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Cancer cells employ an evolutionarily conserved polyploidization program to resist therapy

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ABSTRACT

Unusually large cancer cells with abnormal nuclei have been documented in the cancer literature since 1858. For more than 100 years, they have been generally disregarded as irreversibly senescent or dying cells, too morphologically misshapen and chromatin too disorganized to be functional. Cell enlargement, accompanied by whole genome doubling or more, is observed across organisms, often associated with mitigation strategies against environmental change, severe stress, or the lack of nutrients. Our comparison of the mechanisms for polyploidization in other organisms and non-transformed tissues suggest that cancer cells draw from a conserved program for their survival, utilizing whole genome doubling and pausing proliferation to survive stress. These polyaneuploid cancer cells (PACCs) are the source of therapeutic resistance, responsible for cancer recurrence and, ultimately, cancer lethality.

1. Introduction

Metastatic cancer remains unbeatable. Metastatic cancer eventually becomes resistant to all therapies and kills more than 10 million people per year globally [1–3]. It is generally accepted that the malignant cells of a tumor evolve. This means that multiple genetically distinct subclones of cancer cells that originated from a single initiating cancer cell all exist in the tumor(s) of a single patient, resulting in high cancer cell genetic heterogeneity [4–25]. This genetic heterogeneity is generally accepted as the root of therapeutic resistance: a cell lineage resistant to a class of therapy occurs from random and chance genetic mutation (Fig. 1). We have recently observed that it is likely that resistance is an example of convergent evolution leading to lethal cancer [3]. We believe that resistance is mediated through ecological and evolutionary properties of cancer cells that enter a cell-state transition that includes 1) polyploidization of their aneuploid genome, and 2) exiting of the cell cycle to pause proliferation, forming polyaneuploid cancer cells (PACCs). After stress is removed, PACCs undergo depolyploidization to repopulate the tumor, representing the source of the "rescue effect" associated with the catastrophic event of therapeutic intervention [26].

Here, we place PACCs in the context of polyploidy found in single-celled and multi-cellular organisms. Variously across the tree of life, polyploidy may provide a state that serves both ecological and evolutionary functions. We discuss how, ecologically, polyploid cells may have 1) high survivorship under harsh conditions, 2) higher capacity for producing RNA and protein products, and 3) higher capacity for nutrient uptake. Evolutionarily, polyploid cells may 1) enhance DNA repair, 2) counteract Muller's ratchet, 3) generate heritable variation among their offspring, and 4) permit self genetic modification in which the polyploid cell is able to create progeny that possess a heritable solution to a stressor that threatens the viability of the population.

2. Polyaneuploid Cancer cells

Large polymorphous cancer cells have been described by physicians and scientists since the 1850′s (Fig. 2) [27–58]. The majority of the

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cancer research and treatment development communities have disregarded these cells as irreversibly senescent or destined for mitotic catastrophe and death. A small number of pioneering scientists, including Erenpreisa, Cragg, Illidge, Liu, Walen, Rajaraman, Mirzayans and their colleagues, have now made it clear that these cells - most commonly termed polyploid giant cancer cells (PGCCs), but also referred to as multinucleated giant cancer cells, blastomere-like cancer cells, osteoclast-like cancer cells, pleomorphic cancer cells, large cancer stem cells, and polyaneuploid cancer cells (PACCs) - are important mediators of tumorigenesis, metastasis, and therapeutic resistance. Virtually all cancer cells are aneuploid (having an abnormal number of chromosomes or parts of chromosomes), and this aneuploidy is unique from tumor-to-tumor and cancer cell lineage-to-lineage [54]. PACCs are formed when these aneuploid cells undergo whole genome doubling in response to stress, resulting in multiple full sets of their cancer cell lineage's aneuploid genome, i.e., polyaneuploidy [26]. PACCs are present as a minor component of cell lines from all tumor types examined to date (Fig. 2A). They are also present in patients with nearly all types of metastatic cancer (Fig. 2B).

The totality of data supports a hypothesis that therapeutic resistance arises as a result of the emergence of PACCs within a population of cancer cells (Fig. 3). PACCs appear to be a reversible phase in the life cycle of lethal cancers, i.e., a life history cell-state. They form as a result of cancer cells' response to tumor microenvironment stress that accesses evolutionary and developmental programs for polyploidy, resulting in whole genome doubling (WGD) of the aneuploid genomic complement, increased cell size, and increased cell contents. PACC formation results in a cancer cell phenotype of reversible cell cycle arrest to avoid DNA damage, providing a mutation agnostic universal mechanism of therapeutic resistance. The increased cell size associated with WGD and the pause in cell cycling allows for the production of cellular machinery to cope with stress, increased intracellular nutrients to survive quiescence, and increased genetic material to allow for both genome stability in the short term and access to increased heritable variation over time. After a therapeutic stress, PACCs exhibit the ability to re-enter the cell cycle and undergo depolyploidization to repopulate the tumor with resistant non-polyploid progeny that then make up the bulk of cancer cells within a tumor [27,51,55,59–62].

3. Accessing evolutionary and developmental polyploid programs is a critical step in PACC formation

Resilience to environmental perturbations through WGD and concomitant cell enlargement has been documented across numerous taxa as convergent stress response programs, including prokaryotes (archaea and bacteria), unicellular eukaryotes, and multicellular plants and animals [63–67]. These evolutionary stress response programs are reflected in the developmental programs of human tissue as normal cells respond to physiologic needs and stress. The ability to form PACCs in response to stress, therefore, appears to be a by-product of the convergent polyploid program utilized by noncancerous organisms and cells (Fig. 4). Once accessed, cancer cells can use this program to survive and react to tumor microenvironmental stresses as well as extrinsic therapeutic stresses [68–70].

There are a limited number of ways by which a cell can become polyploid. Importantly, in both the initial generation of and during the life of polyploid cells, DNA replication, karyokinesis, and cytokinesis are not necessarily linked. In addition to cell fusion, polyploidy can be generated through endocycling, mitotic slippage, or endomitosis (Fig. 5) [71–77]. Terminology surrounding the generation of polyploidy can be somewhat confusing, with multiple overlapping terms. Endocycling, also referred to as endoreplication and endoreduplication, is the replication of DNA in S-phase without the cell entering mitosis. This results in a single nucleus with increased ploidy (e.g., 4 N). Mitotic slippage occurs when a cell exits the division cycle just prior to anaphase at the spindle assembly checkpoint [71]. This also results in a single nucleus. Endomitosis, also referred to as cytokinesis failure, occurs during anaphase, resulting in a single nucleus, or in telophase, resulting in a multiple nuclei within a single cell [40,76,78–80]. The mitotic cycle and the exits resulting in polyploidization are tightly regulated through multiple checkpoints that are beyond the scope of this discussion [78,81–90]. Polyploid programs provide increased fitness on evolutionary timescales (across species) as well as within the lifespans of individual organisms (across tissues) [63,74,76,91–93]. The evolutionary programs are engaged in response to environmental perturbations and form the basis for the developmental programs that are observed in specialized tissues in response to extrinsic stresses or metabolic requirements (Tables 1 and 2). These evolutionary and developmental programs demonstrate how polyploidy is adaptive and improves fitness of PACCs.

4. Evolutionary programs for polyploidy across the tree of life

As we explore the presence, mechanisms, and function of polyploid cells across diverse taxa, there are several recurrent themes. First there are ecological advantages to large polyploid cells in terms of surviving stress, proliferative cell cycle arrest, and increased metabolic potential. Second, there are evolutionary advantages in terms of gene repair and opportunities for accelerating rates of evolution. In the following sections we shall explore diverse taxa and evaluate them in terms of the ecological and evolutionary advantages afforded by polyploidy as well as the mechanisms for polyploidization.

