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Cancer: more than a geneticist's Pandora's box

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Abstract

Despite identical genetic constitution, a cancer cell population can exhibit phenotypic variations termed as non-genetic/non-mutational heterogeneity. Such heterogeneity – a ubiquitous nature of biological systems – has been implicated in metastasis, therapy resistance and tumour relapse. Here, we review the evidence for existence, sources and implications of non-genetic heterogeneity in multiple cancer types. Stochasticity/noise in transcription, protein conformation and/or external microenvironment can underlie such heterogeneity. Moreover, the existence of multiple possible cell states (phenotypes) as a consequence of the emergent dynamics of gene regulatory networks may enable reversible cell-state transitions (phenotypic plasticity) that can facilitate adaptive drug resistance and higher metastatic fitness. Finally, we highlight how computational and mathematical models can drive a better understanding of non-genetic heterogeneity and how a systems-level approach integrating mathematical modelling and *in vitro*/*in vivo* experiments can map the diverse phenotypic repertoire, and identify therapeutic vulnerabilities of an otherwise clonal cell population.

Keywords

Non-genetic heterogeneity, multistability, drug-tolerant persisters, phenotypic plasticity, biological noise, epithelial-mesenchymal plasticity, PAGE4

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Introduction

Cancer is thought to originate from an individual normal cell that gains genetic mutation(s) offering it growth advantage over other cells. A clonal population of cells can arise from this 'first' cancer cell; this population has identical genetic composition (Greaves and Maley, 2012; Nowell, 1976). As time progresses, some of these cells can gain additional mutations, thus leading to sub-clones, some of which can be more fit as compared to others and thus undergo natural selection to become the predominant sub-clone(s). Recent studies across clonal populations in cancer cells as well as other biological contexts (such as microorganisms (Davidson and Surette, 2008)) have proposed that phenotypic variations exist among genetically identical cells (Brock et al., 2009). These phenotypic variations are referred to as non-genetic heterogeneity (NGH), highlighting their non-genetic/non-mutational origin. Such non-genetic mechanisms can include a combination of various processes such as stochasticity or noise in gene expression (Balázsi et al., 2011), asymmetry in distribution of molecules during cell division (Huh and Paulsson, 2011), variability in epigenetic status of cells (Bell and Gilan, 2020), promiscuity in protein-protein interaction networks due to disorder in protein structures (Lin et al., 2019) and ability of cells to exhibit multiple phenotypes (multistability) as a result of feedback loops embedded in a gene regulatory network (Evans and Zhang, 2020; Hari et al., 2020). Consequently, cells in a clonal population can have variability in their protein levels, chromatin accessibility status, metabolites etc. which can eventually manifest as different phenotypes. Non-genetic heterogeneity has been shown to offer survival advantages to cells in fluctuating environments such as drug treatment, hypoxia and nutrient deprivation, by facilitating 'bet-hedging', an evolutionary strategy to achieve fitness across environmental conditions (Bell and Gilan, 2020; Pisco and Huang, 2015; Sahoo et al., 2021a; van Boxtel et al., 2017; J. Veening et al., 2008). However, unlike genetic heterogeneity that has been extensively investigated for decades (Mcgranahan and Swanton, 2017), understanding the underlying mechanisms and implications of non-genetic heterogeneity in cancer research is still in its infancy (Barzgar Barough et al., 2021; Lewis and Kats, 2021; Marine et al., 2020; Shlyakhtina et al., 2021).

The 'one gene-one enzyme' hypothesis postulated in 1941 (Beadle and Tatum, 1941) was among the first to propose a one-to-one mapping between genotype and phenotype. However, as we now realize, a phenotype is the outcome of extensive cross-talk among many biological factors that form regulatory networks at various length and time scales, revealing pleiotropy (Tyler et al., 2009) in the genotype-phenotype map. Regulatory networks in biological systems consist of multiple feedback loops which can produce more than one phenotype depending upon cell-intrinsic (e.g., rates of transcription, translation and protein degradation) and cell-extrinsic (e.g., temperature, oxygen and nutrient availability) factors (Brandman and Meyer, 2008). Thus, despite having identical genetic composition, clonal cancer cells can display differences in phenotypic properties such as growth rates (Vega et al., 2004), tumour initiation capabilities (Mani et al., 2008; Pasani et al., 2021) and the ability to evade therapeutic attacks (Paek et al., 2016; Shaffer et al., 2017; Sharma et al., 2010). Intriguingly, cells can switch back and forth among these different phenotypes, driving reversible changes which may or may not be inherited, unlike mutational effects which are irreversible in nature and 'hard-wired' to be passed on to the progeny.

In this review, we first discuss the tacitly assumed essentiality and sufficiency of mutations for some aspects of cancer progression and highlight some observations that cannot be completely explained by the somatic mutation theory alone. Next, we provide evidence of non-genetic heterogeneity observed in clonal cancer cell populations and offer mechanistic details for some of its sources. Finally, we discuss the implications of such heterogeneity in various hallmarks of cancer. We also highlight the contribution made by mathematical models to understand non-genetic heterogeneity and suggest that a systems-level understanding integrating theoretical

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models and experimental observations may provide a better understanding of non-genetic heterogeneity and how this knowledge may be leveraged to restrict aggressive clinical outcomes.

Are mutations necessary for cancer progression?

For many years, DNA mutations have been considered to be the main cause of cancer initiation wherein mutation in an oncogene or tumour suppressor gene can drive an abnormal cell growth. Such mutations are implicitly assumed to be necessary and sufficient for cancer progression, leading to the most popular and widely accepted concept in the field of cancer biology – somatic mutation theory (SMT) – which posits a mutation in a single somatic cell as the first step of cancer (Sonnenschein et al., 2014). This mutation in a cell is considered to be sufficient to perturb its cell cycle regulation leading to uncontrolled cell proliferation. However, many observations in cancer biology do not appear, at least *prima facie,* synchronized with SMT, such as spontaneous regression of childhood neuroblastoma without any cytotoxic therapy (Haas et al., 1988), ependymomas in children (MacK et al., 2014), reprogramming of cancerous cells to normal cells when implanted into normal microenvironments (Bussard et al., 2010; Kasemeier-Kulesa et al., 2008; McCullough et al., 1997; Mintz and Illmensee, 1975), stromal induction of carcinogenesis in epithelial cells (Barcellos-Hoff and Ravani, 2000; Barclay et al., 2005; Maffini et al., 2005, 2004), and the cycling of hepatic cells from cancerous to normal (dormancy) by dialling up or down of the wild type MYC oncogene (Shachaf and Felsher, 2005; Shachaf et al., 2004).

