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The Impact of Polyploid Giant Cancer Cells: The Root of Stress Resilience

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ABSTRACT

Polyploid giant cancer cells (PGCCs) represent a unique and distinct subset of cancer cells, characterized by either an abnormally large nucleus or the presence of multiple nuclei within a single cell. An increasing body of evidence indicates that PGCCs are closely linked to cancer progression, therapeutic resistance, and poor clinical prognosis. However, despite their distinctive morphology, no universal marker has been identified to reliably distinguish PGCCs from other cancer cell populations. This is at least partly because PGCCs arise across various cancer types in diverse contexts, displaying considerable variability in their gene expression profiles. Nevertheless, they share key features, most notably polyploidy and remarkable stress resilience. The exceptional stress resilience of PGCCs arises from various mechanisms, including genome redundancy buffering against genetic damage, dormancy induction for survival in harsh conditions, gene expression changes enhancing hypoxia resistance, and metabolic adaptations supporting growth in resource-limited environments. Collectively, these properties make PGCCs highly resilient to stress, facilitating their persistence and contributing to the progression and aggressiveness of cancer. In this review, we provide a comprehensive discussion of the mechanisms underlying PGCC stress resilience and explore its broader implications for cancer pathogenesis. Understanding these adaptive strategies may offer new insights into cancer biology and reveal potential therapeutic targets to mitigate PGCC-driven malignancy.

1 | Introduction

Polyploid giant cancer cells (PGCCs) are distinctive cancer cells that characteristically have a large nucleus or multiple nuclei. The number of PGCCs increases following radiation and chemotherapy, which are particularly associated with resistance to these treatments. The increase of PGCCs correlates with poor prognosis in diverse types of cancers, including breast, ovarian, and colon cancers [1, 2]. PGCCs are also sometimes observed in cancers without prior treatment [3], shown in hepatocellular carcinoma and prostate cancer [3, 4], and their presence is also linked to increased cancer metastasis and poor prognosis (Figure 1). Therefore, gaining insight into the role of PGCCs in cancer progression and targeting them for therapy is expected to drive advancements in cancer treatment.

Unfortunately, a universal marker for reliably identifying PGCCs has yet to be established, posing a challenge for PGCC research. One reason why it is difficult to determine markers for PGCCs is that PGCCs emerge across various contexts, such

Abbreviation: PGCCs Polyploid giant cancer cells.