5. Archaea

Polyploidy in prokaryotes is reflected in the duplication of the haploid single circular chromosome [94–96]. Multiple advantages of increased genomic material with accompanying increase in cell size have been proposed. Non-genetic advantages include how an increased cell size may facilitate predator avoidance or increase foraging rates and ability [97,98]. At least one species, *Haloferax volcanii*, appears to use genomic DNA as a storage mechanism for phosphate that can be used to synthesize important building blocks including membranes, DNA, and protein [99]. Multiple copies of genes may allow the cell to produce more of the gene product more rapidly. The presence of multiple copies

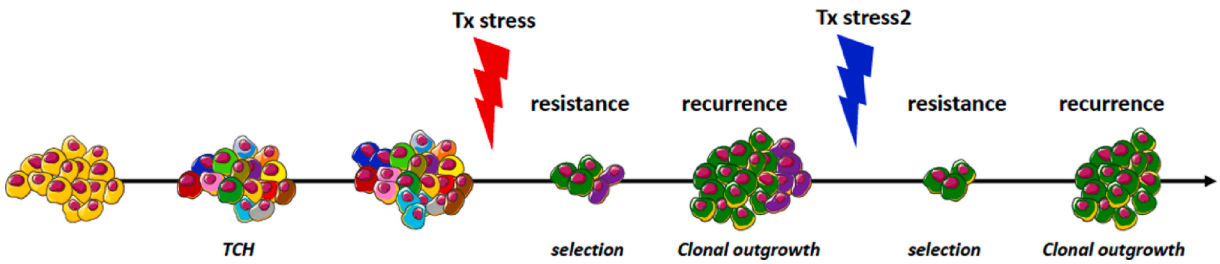

Fig. 1. Classic model of therapeutic resistance as the result of tumor cell heterogeneity. Resistance to therapeutic interventions has classically been attributed to genetic tumor cell heterogeneity: within the billions of cancer cells in a tumor, resistance to therapies evolves by random stochastic chance that endows at least one cancer cell with resistance to a particular therapy [4–24].

of genes provides an interesting yin-and-yang dynamic in regard to genomic mutation. It provides gene redundancy, allowing for mutation in one copy of a gene while retaining the wild-type information in other copies of the gene. This can provide genomic stability while also providing the opportunity for variation that can be inherited by subsequent generations [97]. Another advantage of polyploidy in Archaea is gene conversion, or the non-reciprocal transfer of information between homologous sequences of DNA [100–103]. Gene conversion in a polyploid cell allows the unicellular organism to avoid Muller's ratchet (the accumulation of deleterious genetic variation in the absence of recombination, as in asexual reproduction) [104–108]. One possible method to avoid the accumulation of deleterious mutations over time in haploid organisms such as Archaea is horizontal gene transfer, endowing a polyploid cell with the ability to construct and subsequently select advantageous genetic variants as a survival mechanism [100–102].

6. Bacteria

Bacteria have overlapping systems in response to diverse stresses including changes in temperature, nutrients, and toxins [98,109]. As in Archaea, increased cell size is associated with decreased predation and increased motility [98,110]. As a haploid organism with a single circular chromosome, bacteria too must escape Muller's ratchet to avoid the inevitable extinction that is associated with the random loss of fitness functions [111]. The main defence against the inexorable advancing click of the ratchet and erosion of the genome is recombination [112–114]. It has been demonstrated that in response to stress, a bacterium can increase its spontaneous mutation rate in the absence of DNA damage by upregulating the error-prone DNA polymerase Pol IV and down-regulating enzymes responsible for DNA mismatch repair (MMR) [109]. Multiple other mechanisms exist to increase mutability, including the movement of transposable elements. While these mechanisms result in increasing heritable mutation through generation of multiple mutants, evidence does exist supporting directed mutation. This type of "selected capture" of the beneficial mutation links the sensing of a useful genotype or phenotype to subsequent proliferation, leaving the new mutation unrepaired and immortalized [109,115–118]. This type of directed mutation could be considered a molecular Turing machine with oligonucleotides representing the "tape" and the restriction enzymes effecting transitions [119–122].

7. Eukaryota: protista

Protists are the earliest form of life that contain a nucleus and exist in haploid, diploid, and polyploid states [123–126]. The human pathogen *Entamoeba histolytica*, for example, routinely accumulates polyploid cells and reduplicate their genome several times before cell division occurs. Polyploidy may occur without nuclear division, and the checkpoints that normally prevent DNA reduplication until after cytokinesis in most eukaryotes are not observed in *E. Histolytica* [127]. *In vitro*, the fraction of polyploid cells increases with serum nutrient depletion and decreases again when fresh serum is resupplied [128]. The lack of nutrients, therefore, appears to delink of cytokinesis and karyokinesis from DNA replication [128].

Another protist group, the ciliates, demonstrate both transient and persistent polyploidy. In ciliates, the individual cell has two nuclei each with a specialized role. The "somatic" nucleus builds up extreme polyploidy (~1000 N) while the "germ" nucleus leads to daughter cells. Although diploid, the germ nucleus genome results from both gene loss and several events of WGD. The fitness increase through the persistent polyploidization events (WGDs) is not entirely clear, but it is argued that the increased gene dosage provides for increased metabolism [129].

Protists also appear to demonstrate gene editing. For instance, the ciliate germ nucleus may be fragmented by imprecise elimination (i.e., transposons or microsatellites), resulting in new DNA sequences that can be passed to progeny as heritable mutations [130,131]. Internal gene editing in the somatic nucleus (through mechanisms including DNA polymerase slippage, internal double strand breaks, and recombination reaction transposition), may increase fitness to changing environmental conditions during the lifetime of the organism and in the absence of cell division [132–134]. Upon cell division, the progeny would already possess heritable changes that improve their survivorship under the changed conditions. The haploid Foraminifera *Reticulomyxa filosa* utilizes polyploidy to escape Muller's ratchet [135]. The presence of multiple genomes permits lateral gene transfer, allowing the organism to generate mutations that can be tested for fitness while still maintaining a wild-type genome to ensure stability [98]. It remains unclear if this is an example of self genetic modification versus a form of heritable variability [136–138].

8. Eukaryota: fungi

The first WGD to be discovered in unicellular eukaryotes was in the yeast *Saccharomyces cerevisiae* [93,139]. Yeast cells that are polyploid

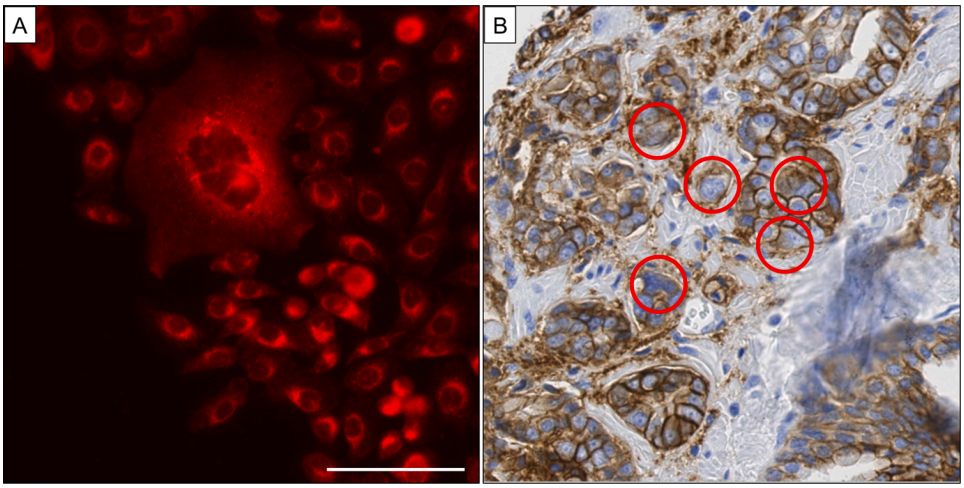

Fig. 2. Polyaneuploid cancer cells. PACCs are observed in cell culture: Panel A demonstrates untreated DU145 cells stained with Nile Red for contrast (scale bar = 200 um). PACCs are also observed in patients: Panel B demonstrates clinically localized prostate cancer (Gleason pattern 4 primary adenocarcinoma) stained with EPCAM to delineate cell borders, examples of PACCs indicated by red circles.