Thus, an alternative to SMT has been proposed recently – although not yet that popular – tissue organization field theory (TOFT) (Soto and Sonnenschein, 2011). TOFT considers cancer to be a tissue-based disease (instead of a cell-based disease as considered by SMT) akin to development gone awry. According to TOFT, cancer arises as a result of simultaneous occurrence of two steps: a disturbed interaction between parenchyma and stroma resulting into altered tissue organization and a weaker inhibitory control exerted by tissue over cell proliferation (Sonnenschein and Soto, 2015). TOFT is further supported by observations that primary tumors can metastasize to only few specific organs, indicating that stroma of an organ plays an important role in determining whether or not cancer cells attached to it can start metastatic growth in it (Tarin, 2011). This concept is endorsed by recent observations suggesting that cancer cells can carry their own stroma ('soil' as per Paget's 'seed and soil' hypothesis (Paget, 1889)) for successful metastasis (Duda et al., 2010). While the discussion about similarities, differences, and complementarity between SMT and TOFT is beyond the scope of this review, the dynamics of cancer metastasis offers an intriguing scenario to dissect the role of mutations in cancer progression.

Despite tremendous advances in high-throughput single-cell sequencing in the last decade, no unique mutational signature has yet been identified for metastasis (Celià-Terrassa and Kang, 2016; Welch and Hurst, 2019). Instead, cellular or phenotypic plasticity – the ability of cells to reversibly switch their phenotypes – has been proposed as a hallmark of metastasis (Bhatia et al., 2020; Biswas and De, 2021; Sacchetti et al., 2021). One of the key axes of phenotypic plasticity during metastasis is epithelial-mesenchymal plasticity (EMP), where cells can transition among a range of phenotypes spread over a spectrum ranging from more epithelial (usually more adhesive and less invasive) to more mesenchymal (usually more invasive and having reduced cell-cell adhesion) (Gupta et al., 2019; Pastushenko and Blanpain, 2019). EMP can have transcriptional (Cieply et al., 2012; Ocaña et al., 2012; Roca et al., 2013; Subbalakshmi et al., 2020; Yang et al., 2004) and/or epigenetic (Jia et al., 2019; Nihan et al., 2019; Ruscetti et al., 2016; Serresi et al., 2021) regulatory control. Thus, the dynamics of complex interconnected networks at various levels of regulation can dictate the propensity of a cell to slide along the 'EMP axis'. Moreover, EMP can influence other axes of plasticity such as stemness/tumour-initiation potential (Celià-Terrassa et

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al., 2012; Jolly et al., 2015), resistance to cell death caused by anchorage independence (anoikis) (Huang et al., 2013), resistance to various targeted therapies and immunotherapy across cancers (Chouaib et al., 2014; Dongre et al., 2017; Sahoo et al., 2021a; Shafran et al., 2021; Tripathi et al., 2016), increasing cancer cell fitness during the metastatic cascade. Thus, EMP is a canonical example of phenotypic plasticity and consequent non-genetic heterogeneity implicated in successful metastasis.

Metastasis is a highly inefficient process (Cameron et al., 2000; Luzzi et al., 1998), during which the local micro-environment of disseminated cells is quite dynamic, and cells need to adapt rapidly to survive the bottlenecks they face. The timescale of obtaining the 'right' mutation that can tunnel cells through that bottleneck is over multiple cell divisions, thus being largely inconsequential to the probability of cells surviving that bottleneck. Moreover, while a newly acquired mutation may enhance the survival likelihood of a circulating tumour cell for a given bottleneck, it can compromise on the ability of the cell to adapt to additional bottlenecks due to irreversible changes in its phenotypic repertoire. Put together, fast and reversible adaptations at a phenotypic (i.e.,(Shachaf and Felsher, 2005) non-genetic) level seem to be playing an instrumental role in enabling cancer metastasis as compared to slow and irreversible adaptations available at a genetic level. Hence, it is not surprising that while cells from various sub-clones of the primary tumour have been seen in circulating tumour cells and capable of metastasizing (Lyberopoulou et al., 2015; Simeonov et al., 2020), no unique mutational foot-prints have yet been deciphered, unlike other hallmarks of cancer, for which mutations in various oncogenes and/or tumour suppressor genes have been pinpointed (Hanahan and Weinberg, 2011; Mantovani et al., 2019). Such plasticity during metastasis can lead to phenotypic (non-genetic) heterogeneity, as witnessed in circulating tumour cells (CTCs) across cancer types (Bocci et al., 2021; Yu et al., 2013). Consistent with observed impact of plasticity on evolvability of cellular traits (Fierst, 2011), non-genetic heterogeneity has been identified to impact evolutionary dynamics in lung cancer beyond genetic heterogeneity as well (Sharma et al., 2019).

Besides metastasis, phenotypic plasticity and non-mutational heterogeneity has been implicated in the emergence of adaptive drug resistance (Boumahdi and de Sauvage, 2020; Oren et al., 2021; Qin et al., 2020), particularly through drug-tolerant persister (DTPs) – a subpopulation of cells that can survive sustained therapeutic attack by entering a reversible slow-proliferation state (**Fig 1**). DTPs adapt to environmental fluctuations through epigenomic, transcriptional and metabolic reprogramming events, and are capable of expanding into a colony (Shen et al., 2020b). Initially reported in lung cancer (Sharma et al., 2010), persisters have been reported in other cancer types as well such as melanoma and colorectal cancer (Hangauer et al., 2017; Karki et al., 2021; Mikubo et al., 2021; Oren et al., 2021; Rehman et al., 2021; Shen et al., 2020a). Intriguingly, DTPs can act as a reservoir subpopulation through which genetically mutated cells can emerge to stabilize diverse drug-resistance mechanisms at a longer time-scale (Ramirez et al., 2016). Thus, genetic and non-genetic mechanisms can be thought to cooperate to allow cancer cell adaptation at different time-scales during the emergence of drug 'resistance' (Hayford et al., 2021; Salgia and Kulkarni, 2018).

Are mutations sufficient for cancer progression?