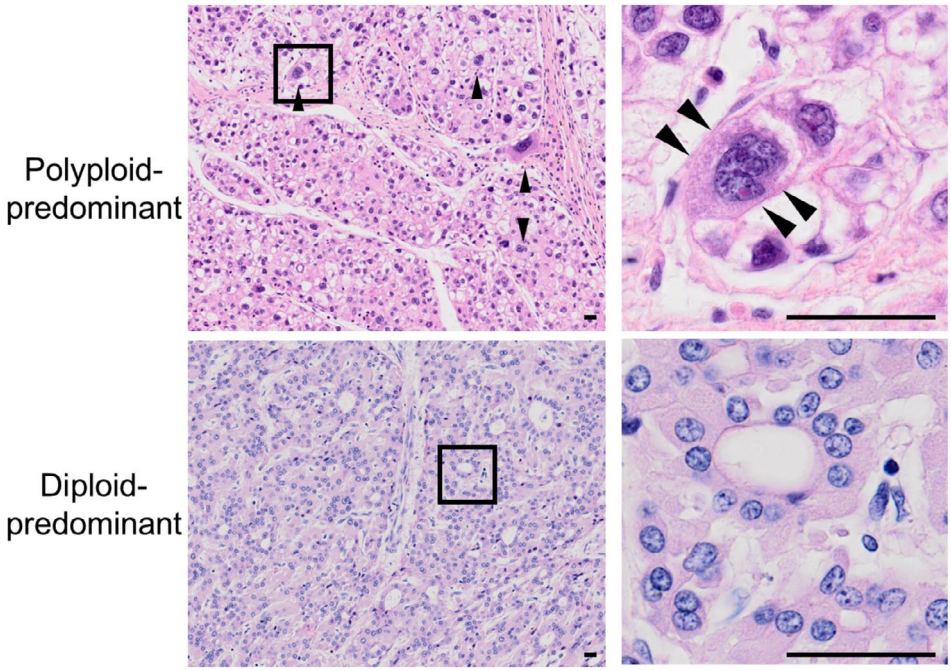

FIGURE 1 | H&E-stained image of a PGCC in human hepatocellular carcinoma without prior treatment. The left panels show HE-stained images of diploid-predominant hepatocellular carcinoma at low magnification and polyploid-predominant hepatocellular carcinoma containing PGCCs. Arrowheads indicate PGCCs. Higher-magnification views of the boxed areas are shown in the right panels. Scale bar, 20 μm.

as in different cancer types and with or without prior treatment history, and they may exhibit diverse gene expression patterns. In addition, it is possible that multiple subsets of PGCCs coexist within a cell population. Some PGCCs have been reported to display characteristics such as cellular senescence or the expression of stem-cell features [5, 6], though these traits do not appear to apply to all PGCCs. On the other hand, PGCCs do seem to share some common characteristics. The most notable feature is their strikingly large size, and at present, many studies detect PGCCs based on their distinct morphology of having a nucleus approximately three times larger than that of other cancer cells. Moreover, PGCCs are polyploid by definition, with an increased genomic content per cell, and typically exhibit strong resistance to various stressors (Figure 2). In this review, we focus on these common characteristics of PGCCs, particularly polyploidy and stress resilience, and discuss their implications for cancer pathogenesis.

2 | Cellular Dynamics Leading to PGCC Formation

Polyploidization is a critical process in PGCC formation. The mechanisms underlying polyploidization, or whole-genome doubling, primarily involve either cell fusion or abnormalities in the cell cycle (Figure 3). Cell fusion, involving the merge of cells from the same or different lineages, generates multinucleated polyploid cells. A classic physiological example is myoblast fusion during skeletal muscle formation. Fusion can also occur under pathological conditions, including viral infections (e.g., cytomegalovirus) and tissue damage such as liver and lung injury [7, 8]. Notably, polyploidization through cell fusion has been reported in several cancers, including colorectal and pancreatic cancer [9, 10].

Cancer cells proliferate through the cell cycle, and disruptions in this process can lead to polyploidization via three main mechanisms. First, cytokinesis failure produces binucleated polyploid cells when nuclear division occurs without successful cytoplasmic separation. This can occur, for example, when lagging chromosomes obstruct the contractile ring [11]. Second, mitotic slippage occurs when cells fail chromosome segregation and exit mitosis prematurely, often induced by microtubule-targeting drugs such as taxanes and vinca alkaloids. Whether cells undergo mitotic death, a form of cell death occurring during mitosis due to prolonged spindle assembly checkpoint activation, or mitotic slippage depends on spindle checkpoint activity and cyclin B degradation [12]. Third, endoreduplication involves repeated DNA replication without mitosis, generating mononucleated polyploid cells, typically in response to DNA damage blocking mitotic entry [13]. In this way, cancer cells often undergo polyploidization through various pathways, especially under stress from anticancer treatments.

Polyploid cancer cells may also be prone to further polyploidization. Their high chromosome content often causes segregation errors, with lagging chromosomes leading to cytokinesis failure. They also have difficulty aligning chromosomes at the metaphase plate, increasing the risk of mitotic slippage. In addition, polyploid cells exhibit elevated replication stress and DNA damage [14, 15], which may trigger G2 arrest and endoreduplication. Given the genomic instability that follows polyploidization, polyploid cancer cells may be susceptible to further polyploidization leading to PGCCs, which need to be investigated in future studies.