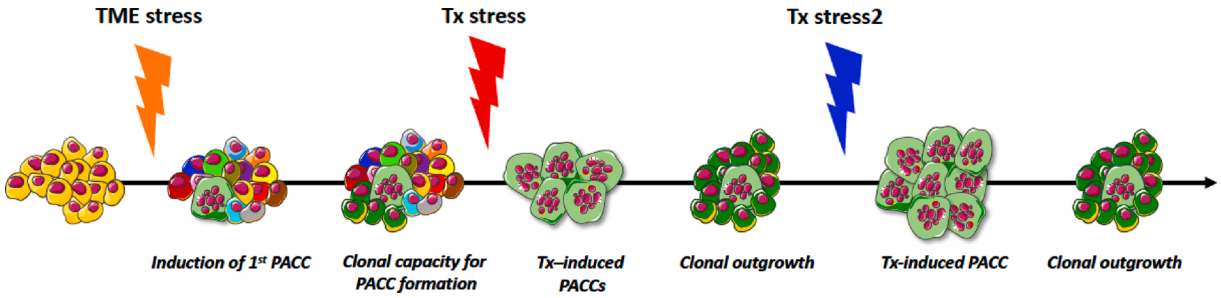

Fig. 3. Therapeutic resistance as the result of tumor cell heterogeneity allowing PACC formation. We hypothesize that resistance to therapeutic interventions is the result of access to an evolutionary/developmental polyploid program that increases DNA content, increases cell size, and induces quiescence as a result of environmental or therapeutic stress. The quiescent state allows the cancer cells to exit the cell cycle and avoid DNA damage and is a universal mechanism of therapeutic resistance that is mutation agnostic [26].

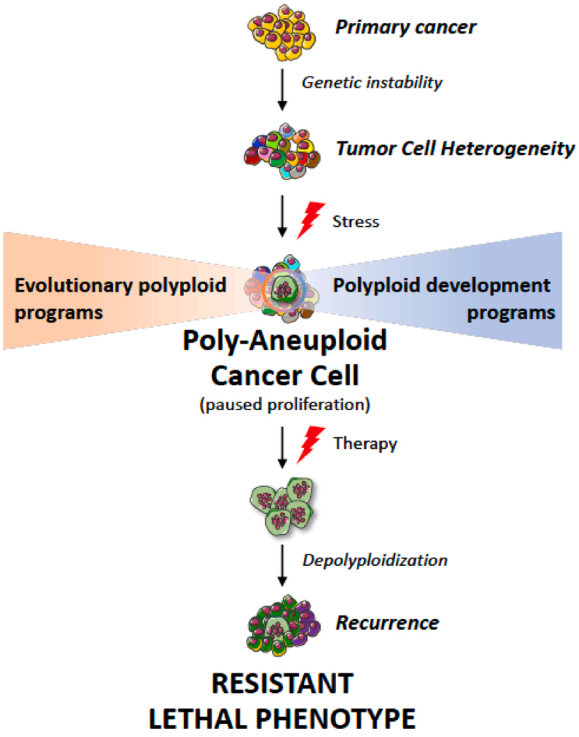

Fig. 4. Access to evolutionary and developmental programs that enable polyploidization and quiescence are the provide the key to understanding PACC structure and function. The formation of polyploid cells is by no means unusual in nature and is observed across both unicellular and multicellular eukaryotic organisms. Plants, fungi, and invertebrates, as well as vertebrate animals demonstrate polyploid cell formation during both development and temporal crises. Once PACCs are formed, they have the necessary characteristics to survive the catastrophic stress of therapy and survive to provide population rescue to a tumor [26].

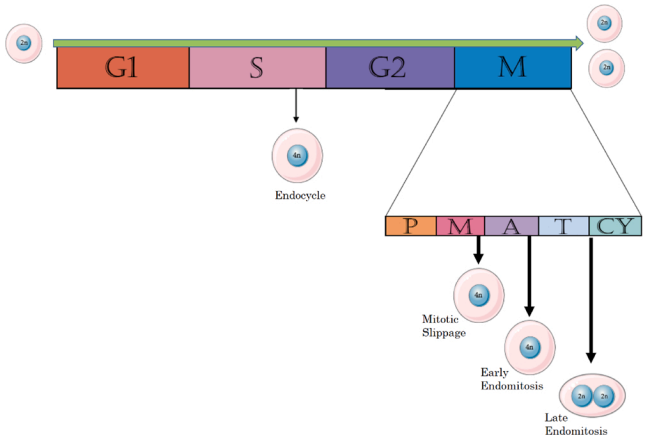

Fig. 5. Cellular mechanisms that generate polyploidy. In addition to cell fusion, polyploidy can be generated through endocycling, mitotic slippage, or endomitosis [71–77]. Endocycling also (endoreplication or endoreduplication) is the replication of DNA in S-phase without the cell entering mitosis. This results in a single 4 N nucleus. Mitotic slippage occurs when a cell exits the division cycle just prior to anaphase at the spindle assembly checkpoint, resulting in a single 4 N nucleus [71]. Endomitosis (cytokinesis failure) occurs during anaphase, resulting in a single 4 N nucleus, or in telophase, resulting in a multinucleated cell [40,76,78–80].

and/or aneuploid survive better and evolve faster under changing and adverse conditions [140]. It has been inferred that this higher fitness is a result of their access to more beneficial mutations and therefore adaptability to novel settings [140–143]. In addition to polyaneuploid yeast cells accessing beneficial mutations or purging deleterious mutations, it has been suggested that cell size is mediated by dosage sensitive genes, i.e., genes that increase cell machinery, thereby increasing fitness [144–148]. Yeast form polyploids through meiosis without cytokinesis in response to toxins or adverse physical conditions. This permits rapid evolution of appropriate stress responses and later a return to a euploid state [140,148–150]. For example, recombination rates are many orders of magnitude higher in *Candida Albicans* during depolyploidization [151]. It is unclear if depolyploidization is by genetic variability in progeny with associated death of unfit offspring or accompanied by self genetic modification with the direct generation of only fit progeny.

9. Eukaryota: plantae

The main route for plant cells to increase volume is by modulating the cell cycle to engage in endocycling [152,153]. The resulting polyploid cells are either mononuclear (with or without separated chromatids) or multinucleated depending on when in M-phase the skip to G1 occurs. Such endoploidy can be somatic and present in only in specific cell types [154]. This differs from plants with species poly ploidy in which all of the somatic cells in their normal state possess a baseline level of polyploidy.

Somatic polyploidy contributes to plant development, function, and whole plant fitness [155,156]. The increased size of polyploid cells provides altered cellular functionality and organismal adaptability. Germinating seedlings utilize polyploidy to enlarge cells that accelerate the stem's emergence from the ground. Vacuoles in these cells provide filler that allows fewer cells to provide the same linear growth, and these vacuoles store energy for additional cell division [157]. Upon emergence from the ground, light negatively regulates endocycling and the mitotic cell cycle returns [158]. In adult plant roots and leaves, endoreplication can substitute for cell proliferation during harsh times such as

Table 1
Evolutionary Polyploidization Programs.