Investigations into mechanisms of cancer initiation have also questioned the sufficiency of genetic mutations in cancer cells. For example, transformation of a normal cell to cancerous melanoma cell has been shown to be triggered by imbalance in physiological factors along with exposure to environmental carcinogen ultraviolet B (UVB) (Berking et al., 2004). Using human skin grafting experiments in immune-compromised mice, it was found that exposing normal melanocytes to

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increased levels of fibroblast growth factor, stem cell factor, and endothelin-3, along with exposure to UVB could transform normal melanocytes to cancerous melanoma within four weeks of treatment, while treatment with individual growth factor along with UVB had no effect (Berking et al., 2004). This study suggests that only an external carcinogen is not always sufficient to initiate cancer; instead, some internal physiological imbalance is crucial as a permissive key to trigger neoplastic transformation. Consistently, another study in UV-induced melanoma argues that the susceptibility or resistance of mice to develop cancer strongly depends upon the presence of variants in the modifier genes along with the pathogenic genetic mutation (Ferguson et al., 2019). Thus, apart from genetic mutation(s), overall genetic make-up of an organism and/or perturbation in local environment may contribute to induction of carcinogenesis, offering possible reconciliation between SMT and TOFT.

A commonly asked question in cancer biology is “if mutations in cancer-associated genes are sufficient for neoplastic transformation, why normal cells carrying similar somatic mutations do not get transformed and develop cancer?” With advancements in DNA-sequencing technologies, it is now possible to detect low-frequency somatic mutations in normal cells (Kennedy et al., 2019). The existence of somatic mosaicism (genetically distinct somatic cells harboured by an individual through DNA structural abnormalities, epigenetic changes and errors in chromosome partitioning), is well established (Youssoufian and Pyeritz, 2002). Thus, genetic instability is not necessarily a unique property of cancer cells but inherent to all somatic cells, further emphasizing the role of altered microenvironment and/or other permissive cues in tumour initiation (Lichtenstein, 2018). For example, deleterious, age-associated, somatic mutations in TP53 gene commonly associated with serous ovarian cancer, are also detected in peritoneal fluid from women without cancer at a very low frequency (Krimmel et al., 2016). Similarly, cancer-associated somatic mutations arising due to clonal expansion of hematopoietic cells have been reported in healthy individuals (Genovese et al., 2014; Xie et al., 2014). Such mutations are also detected in solid tissues of healthy individuals such as skin, colon, endometrium, brain etc (Kennedy et al., 2019). Conversely, in ependymomas – common childhood brain tumours – no significant recurrent mutations were detected in a cohort (MacK et al., 2014).

Together, these studies provide a strong indication that the presence of genetic mutations may not always result into tumour initiation, and that other permissive cues within a cell and/or its local micro-environment may drive neoplastic transformation of normal cells and tumour progression as well.

Evidence of non-genetic heterogeneity in clonal population of cells

The evidence of non-genetic heterogeneity in clonal populations was first noted in microorganisms. For example, *Dictyostelium discoideum* shows a bimodal (two-peak) distribution of motility speed and calcium content upon starvation within 15 minutes. The observed differences also reverted within 15 minutes after restoration of the nutrient medium, indicating reversible state transitions (Goury-Sistla et al., 2012). Similarly, variations in the levels of intracellular cyclic AMP (cAMP) in *Saccharomyces cerevisiae* has been shown to be associated with heterogeneity in growth rate and in acute stress tolerance. Perturbing this heterogeneity can impact these functional traits: while increase in intracellular cAMP levels increases susceptibility to acute heat stress, PKA inhibition decreases it, suggesting that underlying population structures get altered in opposite directions by these perturbations (Li et al., 2018).

While cell-extrinsic perturbations can reveal non-genetic heterogeneity, it may also arise due to cell-intrinsic variations in functioning of homeostasis in cell organelles. For example, variability in

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mitochondrial membrane potential among cells was correlated with that in proliferation rate, stress tolerance and resistance to therapy in yeast, identified using high through-put automated microscopy (Dhar et al., 2019). Similar to unicellular organisms (Elowitz et al., 2002), eukaryotes also exhibit non-genetic cell-to-cell variability. For instance, a clonal population of mouse hematopoietic cells showed a distribution of levels of the stem cell marker Sca-1. While the Sca-1^{high} sub-population with increased expression of PU.1 preferentially differentiated to myeloid lineage, the Sca-1^{low} sub-population expressing higher levels of GATA1 showed greater preference towards erythroid differentiation, highlighting how stochasticity can impact linage choice in the mammalian progenitor cells (Chang et al., 2008),

More recently, a population of cancer cells with identical genetic background has been observed to show differential gene expression and protein levels and consequently functional readouts such as response to drugs and tumour initiation. Advancement in flow cytometry methods, single-cell transcriptomic, lineage tracing and fate-mapping techniques have provided increasing evidence of phenotypic heterogeneity in a genetically homogenous cancer cell population (Celià-Terrassa et al., 2018; Cook and Vanderhyden, 2020; Karacosta et al., 2019; Sasagawa et al., 2013; Specht et al., 2019). Single-cell expression variability is not unique to cancer cells; it has been witnessed among homogenous population of non-cancerous cells too, with important functional implications. For instance, highly variable genes in lung airway epithelial cells were enriched with collagen formation, those in dermal fibroblasts were found to be involved with keratinization, and those in lymphoblastoid cells were enriched with cytokine signaling (Osorio et al., 2020).

Multilineage differentiation programs operated in solid tissues have been proposed as potentially responsible for non-genetic heterogeneity observed in cancer cells. For example, six molecular sub-types of normal fallopian tube epithelium (FTE, cells of origin of serous ovarian cancer (SOC)) were identified using transcriptomic analysis of 4000 normal FTE which was used to deconvolute non-genetic heterogeneity observed in high grade SOC (Hu et al., 2020). Similarly, using single cell PCR gene-expression profiling, non-genetic transcriptional variability observed in human colon cancer was demonstrated to be similar to different lineages of normal colon epithelium (Dalerba et al., 2011). Different single-cell transcriptomics or proteomics methods are offering unprecedented insights into elucidating patterns of heterogeneity in a homogenous cell population. For example, co-sequencing of microRNA-mRNA in individual cells using half-cell genomics approach showed that variability of microRNA levels may drive non-genetic heterogeneity among cells (Wang et al., 2019). Similarly, two distinct cell populations within a melanoma tumor was observed characterized by variable expression levels of MITF (Rebecca and Herlyn, 2020; Tirosh et al., 2016). Further, subpopulations with varying differential EphA cluster morphologies and intrinsic migration potential were observed in breast cancer cells using single-cell assays (Ravasio et al., 2019). Identification of such heterogeneity has revealed that multiple cancer subtypes may co-exist within an individual tumor (Yeo and Guan, 2017). Relative proportions of cells exhibiting distinct subtypes constituting a tumor is expected to be highly dynamic and under constant drug-induced evolutionary pressures.