Intriguingly, recent studies have shown that PGCCs can also emerge through highly distinctive cellular transformations,

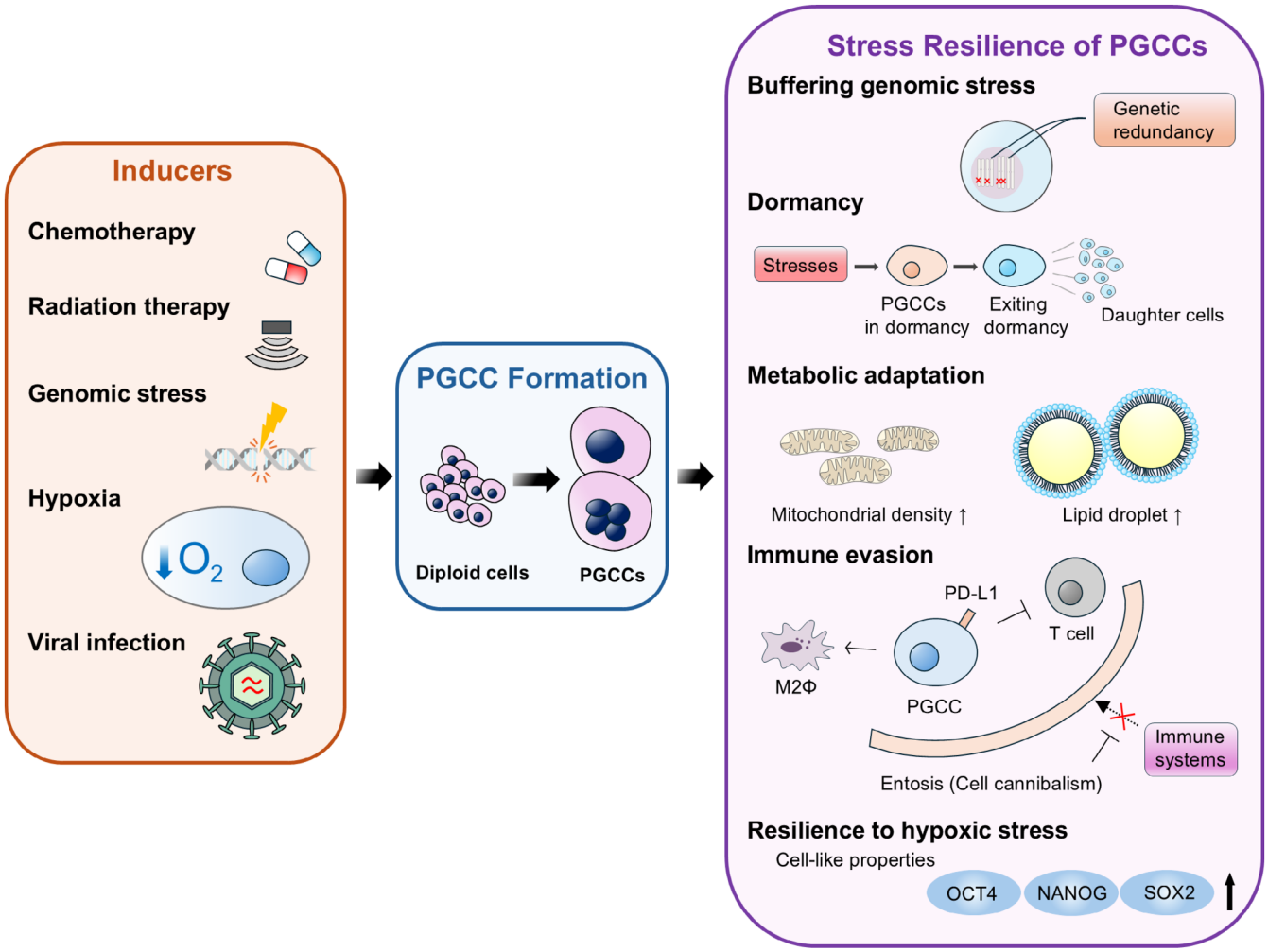

FIGURE 2 | Stressors that induce PGCC formation and the stress resilience exhibited by PGCCs. PGCC formation is induced by various stresses. PGCCs survive these challenges through mechanisms such as genome redundancy, which buffers against genetic damage; dormancy induction, which enables survival in harsh conditions; gene expression changes that enhance hypoxia resistance; and metabolic adaptations that support growth in resource-limited environments. These traits enable PGCCs to persist and contribute to cancer progression.

differing not only from classic cell cycle deviations but also from cell fusion. These transformations involve unique cellular dynamics, such as entosis and nuclear budding, and PGCCs formed in this way accompany membrane-wrapped intracellular cells, referred to as fecundity cells by Liu, et al. [16], which represent a form of cell-in-cell structure associated with PGCCs. Intracellularly formed fecundity cells have also been observed to exhibit unique dynamics, including decellularization, nuclear fusion, and cell cycle synchronization with other nuclei. These cellular dynamics during PGCC formation are reminiscent of those seen in pre-embryogenesis [16].

