The Causes and Consequences of Genetic Heterogeneity in Cancer Evolution

Burrell et al.

Nature,2013

S.Pavitra

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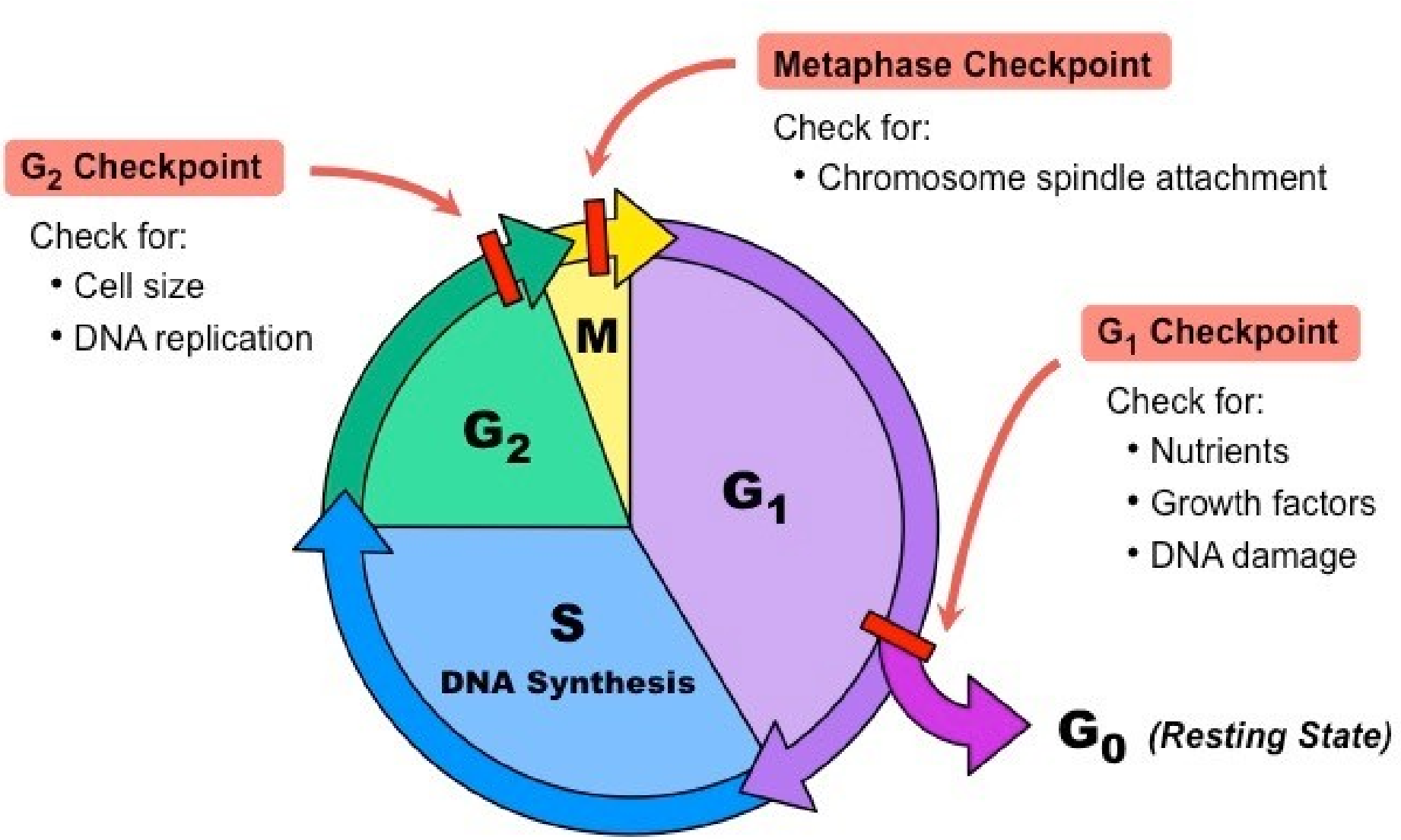
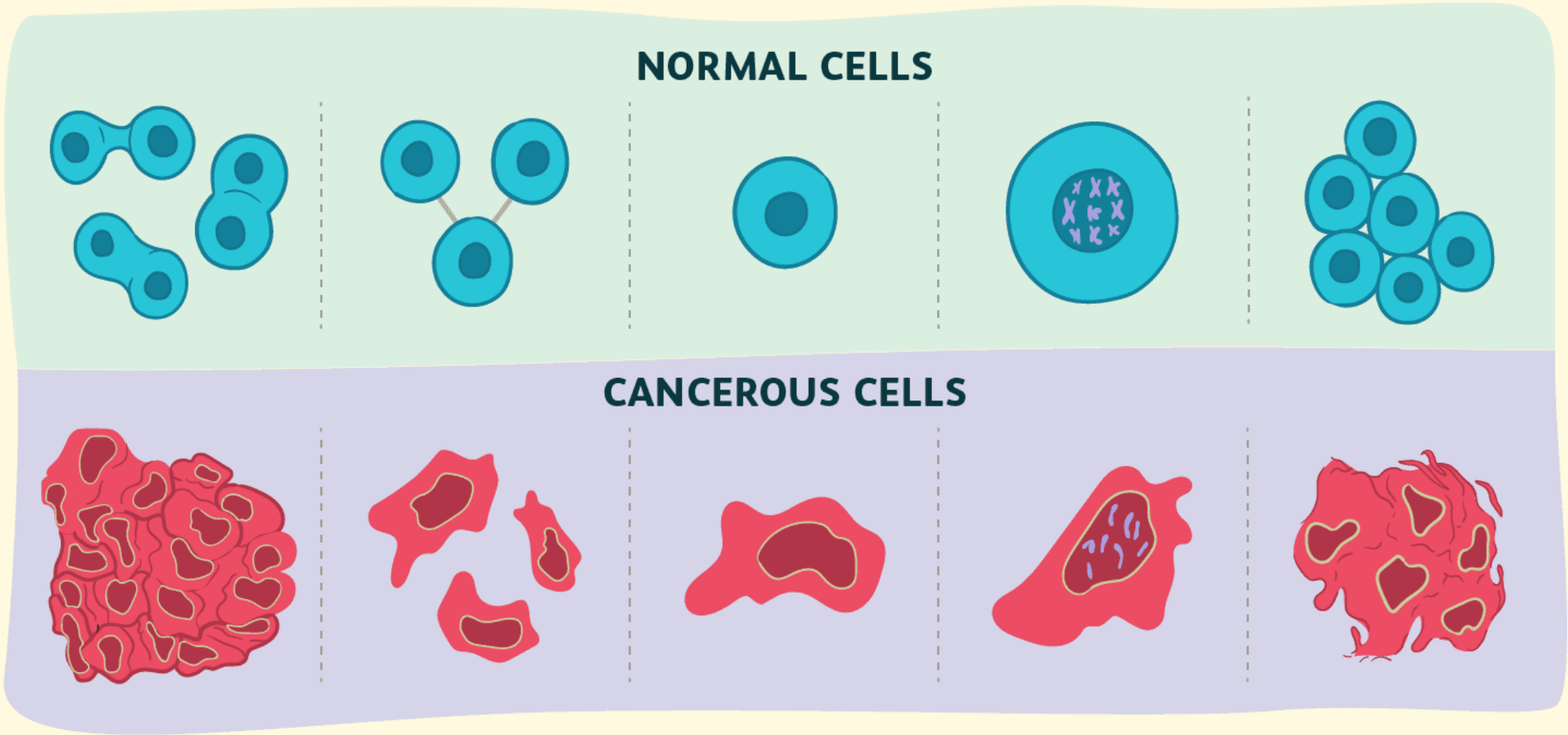
Cell Cycle