An outstanding example of phenotypic plasticity in cancer is EMP which includes transition of cell among epithelial (E), mesenchymal (M) and hybrid E/M states (Celià-Terrassa and Jolly, 2020). Epithelial-mesenchymal transition (EMT) and its reverse mesenchymal-epithelial transition (MET) – which together constitute EMP – are fundamental processes in development and wound-healing where it facilitates movement of cells from one location to another (Nieto et al., 2016). This property of EMT-MET is exploited and benefitted by cancer cells where they not only confer cell motility (Pearson, 2019) but also are implicated in metabolic reprograming (Jia et al., 2021; Krebs et al., 2017), tumour-initiation potential (Grosse-Wilde et al., 2015; Kröger et al., 2019), multi-drug resistance (Shibue and Weinberg, 2017), immune evasion (Chen et al., 2014; Dongre et al., 2017; Sahoo et al., 2021b) and eventually patient survival (George et al., 2017; Tan et al., 2014). Clonal

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population of cancer cells may display a dynamic EMP status depending upon the relative levels of inducers and/or stabilizers of mesenchymal states (EMT-inducers such as ZEB/SNAIL family members) and those of epithelial ones (MET-inducers such as GRHL, OVOL and miR-200 family members) which often regulate the cellular levels of one another through reciprocal feedback loops (Brabletz and Brabletz, 2010; Kvokackova et al., 2021). Various stabilizers of hybrid E/M phenotypes such as NRF2 and NUMB can influence the cell-state transition rates among different phenotypes along the 'EMP axis' (Biswas et al., 2019; Bocci et al., 2019b, 2017; Hong et al., 2015).

At a cell morphological level, EGF-induced EMT in breast cancer cells can be classified into three distinct reversible morphological states as a function in a dose-dependent manner: cobble, spindle and circular (Devaraj and Bose, 2019). Similarly, using Z-cad dual sensor system using an epithelial and a mesenchymal marker together, dynamic changes in breast cancer cells undergoing EMT or MET can be observed, which can help isolate the subpopulation displaying mesenchymal properties from a population consisting of pre-dominantly epithelial like cells (Toneff et al., 2016). Moreover, the percentage of cells in E, hybrid E/M and M states at various timepoints during EMT induction can be quantified using such a sensor and/or single-cell RNAseq data, highlighting patterns of heterogeneity (Cook and Vanderhyden, 2020; Deshmukh et al., 2021; Jia et al., 2019). Reversible changes in the frequency of epithelial and mesenchymal cell states have been seen not only *in vitro*, but also in circulating tumour cell (CTC) composition of cancer patients with each cycle of response to therapy (Yu et al., 2013). Further, there may be heterogeneity in hybrid E/M states as well, as identified in primary skin and mammary tumors (Pastushenko et al., 2018) as well as in breast and lung cancer cells (Brown et al., 2021; Hong et al., 2015; Karacosta et al., 2019; Schliekelman et al., 2015). Thus, EMP is an excellent example of non-genetic heterogeneity where hybrid E/M cells can possess markers/traits of both E and M states within a predominant epithelial or mesenchymal cell population (Andriani et al., 2016; Celià-Terrassa et al., 2018; Grosse-Wilde et al., 2015).

A major reason enabling non-genetic heterogeneity in EMP has been multistability in underlying regulatory networks (Font-Clos et al., 2018; Steinway et al., 2015; Watanabe et al., 2019) which can often introduce asymmetry in "paths" taken by cells during EMT vs. those taken during MET. Indeed, transcriptional profiling of metastatic prostate cancer reveals that expression profile of cells at various timepoints is not just the reverse of those seen as cells underwent EMT (Stylianou et al., 2019). Similar patterns of hysteresis were seen in proteomics of lung cancer cells (Karacosta et al., 2019). Therefore, despite much investigation, we do not have a unique EMP signature that can be applied in a pan-cancer manner to identify whether cells are undergoing EMT or MET at a given time-point, and by extension, a signature that can estimate the metastatic potential of cells.

Non-genetic heterogeneity has also been reported for a trait connected with EMT - Cancer Stem Cells (CSCs). CSCs were earlier thought to occupy the apex of cell differentiation (i.e. hierarchical model), but recent evidence has shown that CSCs and non-CSCs can interconvert among one another at both molecular and functional levels (Tang, 2012; Thankamony et al., 2020). Moreover, CSCs can have multiple categories with varied EMT status – the CD44+/CD24- CSCs in breast cancer are more mesenchymal-like, while the ALDH+ and CD44+ CD24+ ones map to a hybrid E/M phenotype (Asadullah et al., 2021; Bocci et al., 2019a; Colacino et al., 2018; Liu et al., 2014). Such subpopulations may stochastically transition among one another, suggesting that the tumorigenic potential of cancer cells is strongly associated with the intrinsic plasticity rather than CSC multipotency *per se* (Dirkse et al., 2019). Similarly, in lung cancer, different subpopulations (holoclone, paraclone, meroclone) displayed variable tumor initiation capacity and EMT traits (Tièche et al., 2018). They maintained distinct morphology during short term culture and displayed distinct markers and RNA expression profile. While holoclones displayed the maximal epithelial trait, the paraclones displayed the most mesenchymal one, with meroclone being intermediate.

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Moreover, holoclone showed the highest and paraclone the lowest tumor initiation capacity *in vivo*. On the other hand, paraclone showed the highest and holoclone had the lowest drug resistance features (Tièche et al., 2018). Subpopulations of CSCs have also been seen in squamous cell carcinoma (Biddle et al., 2016, 2011) and colorectal cancer (Hirata et al., 2019) among others.