Organism taxa	Type of Program	Purported advantage	References
Archaea	- DNA replication without cell division	- Phosphate storage - Avoid predation - Increased motility - Increased gene dosage - Gene conversion	[94,95,96,97,98,99,100,101,102,103,104,105,106,107,108]
Bacteria	- DNA replication without cell division	- Enable quiescence - Increased mutation rate - Downregulation of error-correcting replication enzymes - Directed mutations	[109,110,111,112,113,114,115,116,117,118,119,120,121,122]
Protists	- Endomitosis	- Increase metabolism - Enable quiescence - Gene editing	[123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138]
Fungi	- Meiosis without cell division	- Increased gene dosage - Increased mutation rate	[139,140,141,142,143,144,145,146,147,148,149,150,151]
Plants	- Endocycling - Endomitosis	- Increased storage - Predator protection - Increased gene dosage	[152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171]
Drosophila	- Endocycling	- Increased metabolism	[172,173,174,175,176,177,178,179,180,181,182,183]

Table 2
Development Polyploidization Programs.

Cell type	Type of Program	Purported advantage	References
Trophoblasts	- Endocycling	- Placental development - Embryo nutrition	[189,190,191,192,193,194,195]
Keritinocytes	- Mitotic slippage	- Buffer for toxin stress - Increased genomic stability	[154,185,196,197,198,199,200]
Megakaryocytes	- Endomitosis	- "Efficient" platelet production	[201,202,203,204,205,206]
Macrophages and osteoclasts	- Cell fusion - Endomitosis	- Increased cell function	[207,208,209,210,211,212,213,214,215,216,217]
Myocytes	- Endocycling - Endomitosis	- Increased metabolism	[218,219,220,221,222,223,224,225,226,227,228]
Hepatocytes	- Endomitosis	- Increased genomic stability - Increased genetic diversity - Buffer for toxin stress - Increased metabolism	[229,230,231,232,233,234,235,236,237]

lack of water, sunlight, or nutrients [76]. For example, during episodes of drought, polyploidy compensates for cell loss by increasing leaf cell size thus moderating water loss [159].

The induction, direction, and termination of polyploidy in plants are not fully understood. Light and hormones can play a role [160]. For example, darkness or nutrient deficiency can induce endoploidy and light stops it [161]. Increased cell size is associated with a proportionally reduced access to and transport of metabolites into the cell as well as upscaling of organelles (e.g. ribosomes, mitochondria) [74,162–166]. Moreover, the increase in cell size and therefore distance for oxidants to diffuse can create an imbalance in reactive oxygen species (ROS) that triggers a shift in metabolism as well as delays the transition from prophase to prometaphase [167–171]. Thus, ROS can drive plant cell enlargement to facilitate chances for survival during stress. Access to programs for non-oxidative metabolism, inactivated apoptosis, and fitness in unknown future conditions would make polyploidy a beneficial strategy during harsh times.

10. Eukaryota: animalia (*Drosophila*)

Polyploidy has been extensively studied in *Drosophila* particularly in regard to development and wound healing [172–177]. Cell size and number are tightly regulated, resulting in an approximate total cell mass that changes in response to whole organism metabolic demands [176,177]. There is evidence in *Drosophila* showing that increased ploidy suppresses cell death in response to DNA damage. Polyploid cells may suppress the expression of pro-apoptotic genes [173,178]. Ploidy and cell size utilize Myc as a central regulator which influences multiple signaling pathways, including ribosome biogenesis as well as Dpp, Hpo, insulin, and mTOR [175]. During the larval stage, many of the fruit fly's cells stop dividing and undergo several cycles of endoreplication, reaching ploidies of >1000 N [179]. This increased DNA material amplifies a cell's biosynthetic capacity [179–181]. Tissue repair in drosophila requires the specialized functions of polyploid cells as well as the proliferation of diploid cells. This balance of polyploid and 2 N cells appears to be mediated by Myc expression [175,179,182]. Through regulation of CyclinE, Myc induces initiation of the endocycle, resulting in cells entering S phase but skipping mitosis [73,175,179,182,183]. Throughout, Myc provides a major driver of mitosis/endocycle coordination [78,89,90]. Myc globally amplifies transcription and decouples DNA synthesis and mitosis, resulting in polyploidy.

11. Development programs for polyploidy across human tissue

Noncancerous cells that form polyploids provide clues into the significance of increased size and increased DNA content of PACCs. PACCS may be able to epigenetically access cellular programs typically restricted to subsets of normal tissue cell types, e.g., megakaryocytes, keratinocytes, macrophages, osteoclasts, and trophoblasts as well as hepatocytes and myocytes [71,76,91,92,172,184–187]. A common theme across these tissue types is a need for the cells to amplify metabolic function to fulfill a physiologic need or enhance survivorship under stress. To generate muscle hypertrophy in response to exercise or injury stress, cardiac myocytes utilize polyploidization. Bone marrow macrophages fuse to create multinucleated giant osteoclasts allowing them to produce higher quantities of acid for dissolving bone matrix. In response to chronic infection, macrophages form giant multinucleated histocytes that can engulf foreign bodies.

In addition, polyploid cells are necessarily, at least transiently, in a state of proliferative cell cycle arrest, defined as G0 or quiescence. In multicellular organisms, the non-proliferative nature of terminally differentiated cells is essential for whole-organism tissue organization and fitness. Restricting proliferation of polyploid cells, especially in tissues experiencing stress and at risk for DNA damage, protects the cell lineage and, consequently, the organism as a whole. Quiescence, therefore, serves to isolate the effects of any DNA damage or disorganized inherited variation, preventing any deleterious (and possibly cancer-initiating) variation from being inherited by future generations of cells [188].

12. Trophoblasts

Placental trophoblasts form giant cells through endoreduplication,

resulting in high levels of ploidy. These large cells are associated with embryo implantation and placental development [189–191] assisting with placental connection and protection. The switch from the mitotic cycle to the non-proliferative endocycle has been extensively studied in trophoblasts and centers on a G2 decision point [192]. This decision point is regulated, in part, by the zinc finger transcription factor Snail which mediates expression of cyclins A and B. In addition, cyclin E coordinates the G1 to S phase transition and is essential for successful endocycling [192–194]. Simultaneously, the cyclin B/Cdk1 complex is not activated, resulting in inhibition of the mitotic cycle [193]. As demonstrated for yeast, trophoblasts undergo depolyploidization as the blastocyst forms [195].

13. Ectoderm: keratinocytes

Keratinocytes are constantly exposed to mutagens in the form of UV irradiation and environmental toxins [185]. Polyploidization may provide a mechanism to protect genome integrity by providing multiple copies of genes and restricting cell division. Some estimates place the percentage of polyploid cells in normal epidermis at up to 50 % [185]. In support of this idea, treatment with genotoxic agents induced differentiation and polyploidization in dividing keratinocytes [154,196]. This suggests that keratinocyte differentiation responds to DNA damage through mitosis checkpoints [197–200]. Similar to what is observed in drosophila, endoreplication appears to be stimulated by Myc and accumulation of cyclin E [154]. Keritinocytes, in response to DNA damage, progress through S-phase but arrest in G2/M which results in polyploidy through mitotic slippage via modulation of multiple checkpoint molecules, including depletion of Cdk1, Plk1, or AUR-A [196,198,198,199,200]. In addition to providing increased gene dosage, it has been suggested that polyploidy with concomitant increase in cell size may allow for cell survival and maintenance of barrier function [200].