Although a variety of cellular processes are thought to contribute to the formation of PGCCs, the molecular mechanisms underlying their development remain poorly understood. Further investigation is needed to identify the primary pathway of PGCC formation and to determine whether PGCCs exhibit distinct characteristics depending on the formation pathway.

3 | Stresses That Drive PGCC Formation

A wide range of cancer therapies has been shown to induce the formation of PGCCs. Among these, exposure to chemotherapeutic agents has been the most extensively studied and is considered a major factor driving PGCC development. Alkylating agents, platinum-based chemotherapies, and topoisomerase inhibitors such as mitomycin C [17], cisplatin [18], and doxorubicin [19] have been shown to induce PGCC formation in various cancer cell lines. Chemotherapeutic agents that disrupt microtubule dynamics, such as taxane-based agents and vincristine, are also known to induce PGCC formation. In addition, recent molecularly targeted therapies, such as PARP inhibitors which impair DNA damage repair, have been shown to induce PGCC formation [20]. Radiation therapy, which induces genomic damage in cancer cells, is also a significant contributor to the formation of PGCCs. Overall, various types of cancer therapies that induce genomic damage or disruption of mitosis in actively proliferating cancer cells can impede cell cycle progression, leading to the formation of PGCCs.

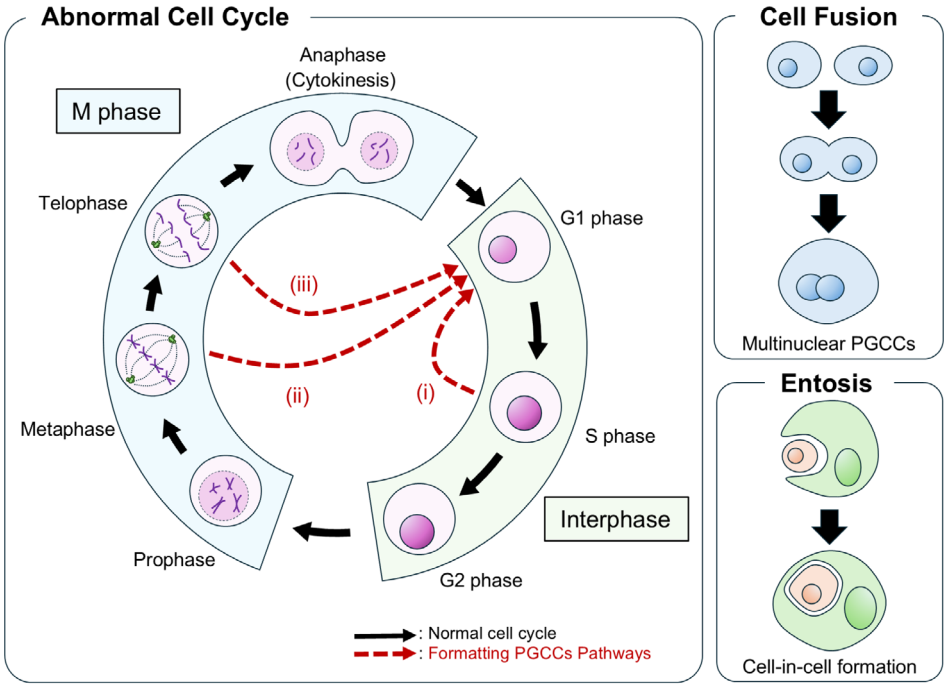

FIGURE 3 | The mechanism of PGCC formation. Cancer cells can form PGCCs via two main mechanisms: cell cycle aberrations within a single cell (left) or fusion of multiple cancer cells (right). The first mechanism can be subdivided by the phase of abnormality: (i) endoreduplication, (ii) mitotic slippage, and (iii) cytokinesis failure. The second, involving multiple cells, includes (iv) cell fusion and (v) entosis.