Another axis connected to EMT that has been seen growing evidence of phenotypic plasticity and heterogeneity is that of drug resistance. Of course, resistance can emerge due to *de novo* existing mutations in a subpopulation of cells and/or additional mutations gained during therapeutic assault, but non-genetic factors can play a role in driving drug resistance too (Marine et al., 2020; Rebecca and Herlyn, 2020; Salgia and Kulkarni, 2018). For instance, a partial or full EMT can drive ER+ breast cancer cells into resistance to tamoxifen and/or docetaxel; intriguingly, tamoxifen-resistant cells tend to be more mesenchymal than their sensitive counterparts, indicating a mutual causal connection between these axes (Prieto-Vila et al., 2019; Sahoo et al., 2021a). Similarly, non-genetic heterogeneity may provide a mechanism to adapt to drug treatment. By using quantitative proteomics and computational modeling, it was shown that immediately after exposure to RAF /MEK inhibitors such as vemurafenib, the $BRAF^{V600E}$ melanoma 'persister' cells show adaptive changes involving brief pulsatile reactivation of MAPK pathway which can activate ERK signaling in neighboring cells too. These pulses enable 'persister' cells to escape cell cycle arrest and sustains long-term resistance at a non-genetic level. This study provides mechanistic detail of role of non-genetic heterogeneity in emergence of drug resistance in a genetically identical population (Gerosa et al., 2020). Additional analysis of drug-tolerant 'persisters' in melanoma has indicated how vemurafenib treatment can trigger cell-state transitions into a more undifferentiated phenotype which is therapeutically resilient (Pillai and Jolly, 2021; Su et al., 2019, 2017). Such transitions are often reversible, as seen for EMT (Tripathi et al., 2020), thus enabling resumption of growth upon drug removal. Also, these drug-tolerant 'persisters' can serve as a reservoir of cells some of which may acquire additional mutations at prolonged timescales, leading to 'stabilization' of the drug-resistant phenotype, as seen in lung cancer cells treated with gefitinib (Ramirez et al., 2016).

The concept of persisters was initially reported in bacterial populations which when exposed to antibiotic drugs show differential killing rates such that majority of bacterial cells (drug-sensitive) show fast killing rates and a steep decrease in their survival while a small fraction of cells show slow killing with relatively slower decrease in their survival (Brauner et al., 2016; Rossi et al., 2019). This biphasic time-kill curve pinpointed the existence of a small fraction of cells called 'persisters', which, when isolated and grown in drug-free medium, repopulated the initial bacterial population consisting of drug-sensitive and persister cells indicating phenotypic switching (Balaban et al., 2004) rather than inherited genetic mutations (Moyed and Bertrand, 1983). Persister cells may arise from dormant bacterial cells even before exposure to antibiotics as suggested from single-cell and flow cytometry studies (Harms et al., 2016; Rossi et al., 2019), suggesting the idea of bet-hedging, an evolutionary strategy to maximize fitness and survival of clonal population in dynamic environment by incorporating phenotypic heterogeneity (J. W. Veening et al., 2008). Moreover, it indicates that within a clonal population, cells can have different interconvertible sub-populations, indicating bistability in biological systems (Feng et al., 2014; Jolly et al., 2018a).

Reinforcing observations are reported in luminal breast cancer using single-cell RNA-sequencing, where a sub-population of 'pre-adapted' cells with reduced levels of estrogen receptor (ERα) and increased properties of quiescence and migration, undergo transcriptional reprogramming upon drug treatment and gather copy number changes to gain long-term resistance to endocrine therapy (Hong et al., 2019). Another study investigating the mechanism of drug resistance in triple-negative breast cancer have shown that after treatment with doxorubicin combined with cyclophosphamide, the residual tumor cells maintained the sub-clonal architecture of untreated tumor; however, their transcriptomic, proteomic and histological profiles were different from that of the untreated tumor

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profiles. Once the drug treatment was stopped, residual tumors gave rise to drug-sensitive tumors with similar expression profiles as that of the untreated tumor, indicating reversible chemotherapy-tolerance (Echeverria et al., 2019). Similar analysis of trajectories of escapees from ALK inhibitor treatment was seen in NSCLC where both genetic and non-genetic mechanisms contributed to gradual adaptation and gained resistance (Velde et al., 2020).

Considered together, emerging evidence along multiple axes of cellular plasticity – EMT, CSCs and drug resistance – strongly endorses the role that non-genetic heterogeneity and consequent possible cell adaptation trajectories can play in facilitating tumor survival, therapy resistance and relapse.

Sources of non-genetic heterogeneity

What are the mechanisms that can results into non-genetic heterogeneity within a clonal population of cells as observed in microorganisms and cancer cells, as well as during embryonic development of a metazoan? Here, we briefly review some canonical sources of non-genetic heterogeneity in different scenarios, and its implications.

Transcriptional noise

Stochasticity in the production of mRNA and turnover rate of mRNA and protein produces gene expression noise, which arises due to random binding of transcription factors to the gene promoter (Mcadams and Arkin, 1997; Raser and O'Shea, 2004). Non-continuous transcription may fluctuate the promoter between an "ON" state which results into transcription burst, producing mRNA transcripts at a high rate or "OFF" state which pauses transcription (Friedrich et al., 2019; Kumar et al., 2015; Raj et al., 2006; Singh et al., 2012). The amount of RNA produced from a particular gene depends upon the frequency, amplitude and duration of transcription burst which may be specific for a particular cell depending upon extrinsic noise such as concentration and availability of general transcription factors (Elowitz et al., 2002). The frequency and size of transcriptional burst also depends upon the composition of the gene promoter which can modulate binding affinities and trans-acting factor concentrations (Hendy et al., 2017). For example, it is shown that presence of TATA box in gene promoter is associated with higher noise (Hornung et al., 2012; Tantale et al., 2016). In addition, transcription bursting also depends upon enhancer-promoter interaction and enhancer strength (Fukaya et al., 2016). Enhancers control spatial and temporal expression of genes by recruiting gene specific transcription factors (Buecker and Wysocka, 2012). Similar to rate of synthesis, rate of degradation of mRNA also influences gene expression noise (Baudrimont et al., 2019). Thus, gene expression noise may differ drastically between genetically identical cells depending upon the multiple factors (Balázsi et al., 2011; Urban and Johnston, 2018) which may bring phenotypic variations in cells (Brock et al., 2009) by imparting variability and/or memory for protein levels in a cell (Sigal et al., 2006).