14. Mesoderm hematopoietic lineage: megakaryocytes

Megakaryocytes are large (50–150 μm) differentiated cells dedicated to the production of platelets in mammals [201–204]. As these cells differentiate and mature, megakaryocytes undergo endomitosis, resulting in a polyploid nucleus that is 16 N on average, but has been observed up to 128 N [201–204]. As they increase in size, megakaryocytes exhibit an invaginated membrane system that is continuous with the plasma membrane, permeates the cytoplasm, and provides the extra membrane necessary for platelet formation and budding [205]. The large size may be necessary to have enough material to generate platelets. Furthermore, polyploidy may amplify the production of RNA and proteins for increased cellular metabolism and platelet production. The increased genomic material and increased cellular machinery results from the cell cycle stalling during late cytokinesis [72,79,204,206]. Telophase takes place with the formation of an apparently normal midzone and cleavage furrow. This is followed by rapid regression of the furrow resulting in a single cell with a single nucleus [201]. Molecular studies reveal that cell cycle disruption is mediated by a series of transcription factors (e.g, RUNX1, FLI1) that interfere with the RhoA pathway and regulate cyclins D and E [201].

15. Mesoderm hematopoietic lineage: macrophages and osteoclasts

Multinucleated macrophages have been observed in multiple granulomatous diseases such as tuberculosis, leprosy, and histoplasmosis, among others [43,207,208]. Multinucleated macrophages commonly form via cell-cell fusion through a well delineated series of steps that include pre-fusion priming of the cells, cell-cell adhesion, membrane fusion and multi-nucleation, and post-fusion reprogramming [209,210]. While it has been demonstrated in multiple systems that multinucleated macrophages can be formed by cell fusion in response to a variety of cytokines including IL4, proliferating macrophages in granulomas may also utilize aborted cytokinesis to increase in size and genome content [43,208,211,212]. The inflammatory microenvironment is a threat to DNA integrity due to the presence of ROS. In macrophages, if DNA double strand breaks are detected, the MRN complex (MRE11, NBS1, RAD50), is activated, leading to a robust DNA damage response (DDR). The DDR is activated by ATM kinase with subsequent downstream activation of CHK2 and p53 [208,213,214].

Bone marrow macrophages also fuse to form osteoclasts, large multinucleated cells for lysing bone matrix [43,209]. Polyploidy in this case serves to increase the production of cell products. Prior to fusion, pre-osteoclasts exit the cell cycle, presumably to protect their genome integrity [215–217]. Fusion is mediated by DC-STAMP, which in turn is regulated by multiple transcription factors, including c-Fos, NFATc1, PU.1, and NF-kb [43].

16. Mesoderm mesenchymal lineage: myocytes

After birth, cardiomyocytes halt cell division and increase their size in response to injury via WGD [187,218]. Polyploid cells with a single nucleus arise via endocycling and multinucleated cells arise through failed cytokinesis. This failed cytokinesis occurs late in the cell cycle during abscission, at which time the cytokinetic furrow regresses [187,219,220]. Entry into S-phase is mediated by the induction of cyclin D1 but M-phase entry is inhibited by the inactivation of CDK1 [221–223]. Rather than dedifferentiate to allow transit through the cell cycle with subsequent hyperplasia, cardiomyocytes increase in size and increase their number of contractile sarcomeres via hypertrophy. This suggests that the increased ploidy both protects the cell lineage from possible DNA damage and underlies a need for increased transcriptional output for subsequent protein synthesis and metabolism [187,219,220]. Polyploid vascular smooth muscle cells have been observed in chronically hypertensive animals [224]. As polyploid vascular smooth muscle cells increase in DNA content, they increase in size with a concomitant increase in RNA and protein. This increase is about twofold in tetraploid cells and fourfold in octaploids [176,225–227]. It appears that polyploid formation occurs in response to oxidative stress [228].

17. Endoderm: hepatocytes

In mammals, hepatocyte polyploidy contributes to both post-natal development and tissue regeneration throughout life. Both single and multi-nucleated polyploid cells can occur depending on the polyploidization pathway [71,184,229,230]. Polyploidy of hepatocytes results from endoreplication, or from failure to complete cytokinesis [229,231,232]. Though controversial, cell fusion seems to provide a rare but recurrent process for generating polyploid hepatocytes under physiological conditions [232]. Though the mechanisms for generating polyploidy in hepatocytes are known, the role played by these polyploid cells remains unclear. It has been demonstrated that proliferating hepatocytes produce a diverse population of progeny with multiple chromosome imbalances. It has been proposed that hepatocytes generate genetic diversity allowing them to adapt to xenobiotic or nutritional injury [71]. Alternatively, increased genomic material may provide a buffer against gene loss (i.e, providing a redundant genome) that would prevent cells from performing their whole organism function [71,233,234]. In addition, and not mutually exclusive to other postulated roles, polyploidization could provide increased cellular machinery as a buffer against oxidative stress [235–237]. A further potential reason for polyploidization may be the need to redirect energy to the production of cellular materials (e.g., RNA, proteins, or lipids) to maintain or increase metabolic activity when resources are limited such as during postnatal growth or regeneration after partial hepatectomy [91,235]. In support of this explanation, polyploid cells have few differentially expressed genes as compared to diploid cells. In these polyploids, WGD does not induce mutations or transcription reprogramming. Instead, they exhibit

increased transcriptional/translational production of cell materials [91].

18. Relevance of evolutionary and development polyploid programs to PACCs

Access to evolutionary and developmental programs that enable polyploidization provide the key to understanding PACC structure and function (Fig. 4). While the evolutionary programs emphasize the complementary response programs of genomic stability and heritable variation, the developmental programs emphasize response programs that allow survival and adaptation to stress secondary to metabolic needs. All of the development programs utilized by normal tissue cells provide roadmaps for understanding the mechanisms by which polyploidy is generated in PACCs. Megakaryocytes provide an extreme example in the human body of multi-lobulated single nuclei. They are a prime example of increasing DNA material to produce more cellular building blocks to increase the machinery necessary to produce platelets. If, for example, PACCs have a single multi-lobulated nucleus versus multiple nuclei, it is likely that they are accessing the development program utilized by megakaryocytes to endocycle. Determining the true nature of PACC nuclear content is a high priority.

Throughout evolution, it appears that polyploidization has been preserved across species as a rapid response to environmental stress by increasing cellular functional capacity and contributing to genome stability while halting proliferation, thereby protecting organisms from deleterious mutations [185,186,238]. The protists, for example, demonstrate that polyploidization increases cellular capacity for increased fitness rather than through increases in gene dosage. Although the protists appear to have a versatile capacity for gene-editing during their polyploid phases, the link between gene editing and heritability remains unclear. Polyploid yeast cells, for example, have been shown to have higher fitness due to initial dampening of deleterious mutations and subsequent access to beneficial mutations that lead to increased heritable variation [140–143].

The depolyploidization programs described in fungi represent early evolutionary programs that form the basis for meiosis programs in eukaryotes and subsequently the presumed depolyploidization programs of PACCs [62,239–241]. For example, within a population of cancer cells induced by radiation to undergo mitotic catastrophe, a subset of PACCs are formed which subsequently undergo depolyploidization to form non-polyploid progeny [62,242]. It appears that successful depolyploidization is linked to expression of meiotic-specific pathway genes including SYCP2, SYCP3, DMC1, SPO11, REC8, STAG3, and MOS [62]. Alternatively, in ovarian cancer, PACCs appear to form in response to stress and produce progeny by amitotic mechanisms, e.g., budding [38,243,244]. It has been demonstrated that a single multinucleated cancer cell can reform an entire tumor population [55]. The mechanisms by which PACCs produce progeny need to be delineated in detail.