In addition to being a consequence of cancer therapies, PGCCs can also emerge in response to the stress that is inherently associated with cancer itself. For example, hypoxic stress [21, 22] or infection with oncogenic viruses such as hepatitis B virus and Epstein–Barr virus [23] can promote PGCC formation. This possibility highlights that PGCCs may emerge endogenously, driven by cancer-associated stress factors intrinsic to the tumor environment and independent of therapy. Indeed, PGCCs are observed in various types of cancers with no prior history of treatment, such as ovarian cancer [24], breast cancer [25], rectal cancer [26], liver cancer [3], and glioma [27]. For example, hepatocellular carcinoma sometimes exhibits genome doubling, which is often accompanied by PGCCs that may arise from intrinsic genomic instability within cancer cells [3]. PGCC formation is driven by various endogenous factors, including external stresses and intrinsic mechanisms, and in any case contributes to stress resistance as discussed below.

4 | Dormancy in PGCCs

PGCCs induced by stresses, including but not limited to chemotherapy [6], radiation therapy [28], and hypoxia [21] often undergo cell cycle arrest when generated experimentally in vitro. These cells were previously considered to be in a state of cellular senescence, as they frequently express senescence-associated markers, such as senescence-associated beta-galactosidase [29, 30]. Cellular senescence is defined as an irreversible cell cycle arrest and is characterized by features including proliferation arrest, expression of anti-apoptotic genes, and the secretion of various bioactive molecules [31, 32]. However, markers commonly used to indicate senescence, including senescence-associated beta-galactosidase, can also be present in non-senescent contexts [33]. Moreover, PGCCs induced under various conditions have been reported to retain the ability to produce daughter cells, thereby contributing to treatment resistance and tumor relapse [1, 34, 35]. Because of this, perspectives on the relationship between PGCCs and cellular senescence have shifted, and it is now recognized that not all PGCCs necessarily exhibit a senescent state [20, 29].

Although cell cycle arrest is not always irreversible, PGCCs formed under severe stress often enter a temporary dormant state, allowing them to evade anticancer mechanisms. Therapies that induce PGCC formation often cause extensive genomic damage and activate cell cycle suppressors such as p53, leading to dormancy [18, 20]. Autophagy, activated by mitochondrial damage via the AMPK-mTOR pathway, has also been reported as a critical mechanism for the induction of dormant PGCCs, although the detailed process by which autophagy directly induces cell cycle arrest and dormancy remains to be fully elucidated [36]. In addition, polyploidization itself can promote arrest through p53 activation mediated by the PIDDosome and Hippo pathways, which are triggered by centrosome amplification [37, 38]. Notably, PGCCs can escape dormancy through ploidy reduction, a process critically dependent on their prior polyploid state [1, 19]. This suggests that polyploidy plays a crucial role in maintaining the dormancy and survival of PGCCs, and that ploidy status is an important factor in switching between dormancy and a proliferative state.

Since many anticancer treatments act in a cell-cycle-dependent manner, dormancy allows PGCCs to resist therapy and contributes to disease relapse [39, 40]. Dormancy of cancer cells is also closely associated with their ability to evade immunosurveillance

[40]. While PGCCs exhibit traits beyond dormancy, this state likely serves as a key survival strategy supporting their long-term persistence.

5 | Polyploidization and Genomic Stress

Genomic damage is a major trigger of PGCC formation, arising not only from anticancer therapies but also from persistent endogenous stresses. Actively proliferating cancer cells experience replication stress and mitotic errors, along with genomic instability such as global hypomethylation and activation of endogenous retroelements [41, 42]. These intrinsic and therapy-induced stresses likely drive PGCC formation.

PGCCs are polyploid and thus harbor increased genome content. Recent studies suggest that polyploidization itself can exacerbate genomic damage. For example, it may impair DNA replication fidelity by causing protein shortages during the G1/S transition [14]. Polyploid cancer cells are also prone to chromosomal instability, with their high chromosome content increasing the risk of segregation errors. Lagging chromosomes can undergo extensive clustered rearrangements, a phenomenon known as chromothripsis [43]. Such damaged lagging chromosomes can sometimes be reincorporated into the nucleus [44], further contributing to genomic instability in polyploid cells. Overall, polyploid cells accumulate disproportionately high levels of genomic damage relative to their ploidy [15]. This excess damage can, in turn, impair cell cycle progression and promote further polyploidization, creating a self-reinforcing cycle.