Transcriptional noise has been implicated as a source for cell-fate decision making in yeast (Blake et al., 2006), bacteria (Süel et al., 2006) and many mammalian systems (Moris et al., 2016). More recently, it has been shown to influence cancer progression. In leukemia, depletion of the acetyl-transferase KAT2A enhances transcriptional bursting and variability, depletes leukemic stem-like cells and delays disease progression (Domingues et al., 2020).

Conformational noise

Intrinsically Disordered Proteins (IDPs) are proteins, which unlike many other proteins, lack a well-defined 3D structure either locally or throughout the protein and display a high degree of flexibility which can confer 'conformational noise' due to promiscuity in their interactions (Mahmoudabadi et

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al., 2013). Due to their high conformational flexibility, IDPs serve as a determinant of protein activity and can be often present as hub protein in biochemical networks (Haynes et al., 2006; Patil et al., 2010). IDPs display faster binding/unbinding rates with their ligands and may undergo transition from disordered to ordered state upon binding with their partner or post-translational modification, thus may amplify promiscuity and bring stochasticity in interactions in biochemical networks (Bah et al., 2015; Chakrabortee et al., 2010; Jolly et al., 2018a; Lin et al., 2018). For example, many drivers of EMT such as ZEB1 and OVOL1/2 (Saxena et al., 2020) have been predicted to contain intrinsically disordered regions (Mooney et al., 2016), adding to the long list of oncogenes and/or tumor suppressor genes where IDP regions have been reported consistently (Lin et al., 2019).

For example, an IDP associated with prostate cancer – Prostate Associated Gene 4 (PAGE4) – has been implicated in phenotypic heterogeneity (Kulkarni et al., 2017; Singh et al., 2021). PAGE4 is phosphorylated by two kinases, namely Homeodomain Interacting Protein Kinase 1 (HIPK1) and CDC-Like Kinase 2 (CLK2). PAGE4 activates the Activator Protein-1 (AP-1). HIPK1-PAGE4 has a stronger affinity to AP-1 when compared to CLK2-PAGE4. Experimental studies and mathematical modelling have shown that as a result of differential phosphorylation of PAGE4 which leads to altered AP-1/androgen receptor (AR) regulatory circuit, prostate cancer cells can have a spectrum of phenotypes with varying sensitivity to the standard-of-care androgen deprivation therapy (ADT). Furthermore, the fact that a majority of transcription factors are intrinsically disordered (Niklas et al., 2018; Staby et al., 2017; Tsafou et al., 2018; Zhang and Tjian, 2018) lends further credence to the argument.

Epigenetic regulation

Apart from genetic changes, changes in chromatin such as covalent modification of chromatin components such as DNA methylation and histone modification can be inherited (Gerlinger et al., 2012). DNA hypermethylation and hypomethylation have been extensively studied in cancer which may result into inactivation of tumor suppressor genes or activation of oncogene (Feinberg et al., 2016; Kazanets et al., 2016). Recently, using single-cell RNA sequencing of naïve and drug-resistant acute myeloid leukemia (AML) patient samples, the occurrence of non-genetic BET inhibitor resistance in AML was observed (Bell et al., 2019). This resistance was shown to be driven by epigenetic mechanisms driven by transcriptional plasticity. Similarly, reversible drug-tolerance observed in non-small cell lung cancer cells was driven by epigenetic changes (Sharma et al., 2010). These studies highlight the role of epigenetic changes in non-genetic cancer cell adaptation and pinpoints compensatory mechanisms used by cancer cells to overcome drug sensitivity that can be potential therapeutic targets (Bell et al., 2019).

Tumor microenvironment

Tumor microenvironment shows a high degree of heterogeneity in terms of angiogenesis which modulates oxygen and nutrient availability, composition of stromal and immune cells, endothelial cell density and extra cellular matrix composition (Quail and Joyce, 2013; Saxena and Jolly, 2019). Hypoxia, for instance, confers certain phenotypes to tumor cells present in hypoxic regions such as stemness (Louie et al., 2010), EMT (Liu et al., 2017) and chemoresistance (Chen et al., 2015). Similarly, varying spatial localization of stromal cells and immune cells with respect to cancer cells can govern the autocrine/paracrine impact they can have on each other. For example, cancer-associated fibroblasts (CAFs) have been shown to expand breast cancer stem cell population by secreting prostaglandin (PGE2) and IL-6 (Rudnick et al., 2011), promote migration and invasion mediated by high expression of COX-2 in nasopharyngeal carcinoma (Zhu et al., 2019) and facilitates neo-angiogenesis in hepatocellular cancer via placental growth factor (Liu et al., 2019). Further, not all fibroblasts are pro-tumor; a subset of them, as identified via single-cell analysis, can also support anti-tumor immunity (Hutton et al., 2021). Similarly, neutrophils may exert pro- or

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anti-tumor effects and these subpopulations may also interconvert among one another (Furumaya et al., 2020), reminiscent of macrophage phenotypic heterogeneity exhibited along the M1-M2 axis. Also, feedback loops formed between immune cells and/or cancer cells of varying phenotypes can allow for dynamic phenotypic composition in a tumor, thus influencing its prognosis (Li et al., 2019). Thus, both cell-autonomous (transcriptional, conformational noise and epigenetic changes) and non-cell-autonomous (tumor-stroma interaction) can amplify non-genetic heterogeneity in cancer.

Mathematical models to understand non-genetic heterogeneity

In 1957, Waddington proposed an epigenetic landscape model to explain how a pluripotent stem cell can differentiate into multiple lineages represented as valleys (Waddington, 1957) (**Fig 2A**). From a dynamical systems theory perspective, these valleys represent “attractors” in a high-dimensional landscape. These “attractors” correspond to stable gene expression patterns defining a phenotype, and for a given gene regulatory network (GRN), these “attractors” can be identified by simulating its emergent nonlinear dynamics (Ferrell, 2012; Jia et al., 2017; Wang et al., 2011). Many GRNs driving phenotypic plasticity are multistable in nature, i.e., they have multiple attractors. Thus, cells having these GRNs can acquire more than one phenotype, and can also switch among them under the influence of biological perturbations or noise (Li and Balazsi, 2018; Sahoo et al., 2020; Wooten and Quaranta, 2017) (**Fig 2B**). Considering the large number of genes in eukaryotes and their web of complex interactions, there can be many possible “attractors”, but the conditions imposed by underlying network topology can restrain the “solution space” to enable acquisition of only a few attractors. These conditions are akin to conditions imposed by energy minimization principles during protein folding, such that only a limited number of protein configurations are achieved, starting from a given amino acid sequence. Thus, cells can be postulated to traverse in a landscape where each “attractor” corresponds to stable phenotypes and has a specific basin of attraction (Agozzino et al., 2020). During cancer progression, various genomic changes may alter access to various cell types/attractors, thus modifying the underlying landscape (Huang et al., 2009).