19. Potential for PACCs to create therapeutic resistance mechanisms

The generation of WGD of aneuploid cancer cells and the resultant polyaneuploidy is now well documented in the cancer literature [236,245]. It is not established, however, whether this polyploidization is 1) an obligate step of a resistance program of randomly generated clones as part of existing tumor cell heterogeneity [4,10–12,15]; 2) a means of inducing quiescence to increase cellular machinery to survive while protecting genomic material for future progeny [30,38,42,45,57,246,247]; 3) a means to increase genetic stability to prevent apoptosis in a cell with damaged DNA while also allowing increased genetic instability to create heritable variation [75,76,92,173,248–251]; and / or 4) a potential means of generating self genetic modification (Fig. 6).

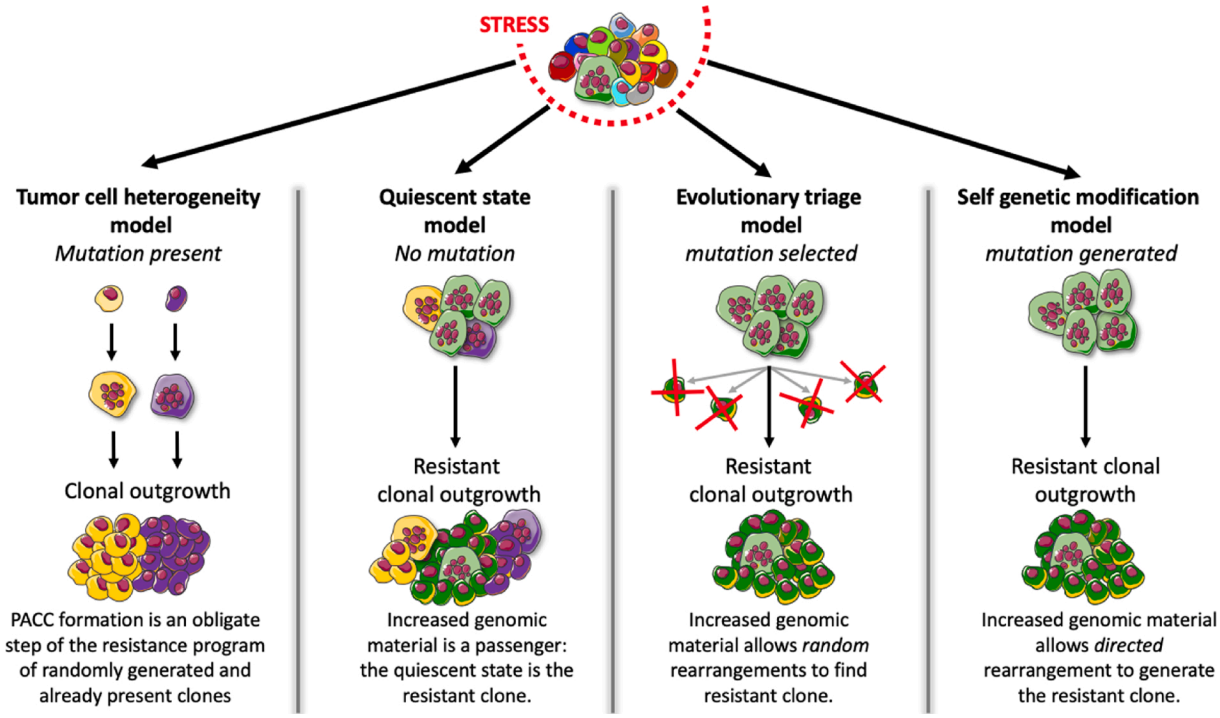

Fig. 6. Models to explain how PACCs may contribute to the evolution of resistance. Polyaneuploid cells appear to be part of a central pathway in the generation of therapeutic resistance. It is not established, however, whether this polyploidization is 1) an obligate step of a resistance program of randomly generated clones as part of existing tumor cell heterogeneity [4,10–12,15]; 2) a means of inducing quiescence and increasing cellular machinery to survive while protecting genomic material for future progeny [30,38,42,45,57,246,247]; 3) a means to increase genetic instability to create heritable variation [75,76,92,173,248–251]; and / or 4) a means of generating self genetic modification [109,115–118].

19.1. The ecological concept of a fundamental niche

Polyploidy either protects the cell through quiescence, potentially accelerated evolution, or both. Accelerated evolution would occur through two pathways, either evolutionary triage through heritable variation and, controversially, some form of self genetic modification, also referred to as genetic assimilation, gene editing, or adaptive mutation. Regardless of the pathway, a clear definition of the ecological concept of a fundamental niche is required [252].

The fundamental niche of an organism – or of a cancer cell – represents the range of environmental conditions over which the organism can maintain a viable population. For cancer cells, the fundamental niche is the tumor microenvironment that allows the cells of the newly initiated clade to proliferate and accumulate mutations that lead to the establishment of a successful tumor population. Experiencing conditions inside or outside of its fundamental niche pose two very different eco-evolutionary challenges. Evolution acting on organisms within their fundamental niche selects for adaptations that allow the organism to succeed relative to others. While individuals will increase in frequency, those with a less fit trait will die off due to the presence of the fitter one. This is the typical context for evolutionary triage where far more individuals are born than can survive. Having more heritable variation accelerates evolution by increasing the likelihood of having fitter individuals causing the less fit to die off. It is well accepted that heritable variation is the predominant driver of natural selection for organisms primarily experiencing ecological conditions within their fundamental niche (Fig. 7).

What happens when environmental conditions deteriorate so drastically that the organism it is now outside of its fundamental niche? In the absence of a rapid return to favorable conditions, the organism will migrate to more favorable conditions or simply go extinct at that location. Alternatively, the organism could enter a protective quiescent state, halting reproduction and therefore protecting its genomic material from assault, and wait until conditions or its own fitness change. As another strategy, the organism could evolve traits that expand its fundamental niche to include the otherwise harsh conditions. In the tumor cell heterogeneity model of therapeutic resistance, a resistant clone has randomly been generated in the population through stochastic mutations as a result of genetic instability (Fig. 6). In this model, polyploidization represents a transitory phenotype that the already-resistant clones employ prior to repopulating the tumor. This transitory cell state most likely represents a strategy of the cell to enter quiescence to ensure genome integrity in the presence of the therapeutic stress.