Although polyploidization and genomic damage are closely linked, PGCCs exhibit notable resistance to DNA-damaging anticancer therapies. This resilience is partly due to genomic redundancy, which buffers against gene loss. In diploid cells, damage to one allele can disrupt gene expression and trigger cell death, whereas polyploid cells retain multiple intact copies, maintaining function despite partial damage. Consequently, polyploid cancer cells better withstand treatment-induced cell cycle arrest and apoptosis [15]. Polyploidization appears to enhance cell survival even in the face of substantial genomic damage, and PGCCs, whether induced by therapy or endogenous stress, act as durable reservoirs that survive despite extensive genomic abnormalities.

6 | Resilience to Hypoxic Stress

Hypoxia, a hallmark of the tumor microenvironment, is among the most extensively studied factors driving PGCC formation, alongside radiation and chemotherapy. Studies have demonstrated that treatment with cobalt chloride, a prolyl hydroxylase inhibitor that stabilizes HIF-1α and mimics hypoxic conditions, promotes PGCC formation across various cancer cell lines [2, 21, 45]. The PGCC formation induced by hypoxia has been shown to result from the downregulation of Cyclin D1 expression during the G2 phase of the cell cycle, coupled with the inhibition of subsequent cell cycle progression [21]. Importantly, after treatment with cobalt chloride, PGCCs persist while diploid cancer cells are eliminated, highlighting the enhanced resilience of PGCCs to hypoxic conditions [21].

Several mechanisms can explain the remarkable resistance of PGCCs to hypoxic stress. One key factor is the acquisition of stem cell-like properties by PGCCs. This phenomenon aligns with the well-established concept that hypoxic conditions can induce and maintain stemness in cancer cells [46, 47]. Indeed, PGCCs induced by hypoxia have been shown to exhibit increased expression of stem cell-related genes such as OCT4, NANOG, and SOX2 [22]. This cellular reprogramming enables PGCCs to better withstand the harsh, oxygen-deprived tumor microenvironment. Furthermore, the dormancy observed in PGCCs significantly lowers their energy requirements, demonstrating an important strategy in response to the extreme conditions of hypoxia. In addition to reduction of metabolic demands, PGCCs exhibit significant metabolic adaptability. Notably, the accumulation of lipid droplets within PGCCs serves as an energy reservoir, enabling them to endure prolonged hypoxic stress [48]. At the same time, an increase in mitochondrial content supports sustained ATP production, even in oxygen-deprived environments, further enhancing their survival capacity under hypoxic conditions [48]. Through these multifaceted mechanisms, PGCCs not only enhance their resilience to hypoxic conditions but also gain the capacity to promptly resume proliferation once the hypoxic stress is alleviated [49].

7 | Metabolic Adaptation as a Key to Survival

Another hallmark of cancer is altered metabolism. Cancer cells have a preference for glycolysis over oxidative phosphorylation to generate ATP even in the presence of oxygen, a phenomenon termed the Warburg effect [50]. Actively proliferating cancer cells also demonstrate upregulated lipid biosynthesis to provide essential components for membrane construction, energy storage, and signaling molecules [51]. Furthermore, cancer cells exhibit unique amino acid metabolic adaptations, particularly a heavy dependence on glutaminolysis, where glutamine functions as a vital metabolic fuel [52]. Notably, PGCCs have been found to display even more pronounced and distinctive metabolic alterations compared to other cancer cells with these metabolic traits.