Non-genetic heterogeneity in a clonal population indicates the presence of multiple stable states (or attractors) of the same GRN. Each attractor can have sub-attractors which make its surface rugged (Chang et al., 2008); in other words, each “macro-state” can have multiple “micro-states". Owing to various cell-intrinsic and cell-extrinsic factors underlying biological noise (Balázsi et al., 2011), stochastic perturbations may result into establishment of outlier or edge cells which are present near the borders of a given basin of attraction (Brock et al., 2009; Gopalan et al., 2021). Similarly, during metastasis, the presence of hybrid epithelial/mesenchymal (E/M) phenotype(s) can accelerate disease progression due to their enhanced ability to switch to more epithelial or more mesenchymal ones (Goetz et al., 2020; Jolly et al., 2018b; Ruscetti et al., 2016). Further, the presence of different subpopulations in multiple cancers in well established. For instance, using a Markov model of stochastic cell transition, it was shown that a subpopulation of cells will return to equilibrium phenotypic proportions with time, thus breast cancer stem cells arise from non-cancer stem like cells *de novo* highlighting the role of stochasticity in enabling phenotypic heterogeneity in a clonal cell population (Gupta et al., 2011). Another study in small cell lung cancer (SCLC) used Boolean modeling of underlying GRN to show that the network dynamics can stabilize neuro-endocrine/ epithelial (NE) or non-neuroendocrine/mesenchymal-like (ML) phenotypes which act as attractors. Additionally, they also found that when NE and ML cells are treated with cytotoxic drugs, these cells converged towards a hybrid state displaying surface markers of both NE and ML, possibly as a strategy to escape cytotoxic effects of the treatment (Udyavar et al., 2017).

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Similarly, in melanoma, identification and simulation of an underlying GRN enabled four different attractors which mapped to four distinct phenotypes reported experimentally – proliferative, neural crest-like, intermediate/transitory and undifferentiated (Pillai and Jolly, 2021; Rambow et al., 2018). This computational analysis could also recapitulate the cell-state transition trajectory observed experimentally upon treatment with vemurafenib through single-cell analysis (Su et al., 2019), offering a platform to identify novel perturbations that can enrich or deplete certain phenotypes.

Mathematical models have helped construct the landscapes of cell-state transitions associated with non-genetic heterogeneity in cancer, such as those for EMT, CSCs, metabolic reprogramming and drug resistance (Kang et al., 2019; Ling et al., 2021; Sahoo et al., 2021a; Sarkar et al., 2019). Particularly, in EMT, the concept of partial EMT, also referred as hybrid E/M phenotypes, has been largely championed by mathematical models decoding the emergent dynamics of highly inter-connected mutually inhibitory feedback loops involving miR-200/ZEB and miR-34/SNAIL (Lu et al., 2013; Tian et al., 2013). These models predicted that, contrary to previous assumptions, hybrid E/M states are not mere intermediates or 'metastable' states, instead stable phenotypes that cells can acquire. Further, such mechanistic mathematical models have made experimentally testable predictions about factors stabilizing hybrid E/M states. Validating those predictions *in vitro* led to identification of 'phenotypic stability factors' (PSFs) – GRHL2, OVOL1/2, NRF2, NUMB, NFATc among others (Biswas et al., 2019; Bocci et al., 2019b; Hong et al., 2015; Pastushenko and Blanpain, 2019; Subbalakshmi et al., 2020). Mathematical models have also elucidated the cell-state transition dynamics upon EMT induction, identifying multiple "micro-states" and/or hybrid E/M phenotypes that cells acquire *en route* to EMT in a dose- and/or time-dependent manner (Celià-Terrassa et al., 2018; Deshmukh et al., 2021; Font-Clos et al., 2018; Sha et al., 2020; Steinway et al., 2015; Zhang et al., 2014). Predictions made by mathematical models for coupled EMT-stemness networks (Jolly et al., 2014) about high tumor-initiating potential of hybrid E/M phenotypes have also been recently validated *in vitro* and *in vivo* (Bierie et al., 2017; Kröger et al., 2019; Pastushenko et al., 2018). For instance, the presence of hybrid E/M cells was associated with worst survival in breast cancer patients and enriched for stem-like cells in different types of breast cancer cell lines with properties such as increased mammosphere formation and higher ALDH1 levels (Grosse-Wilde et al., 2015). Another insight gained by mathematical models of EMT has been that various positive feedback loops in a GRN drives plasticity among epithelial, mesenchymal or hybrid E/M phenotypes (Hari et al., 2020). Indeed, breast cancer cells with the miR-200/ZEB positive feedback loop perturbed via CRISPR had reduced metastatic potential *in vivo* (Celià-Terrassa et al., 2018), suggesting that mathematical models can not only elucidate the dynamical principles of non-genetic heterogeneity and cell-fate transitions in cancer, but also pinpoint specific therapeutic vulnerabilities to be tested.

The functional role of feedback loops and gene expression noise in enabling drug resistance was recently investigated using synthetic gene network circuits to deconvolute noise from the mean expression of puromycin resistance gene with inducible positive and negative feedback loops in Chinese Hamster Ovary cells. This study demonstrated that greater noise emerging from positive feedback loop increased drug resistance at higher concentration of puromycin but at lower drug concentration, it delayed long-term adaptation. Further, a positive correlation between low noise as a result of negative feedback circuits and mutational adaptation driving stable drug resistance was observed (Farquhar et al., 2019). The crosstalk of various positive and negative feedback loops in a cell can therefore influence its sensitivity to various chemotherapeutic assaults, leading to fractional killing (Miura et al., 2018; Paek et al., 2016; Spencer et al., 2009). Such non-genetic heterogeneity in a clonal cell population, upon the influence of drug-induced reprogramming, can lead to rare and stably resistant subpopulation of cells (Shaffer et al., 2017). Population dynamics models capturing such reversible (non-genetic) and/or stable (genetic) resistance scenarios can

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suggest combinatorial and/or sequential therapeutic strategies to prevent or delay the emergence of tumor (re) growth (Cassidy et al., 2021; Gunnarssson et al., 2020; Sahoo et al., 2021a).