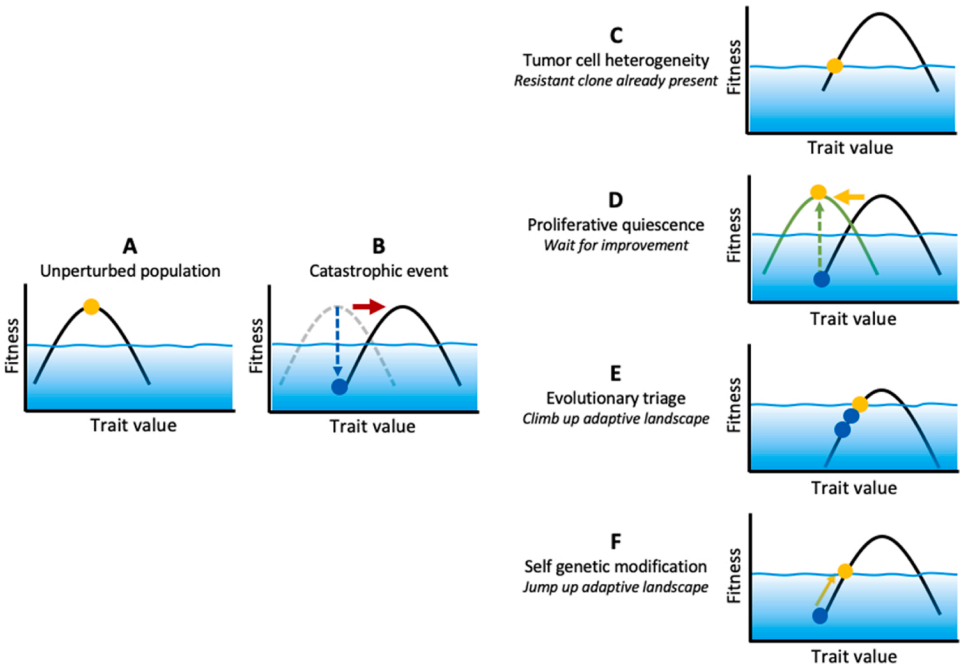

Fig. 7. Evolutionary and ecological dynamics along adaptive landscapes. Panel A shows the adaptive landscape (solid black line) for a population within its fundamental niche (shown as the solid yellow circle) that demonstrates both ecological fitness and evolutionary equilibrium (peak of the adaptive landscape) where the y-axis is fitness (measured as per capita growth rate) and the x-axis represents a heritable trait value. **Panel B** demonstrates a drastic change to the environment that dramatically shifts the original adaptive landscape (dotted line) to a new adaptive landscape (solid line). Under these new conditions the population with the identical trait value (solid blue circle) may find itself outside of its fundamental niche (i.e., "underwater") and therefore nonviable. **Panel C**: Alternatively, consistent with the tumor cell heterogeneity model, this catastrophic loss in population size may identify a rare clone that can survive in the altered landscape and recover its viability (yellow circle at the "waterline"). **Panel D:** If the population can wait out the change in landscape (i.e., "hold its breath"), the population can be rescued if conditions improve and the original adaptive landscape is re-established. **Panel E**: Evolutionary triage can drive the population's trait value along the new fitness landscape until an eco-evolutionary equilibrium is re-established. While evolutionary triage is effective to adapt to slow changes in the landscape, it is unlikely to be effective in response to a catastrophic event. **Panel F**: If the population's trait value is outside of its fundamental niche (solid blue circle) then it is doomed to extinction unless it can evolve fast enough to achieve a viable trait value (solid yellow circle). Via PACCs, the controversial concept of self genetic modification may provide the most efficient (or perhaps the only) way for this evolutionary jump to occur. This will expand the fundamental niche of the population to now include the otherwise disastrous conditions. Once recovered (solid yellow circle), evolutionary triage can resume evolution towards an eco-evolutionary equilibrium.

19.2. Evolutionary triage to create heritable variation

Natural selection by evolutionary triage is particularly effective when the cancer cell population is well within its fundamental niche [253–256]. Within its fundamental niche, the tumor environment is favourable and there are no stressors that threaten the viability of the population of cancer cells. Cancer cells can persist even if their total phenotypic trait values are far away from an evolutionary optimum and progressive evolution is underway towards ever more fit individuals. Under these circumstances, through proliferation and cell deaths, natural selection can drive cell lineages towards evolutionary optimum. The only threat to the extant cancer cells is their replacement by cells with fitter trait values. When a species or cancer cell population resides in its fundamental niche, evolution is more about outcompeting a neighbour rather than surviving exogenous environmental stressors.

Theoretically, PACCs could play an evolutionary role by accelerating evolution by generating a wider array of heritable variation in their offspring. These 2 N + offspring would then undergo evolutionary triage as fitter variants prosper at the expense of other 2 N + members of the population. When the cancer cell population resides within its fundamental niche, PACCs would allow for faster evolutionary tracking of changing tumor microenvironments, faster evolution towards evolutionary optimum, and more rapid diversification of cancer cell types within a heterogeneous tumor. A mechanism by which PACCs simply increase the heritable variation among their 2 N + offspring would be an inefficient way of generating evolutionary rescue when the stressor pushes the cancer cell population outside of its fundamental niche. By creating genetic shotgun blasts of variation, PACCs could create what Goldschmidt termed “the hopeful monster” [257–259]. For cancer, the hopeful monster would be that rare chance 2 N + cancer cell that now possesses traits that make the stressful environment a part of its fundamental niche. Such evolution is seen as being saltatorial, creating large jumps in the trait values of the organism. While controversial, such evolution does occur in multicellular animals and is also associated with whole species polyploidy and a source of evolutionary rescue [260–263].

If genetic instability followed by evolutionary triage were the primary mechanism at play, multiple different clones, each with unique genetic variation, would be produced, but only a subset of these would survive while the rest would die off. When studied in an *in vitro* microfluidics environment designed to simulate stress, PACCs generate resistant progeny without concomitant generation of multiple non-viable progeny [51,68]. This suggests an alternative mechanism other than genetic instability (Fig. 7).

19.3. Quiescence as a mechanism to protect the genome

The polyploid program, as an inherent non-proliferative quiescent state, protects cells from immediate genome damage. In this cell state, PACCs can adapt a new function for WGD that is not a traditional evolutionary or developmental reason for polyploidization. Ecologically, the PACC state may provide higher survivorship during times of extreme stress. Under the stressor, a population comprised only of 2 N + cells far outside of its fundamental niche may have extremely low viability. Even as the population collapses, PACCs may provide a means for the cancer cells to simply survive [51,68,264]. Once conditions improve, the PACCs can re-establish the highly proliferative 2 N + state. In this model, there is no mutation to generate a resistance phenotype - quiescence to protect genome integrity is sufficient. This is akin to many protists forming an encysted non-proliferative state that survives harsh environmental conditions that are unfavourable for proliferation [128]. Quiescence, senescence, polyploidy, and cancer are clearly closely related but their intersecting biology remains poorly understood [45]. As previously noted, these large amorphous cancer cells were disregarded and not deemed to be functionally important because they were considered to be irreversibly senescent or destined for mitotic catastrophe. Our own studies suggest that only a minority of PACCs induced by chemotherapy exhibit canonical senescence biomarkers (data not shown). Studies conducted in yeast, Drosophila, cancer models, and clinical data suggest, however, that the polyploid state mediates therapy-resistant phenotypes [46]. Furthermore, there is evidence that a population of cancer cells can survive chemotherapy and radiotherapy by entering a reversible senescent state called therapy-induced senescence (TIS) that displays many of the features of the normal physiological senescence phenotype [46,265]. Determining the relationship of stress induced whole genome doubling with concomitant exiting of the active cell cycle with be critical in defining the roles of quiescence versus senescence versus paused proliferation in PACC biology.

19.4. Self genetic modification as a mechanism to alter the genome

Effecting evolutionary rescue by producing a plethora of genetic variants would be wasteful of offspring as most would simply die and, at best, only a small percentage might have trait values that include the now stressful conditions as part of their fundamental niche. It would be much more efficient if PACCs used their capacity for increased RNA and protein production and increased intracellular genetic variability to assess their lack of viability under the stressor, and respond by enacting a metabolic solution that can then be back-encoded into the DNA itself, i.e., self-captured mutation [109,115–117]. This could then form the basis for budding off 2 N + cells that already carry a heritable solution to the stressor. Such evolution is controversial and has variously been described as genetic assimilation, gene editing, or adaptive mutations and is not widely accepted as an evolutionary mechanism [116,266–269]. In 1953, the founder of systems biology Waddington proposed genetic assimilation as a feedback between acquired traits and genetic encoding [270,271]. More recently genetic assimilation has been proposed for similar observations in yeast [272]. Bacteria have evolved overlapping systems to respond to a variety of stresses including changes in temperature, nutrients, and toxins [98,109]. Multiple mechanisms to increase mutability exist, including the movement of transposable elements, exist. While these mechanisms result in increasing heritable mutation through generation of multiple mutants, it has been argued that evidence also supports the selective capture of directed mutations [109,266–268,273–279].