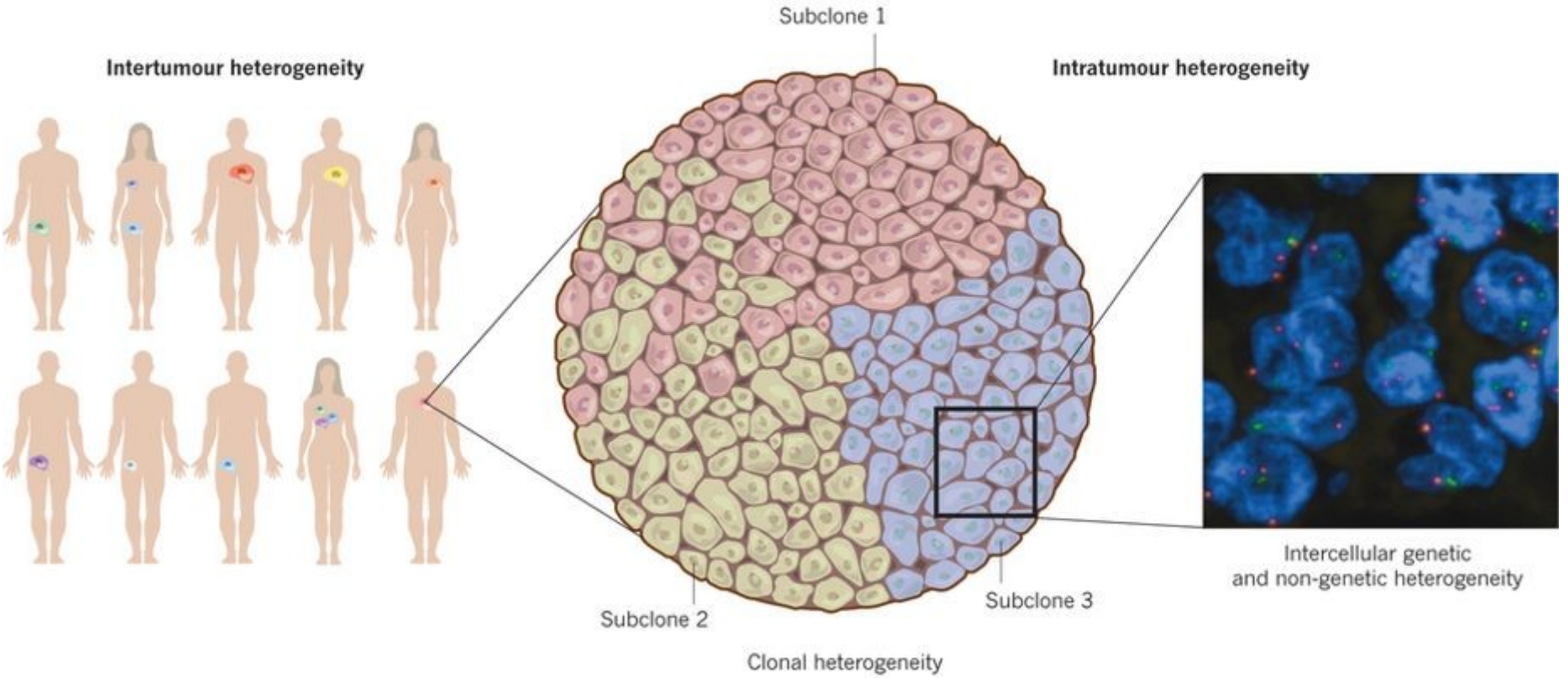


https://ib.bioninja.com.au/standard-level/topic-1-cell-biology/16-cell-division/cell-checkpoints.html



https://www.verywellhealth.com/cancer-cells-vs-normal-cells-2248794

Inter / Intra Tumor Heterogeneity



Why changes across tumors?

- genetic events of transformation interact with cell-intrinsic biological properties
- Distinct signalling pathways
- within a cohort of tumours, the same gene may be affected by point mutation, DNA methylation, copy number alteration, or a combination of the three

Intratumour heterogeneity and tumour evolution

- Diversity of expression of protein biomarkers
- Intercellular genetic variation,
- followed by selective outgrowth of clones that have a phenotypic advantage within a given tumour micro-environmental context
- Linear Evolution: clonal sweep by a domina t subclone
- Branched Evolution: subclones evolve in parallel

  genetically heterogeneous subclonal lineages in solid tumours could also be maintained by distinct stem cells

- At metastatic sites: new microenvironment

- the subclones occupying each niche evolve relatively independently of one another

- intermingled heterogeneous clones are observed within single biopsies.