Conclusion

Non-genetic heterogeneity can confer fitness advantage to a clonal population of cancer cells during metastasis, acquisition of therapy resistance and tumor progression. Such heterogeneity can arise from various sources of biological noise within a cell as well as due to multistable dynamics of various underlying networks. Integrated and iterative mathematical-experimental approaches have been instrumental in identifying the sources and implications of non-genetic heterogeneity in cancer. Developing therapeutic strategies which can target the sources of such heterogeneity in isogenic cancer cells may result in higher efficacy in preventing metastasis and tumor progression.

Figures

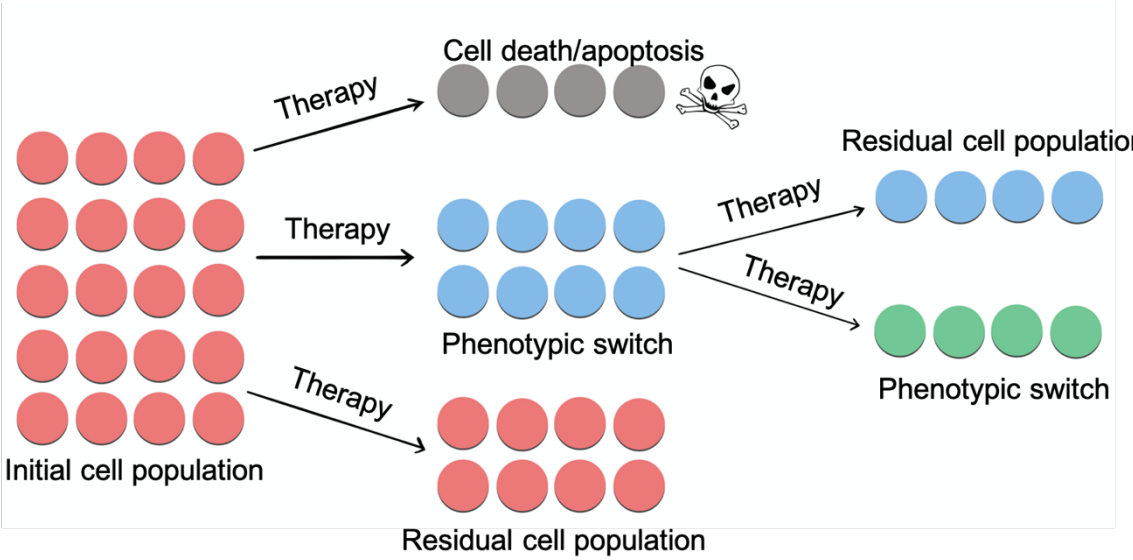

Fig 1: Non-genetic heterogeneity in a cell population and its impact on therapeutic efficacy. *Upon exposure to a given therapy, a majority of cancer cells die (fractional killing), but a few of them can survive either due to pre-existing mutations or due to non-genetic adaptations such as a phenotypic switch. Application of another therapy may lead to further phenotypic diversification.*

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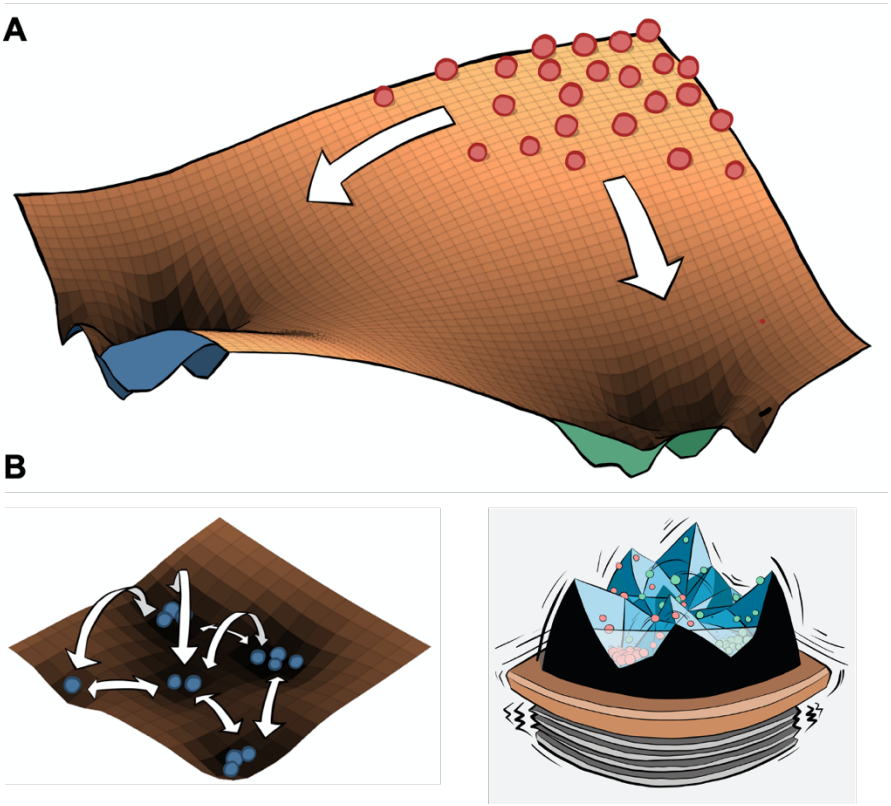

Fig 2: Waddington landscape and phenotypic plasticity. *A) Schematic of the Waddington's landscape showing multiple different paths that the cells can take during embryonic development (each ball represents a differentiating cell, each valley represents a phenotype). B) (left) In case of multistability, cells can switch back and forth among various phenotypes (valleys). (right) Biological noise due to various sources (transcriptional, conformational etc.) can drive phenotypic plasticity.*

Conflict of Interest

The authors declare no conflict of interest.

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Author contributions

MKJ conceived and supervised the article. All authors contributed to writing and editing the article.

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