was correlated with the cellular abundance of specific enzymes responsible for lipid elongation or unsaturation. Biophysical membrane assays reported a tight maintenance of membrane properties such as fluidity, lipid diffusion and order which remained unaltered under hypoxic stress. No variations in the plasma membrane lipidome under hypoxia and normoxia underlines homeostasic maintenance of membrane biophysical attributes. Enhanced migration and invasion under hypoxic states was seen and likely stems from a decreased cell cortical stiffness along with reduction of actin volume. Finally, facile tether dynamics as observed could be critical factor responsible for higher migratory potential in hypoxic pancreatic

cancer. In summary, we show a correlation or lack thereof distinctive lipid remodelling both a global and plasma membrane levels upon hypoxia induction in pancreatic cancer and how the same is buffered driving a homeostatic membrane response. The latter could account for a robust migration and invasion phenotype in hypoxic pancreatic cancers. Deeper understanding of the molecular mechanisms behind this phenomena could furnish tangible avenues for therapeutic targeting of pancreatic cancer using membrane-centric interventions.

**Data availability**

The data described in this article will be shared upon request. Inquiries should be directed to and will be fulfilled by the lead contact Shobhna Kapoor (shobhnakapoor@chem.iitb.ac.in), Department of Chemistry, Indian Institute of Technology Bombay, India.

**Conflict of Interest**

The authors declare no conflict of interests.

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