In cancer cells, lipid metabolism is characterized by increased fatty acid synthesis and uptake, often leading to the accumulation of lipid droplets [51]. These lipid droplets play a pivotal role in promoting cancer cell survival and treatment resistance by sequestering free fatty acids to prevent cellular damage or absorbing lipophilic anticancer drugs, thereby lowering their intracellular concentrations [53]. Hypoxic conditions can induce lipid droplet formation, which is also thought to contribute to cancer cell resistance to hypoxia [54]. Notably, PGCCs exhibit a markedly higher degree of lipid droplet formation compared to other cancer cells [55]. In PGCCs, the elevated expression of the PLIN4 gene, which stabilizes lipid droplets, is implicated in treatment resistance in triple-negative breast cancer and may represent a potential therapeutic target [56]. Another study investigating cholesterol dynamics in radiation-induced PGCCs revealed that PGCCs have an increased cholesterol demand and rely on it for both survival and progeny formation [57]. Inhibitors of ASAH1, which disrupt ceramide and cholesterol homeostasis, and simvastatin, a cholesterol synthesis inhibitor, have been shown to suppress

the generation of progeny from PGCCs, suggesting that targeting cholesterol metabolism may hinder PGCC-driven cancer progression [57, 58]. Together, these insights underscore the role of altered lipid metabolism as a key contributor to the stress resistance of PGCCs.

Alterations in mitochondrial dynamics have also been observed in PGCCs. Studies using human cancer cells and mouse xenograft models have reported increased mitochondrial content in PGCCs induced by paclitaxel or cisplatin treatment [36, 48]. The accumulation of damaged mitochondria activates autophagy via the AMPK–mTOR pathway, which has been shown to be essential for PGCC formation [36]. Similarly, research using bladder cancer cell lines has demonstrated increased mitochondrial density, elevated ROS levels, and lipid droplet accumulation in cisplatin-induced PGCCs [48]. Notably, zoledronic acid, a drug widely used for treating osteoporosis, has been shown to suppress these mitochondrial changes and reduce PGCC survival (Table 1) [48]. These findings show the importance of altered mitochondrial characteristics in sustaining PGCC viability.

In summary, PGCCs undergo dynamic metabolic reprogramming, particularly in lipid metabolism, which appears to be crucial to their remarkable stress resilience. Targeting these metabolic changes offers a promising avenue for developing novel therapeutic strategies against PGCCs.

8 | Unique Strategies of PGCCs to Evade Immune Attacks

In recent years, immune checkpoint inhibitors have emerged as a key class of cancer therapeutics. Despite their remarkable efficacy in certain cases, many patients fail to respond adequately [62]. Elucidating how cancers evade antitumor immunity is critical for improving current therapeutic strategies.

The impact of PGCCs on antitumor immunity remains largely unclear. However, their reported gene expression profiles suggest that they may influence the surrounding immune microenvironment. For example, PGCCs sometimes display features of cellular senescence with high expression of senescence-associated secretory phenotype factors, such as IL-1β and IL-8 [63]. PGCCs induced by docetaxel or cisplatin treatment have also been reported to show elevated TNFRSF9 expression, a receptor upstream of NF-κB signaling [64]. These gene expression patterns suggest that PGCCs may secrete cytokines, thereby modulating their surrounding microenvironment. Some PGCCs have also been shown to express high levels of PD-L1, a key molecule in immune evasion that inactivates T cells [65]. In addition, IL-33 secreted by tumor cells induces PGCC formation and promotes the expansion of ST2-expressing type 2 innate lymphoid cells, contributing to immune exhaustion [66]. Although it remains unclear whether PGCCs themselves overexpress IL-33, an IL-33-enriched microenvironment surrounding PGCCs may enhance their immune evasion. Furthermore, hypoxia-induced PGCCs and their progeny in glioma have been shown to promote the induction of immunosuppressive M2 tumor-associated macrophages [49]. Collectively, these findings suggest that PGCCs play a key role in shaping an immunosuppressive tumor microenvironment.

In addition to altered expression profiles of PGCCs and their microenvironment, fecundity cells [16] may also contribute to immune evasion. When cancer cells are engulfed by adjacent host cells to form cell-in-cell structures, they may evade immune surveillance because immune cells cannot directly recognize these formations. Although the mechanisms underlying cancer cell engulfment to form PGCCs remain unclear, this cannibalistic process may protect cancer cells from both anticancer drugs and immune responses.

Furthermore, PGCCs may uniquely express neoantigens compared to other cancer cells. Neoantigens, arising from genomic alterations, are recognized by the immune system as cancer-specific antigens [67]. Since PGCCs harbor numerous genomic abnormalities [15], they may express a broader range of neoantigens. However, the coexistence of multiple normal alleles alongside mutated ones could reduce overall neoantigen presentation, potentially aiding immune evasion.