- This intercellular heterogeneity increases **phenotypic variation**, broadening the pool of cells that are subject to **selection**, and therefore the likelihood of selective expansion of multiple different sub clones and the **emergence** of a complex subclonal tumour architecture

Genomic Instability

- a prominent source of genetic diversity within tumours
- Cells are subject to selection in a given micro-environmental
- can arise through various routes, leaving distinct genomic footprints and differentially affecting tumour evolution

Genomic Instability and Tumor Evolution

- In normal cells,genome is replicated and divided with high fidelity.
- Most solid tumours and haematopoietic malignancies display at least one form of genomic instability
- Genome instability provides benefit to tumor evolution.
- leads to tumour regrowth after oncogene withdrawal.
- promotes loss of heterozygosity of tumour suppressor genes

Genomic feature	Description	Possible mechanisms
Whole-genome duplication	Duplication of the entire DNA complement	Cell fusions, cytokinesis failure, metaphase or anaphase defects, or endoreduplication[72]
Chromosomal loss and gain	Loss and gain of whole chromosomes and segments of chromosomes	Mitotic defects: abnormal spindle geometry[75,78,79], centriole amplification[75,78], mitotic checkpoint defects[73,74] or hyperstable microtubules[76,77] Pre-mitotic defects: cohesin mutations[118], DNA replication stress[27,28,82,87], DNA damage repair defects[81] or telomere dysfunction[80,95]
Chromothripsis	Extensive genomic rearrangements involving one or more chromosomes	Ionizing radiation, micronucleus fragmentation or replication defects[86,94,119]
Translocations	Chromosomal rearrangements resulting in fusion of two chromosome arms	Non-homologous end joining, aberrant lymphocyte DNA recombination mechanisms and cytokinesis-induced DNA damage[84,85,120]
Tandem duplications	Sequential copies of a genomic segment that often spans several genes	Unknown[121,122]
Loss of heterozygosity at fragile sites	Copy number imbalance or gene conversion at genomic loci that are particularly sensitive to replication stress	DNA replication stress[27,82]
Focal deletions	Deletion of less than 5 megabases	Chromosome breakage or DNA replication stress[82]
Focal amplification	Amplification less than 5 megabases	Double minute chromosomes generated through chromosome breakage[123]
Hypermutation	Elevated mutation rate, leading to abundance of somatic mutations	DNA mismatch repair defects[68], *BRCA2* mutations[70] and proofreading defects[67]
Kataegis	Localized hypermutation	AID/APOBEC activity[61]
C·G>T·A transitions	Base changes	Ultraviolet radiation-damage[63], alkylating agents[7] and spontaneous deamination of methylated cytosines[50]
C·G>A·T transversions	Base changes	Base excision repair defects[64], tobacco-related DNA damage[22] and cytotoxic chemotherapy[6]

Mechanisms of genomic instability

- Different mechanisms of instability can lead to particular distributions of point mutations
- replication stress is associated with an enrichment of mutations in large genes
- microsatellite instability may affect specific genes more frequently than others owing to the nucleotide composition of those genes
- Highly localized clusters of mutations that are associated with chromosomal rearrangement, known as kataegis, may be caused by the action of the a family of cytidine deaminases in breast cancer

Variation in genomic instability over time

- In a study of clear-cell renal carcinoma:chromosomally unstable metastases arise from a tetraploid subclone in the primary tumour
- In a study of breast cancer, researchers made use of variant allele frequencies and copy number events that were derived from whole-genome sequencing reads to dissect the temporal sequence of mutations
- temporally separated biopsies may give strikingly different pictures of a tumour's genomic landscape

Questions and Directions

- how heterogeneity affects tumour progression
- examine in greater depth the relationship between the rate of instability and the complexity of subclonal architectures
- approaches to limit cancer diversity, adaptation and drug resistance

Thank You.