Experimentally, we do not observe the death of mutant clones that should be generated by heritable variation. The acquisition of drug resistance appears to occur without the random mutations and creative-destruction explained by heritable variation [68,280,281]. Thus, it appears that PACCs have the means to assess the stressor, identify a solution, and then alter genes or epigenetics to respond appropriately. If this is true, rather than just being the recipe of inheritance dictating phenotypes and traits, the genetic architecture itself becomes a trait that offers a remarkable source of phenotypic plasticity that enables a form of self genetic modification. The capacity for self genetic modification would then be an adaptation produced by natural selection, providing an alternative and more efficient, albeit controversial, means for adapting to novel stressors [282,283]. Evolutionary triage may be too slow and too wasteful of unviable offspring to effect evolutionary rescue, particularly when conditions leave the current population far outside of its fundamental niche. Self genetic modification, if it exists, may be the pathway by which polyploidy allows single celled organisms and cancer cells to extend their fundamental niche to include otherwise disastrous conditions.

19.5. Genome chaos as a mechanism to alter the genome

These potential strategies to evolve the genome of PACCs in response to stress, regardless of mechanism, can be framed as a microevolutionary modifications - limited changes to the genome over time to improve survival. It is also possible that PACCs utilize a more macroevolution

strategy - large and rapid changes to the genome through the formation of chaotic genomes, e.g., through chromosome fragmentation [243,284–286]. Stress can lead to shattered chromosomes that can be randomly rejoined throughout the genome, resulting in chromothripsis and increasing karyotype complexity [284,287,288]. The genome system theory proposes that chromosomes act as gene topologic organizers (karyotype coding) and function to drive macroevolution through genome based rather than gene-based inheritance [284]. Understanding the interplay of microevolution and macroevolution systems will be critical to understanding how PACCs evolve resistance to microenvironment and treatment stresses [243].

20. Conclusion

The capacity for cells to assess stressors, identify solutions, and alter its genes or epigenetics in ways that results in viable solutions must have been advantageous since life inhabited settings where drastic environmental changes occur. Unicellular life has been present on Earth for most of its 4.5 billion year old history, and present for at least half of this time in surface environments where conditions like redox, light, and pH change ceaselessly [289–292]. Thus, organisms with capacities for assessing being removed from their fundamental niche, for enduring the time outside of the fundamental niche, and for accelerated evolution to yet again become viable, have been selected for over billions of years. Although not widely discussed in the cancer literature, polyploidy as a means to endure, come through, and maybe even assess the harsh conditions is likely a robustly evolved capacity for the many different kinds of cells and organisms that employ it during their life in variable settings.

PACCs represent a formidable challenge to managing and curing cancer. As the source of therapeutic resistance, PACCs appear to be the primary source of cancer's lethality. Targeting PACCs is a difficult task since they represent such a tiny fraction of the overall tumor cell burden and are actually formed in response to external stress, including therapy. Further work is required to understand the mechanisms by which PACCs are formed and how these mechanisms can be targeted. It is clear that multiple strategies will need to be combined that both eliminate the bulk a large number of the 2 N + cancer cells that make up the bulk of the cancer cell population and a strategy to kill the few in number, but critically important PACCs. One potential strategy will be to identify and eliminate or prevent the stresses that cause PACCs to initially form in the primary tumor microenvironment. This would prevent the initiation of lethal phenotype and formation of metastasis initiating cells. This opens the door for potential prevention strategies, potentially by inhibition of the formation of reactive oxygen species [293–295]. This type of strategy may not be possible, however, when an extrinsic stress such as chemotherapy is needed to eliminate large populations of proliferating cancer cells. Drawing from ecology, successful strategies will likely require an evolutionary double bind whereby an organism is forced to adopt an adaptive response to an environmental stressor which then makes it vulnerable to a second, different stressor [24,296].

For cancer populations, we envision that the first strike would take the form of an anti-proliferative agent, e.g., chemotherapy to eliminate the majority of 2 N + dividing cancer cells. Killing the surviving PACCs will require a novel second-strike therapy that specifically targets their unique vulnerabilities (Fig. 8). Clues to these potential susceptibilities are beginning to be identified. As the programs that control polyploidization are defined (Fig. 4), multiple inhibitors of the cell cycle checkpoints are clinically available, ready to be applied in strategic manners [297–301]. Aneuploidy itself and the necessity for appropriate chromosome segregation likewise offers multiple therapeutic targets [302–305]. Many agents along these pathways have been developed but have failed in the clinic because they have been given non-discriminately to the whole population of cancer cells. The large size and increased cellular contents of the PACCs offer potential targets secondary to altered metabolic pathways, e.g., lipid biosynthesis, as well as protein homeostasis and cell energetics [293,306,307]. Quiescence and therapy induced senescence also offer unique strategies, again if applied in a double bind fashion [308–310]. Moreover, the abnormal morphology of PACCs suggests that there may be unique cell surface antigen profiles that can be exploited for directed antigen-conjugation to deliver a toxic payload to the cells. Targeting PACCs must be a high priority as they are the key to therapeutic resistance and the incurability of cancer.

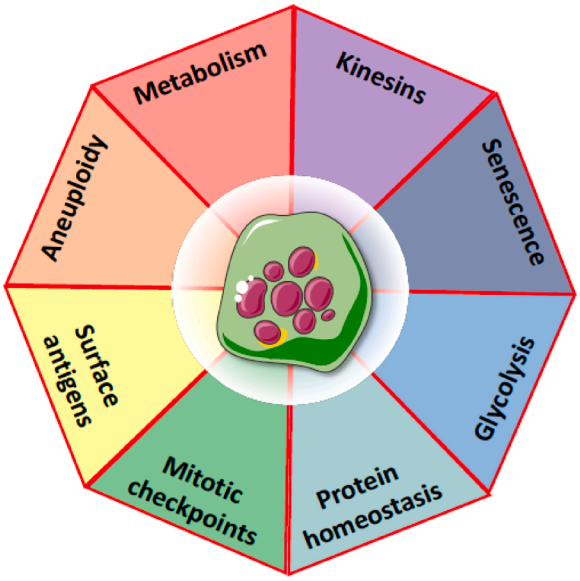

Fig. 8. Targeting polyaneuploid cancer cells for therapeutic destruction. Targeting PACCs is a difficult task since they represent such a tiny fraction of the overall tumor cell burden and are formed in response to external stress, including therapy. Drawing from ecology, successful strategies will likely require an evolutionary double bind whereby an organism is forced to adopt an adaptive response to an environmental stressor which then makes it vulnerable to a second, different stressor [24,296]. For cancer populations, we envision that the first strike would take the form of an anti-proliferative agent, e.g., chemotherapy to eliminate the majority of 2 N + dividing cancer cells. Killing the surviving PACCs will require a novel second-strike therapy that specifically targets their unique vulnerabilities. Vulnerabilities are being identified based on the unique structure and functions of the PACCs, including targeting the cell cycle [297–301], aneuploidy [302–305], metabolism [293,306,307], and senescence [308–310].

Declaration of Competing Interest

Dr. Pienta is a consultant for CUE Biopharma, Inc., is a founder and holds equity interest in Keystone Biopharma, Inc., and receives research support from Progenics, Inc. The other authors declare no conflicts of interest.

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