Thus, PGCCs are thought to affect antitumor immunity by altering both their intrinsic properties and their influence on the surrounding microenvironment, although the precise mechanisms remain unclear. PGCC formation may represent a key strategy for cancer cells to evade immune attacks. Further studies are needed to clarify whether PGCC presence affects the efficacy of immunotherapies.

9 | Conclusion

In this review, we have discussed the stress resilience of PGCCs from multiple perspectives. Rather than being mere byproducts of cellular damage, PGCCs represent a critical survival strategy that enables cancer cells to endure various stressors, including anticancer therapies. PGCCs also contribute to cancer progression by promoting regrowth after cell cycle arrest and acquiring stem cell-like properties, as highlighted in other reviews [2, 68, 69]. Therapeutic strategies targeting PGCCs are under investigation, with compounds such as zoledronic acid, mifepristone, and carfilzomib showing promising potential [20, 48, 59–61].

Although significant progress has been made in characterizing PGCCs, inconsistencies in their reported features remain. These discrepancies likely arise from differences in experimental approaches, including cell line selection and induction protocols. While stress resilience is emerging as a defining feature, it remains unclear whether PGCCs share common traits across cancer types or exhibit context-specific variations. In addition, the similarities and differences between PGCCs and polyaneuploid cells with lower ploidy levels remain unclear. When PGCCs are defined as cells with extremely high ploidy, such as octaploid or higher, this high ploidy may provide greater resilience to genomic damage through increased genomic redundancy. It may also improve tolerance to other stresses, including hypoxia and metabolic stress, although this has yet to be studied. Moreover, most current knowledge is derived from in vitro studies and clinical samples, while in vivo data remain limited but are gradually increasing in some model organisms [18, 20, 36]. This emerging in vivo evidence points to PGCCs as a fascinating yet still largely unexplored area of cancer biology. Experimental systems

TABLE 1 | Therapeutic agents reported to be effective against PGCCs.

Mechanism of action	Drug name	Types of cancer	Notes	References
Proteasome inhibitor	Bortezomib, Carfilzomib, Oprpzomib	Breast cancer	Enhances apoptosis and cell death in combination with doxorubicin	[59]
AXL inhibitor	Pyronaridine, Dubermatinib (TP-0903)	Breast cancer	Inhibits epithelial-mesenchymal transition and cell migratory abilities involved in the formation and maintenance of PGCCs	[59]
Bisphosphonates	Zoledronic acid	Bladder cancer	Effective after cisplatin treatment	[48]
Ferroptosis inducer	ML162, RSL3	Breast cancer	The elevated ROS level of PGCCs is essential to ferroptosis sensitivity.	[60]
FOXM1 inhibitor	Thiostrepton	Breast cancer	Effective after docetaxel treatment	[60]
HDAC inhibitor	Vorinostat, Romidepsin	Breast cancer	HDAC inhibitors also induce polyploidization in breast cancer cells.	[60]
Antiprogestogen	Mifepristone	Ovarian cancer, Breast cancer	Effective in combination with olaparib	[20]
RNA synthesis inhibitor	Actinomycin D	Breast cancer	Effective against PGCCs that are resistant to conventional chemotherapeutic agents	[60]
Microtubule-targeting agent	ST-401	Colon cancer, Glioblastoma	Mildly inhibits microtubule polymerization and suppresses the formation of PGCCs by inducing interphase cell death	[61]

that more accurately recapitulate the tumor microenvironment will help elucidate how PGCCs interact with their surroundings and contribute to cancer progression. New approaches, such as PGCC detection using recent advances in AI-based image recognition, may also provide valuable tools for studying PGCCs, especially given the current lack of reliable markers [34, 70]. Ultimately, such advances will inform the development of novel therapeutic strategies targeting these resilient and elusive cells.

Author Contributions

Yuta Ogawa: writing – original draft, writing – review and editing. **Lydia Fisher:** writing – review and editing. **Tomonori Matsumoto:** conceptualization, project administration, supervision, writing – original draft, writing – review and editing.

Ethics Statement

Approval of the research protocol by an Institutional Review Board.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

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