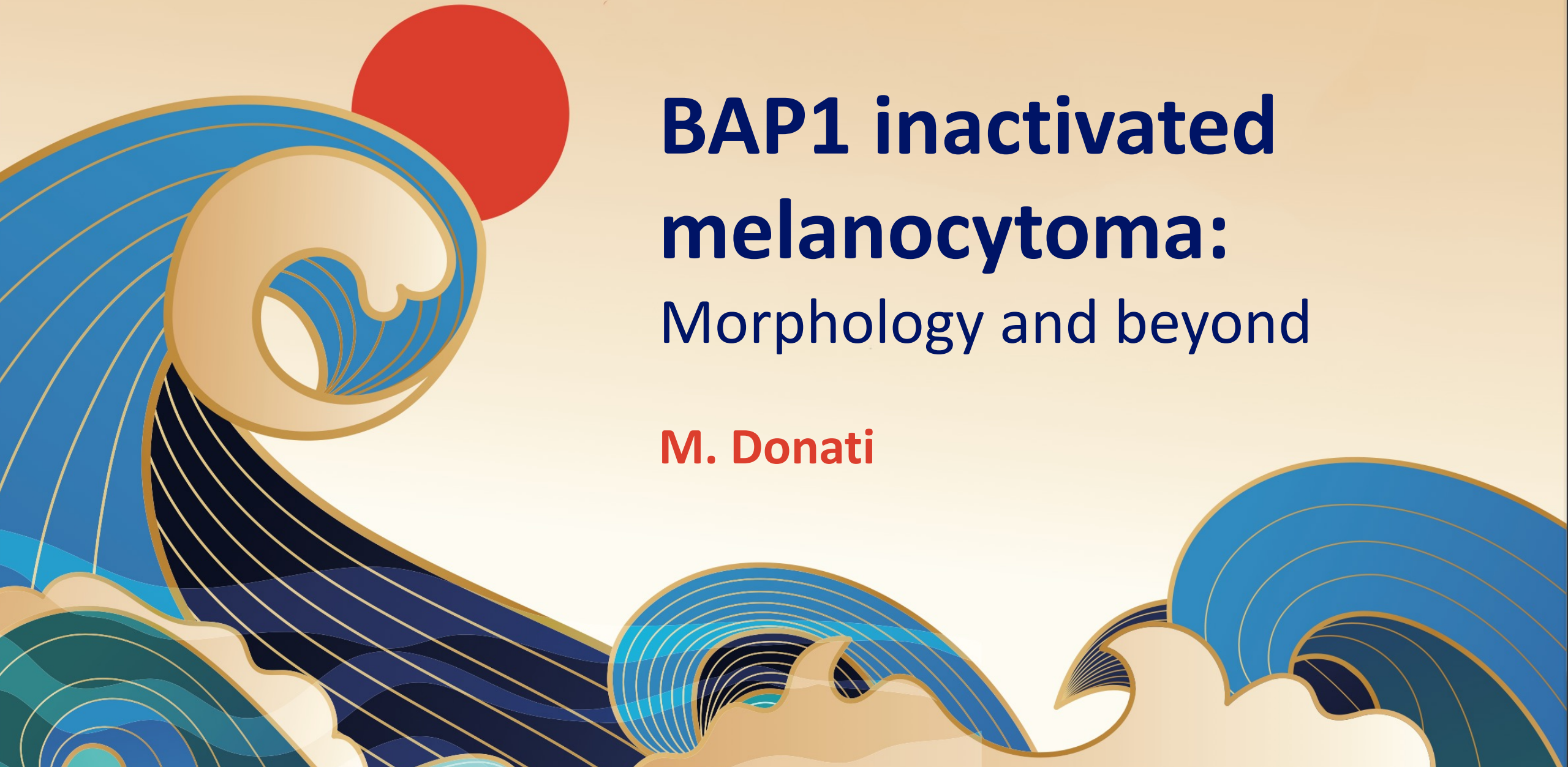


BAP1 inactivated melanocytoma:

Morphology and beyond

M. Donati

Pathology - Research and Practice 259 (2024) 155162

Contents lists available at ScienceDirect

Pathology - Research and Practice

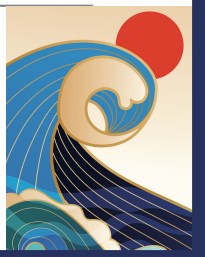
journal homepage: www.elsevier.com/locate/prp

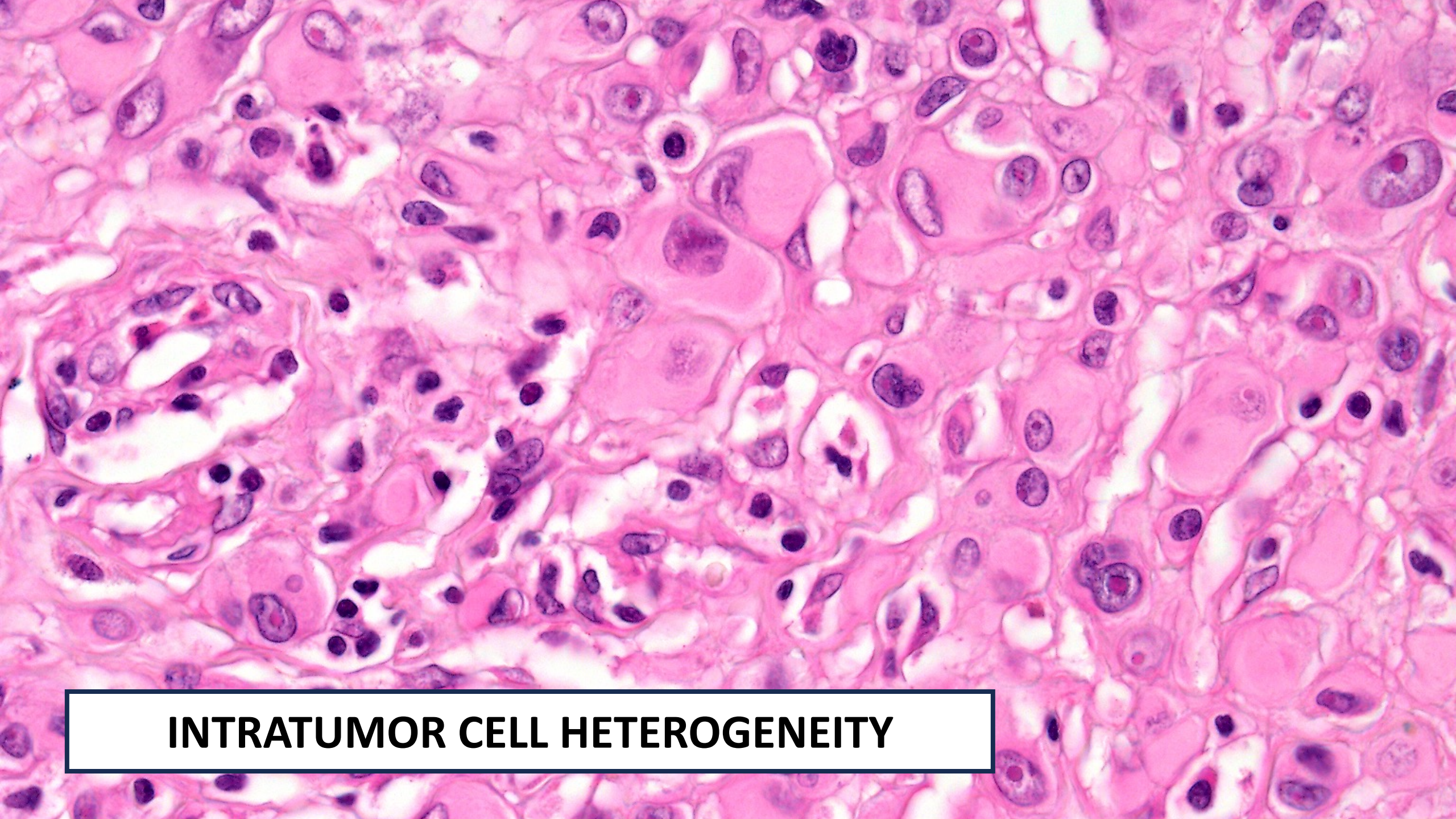
Review

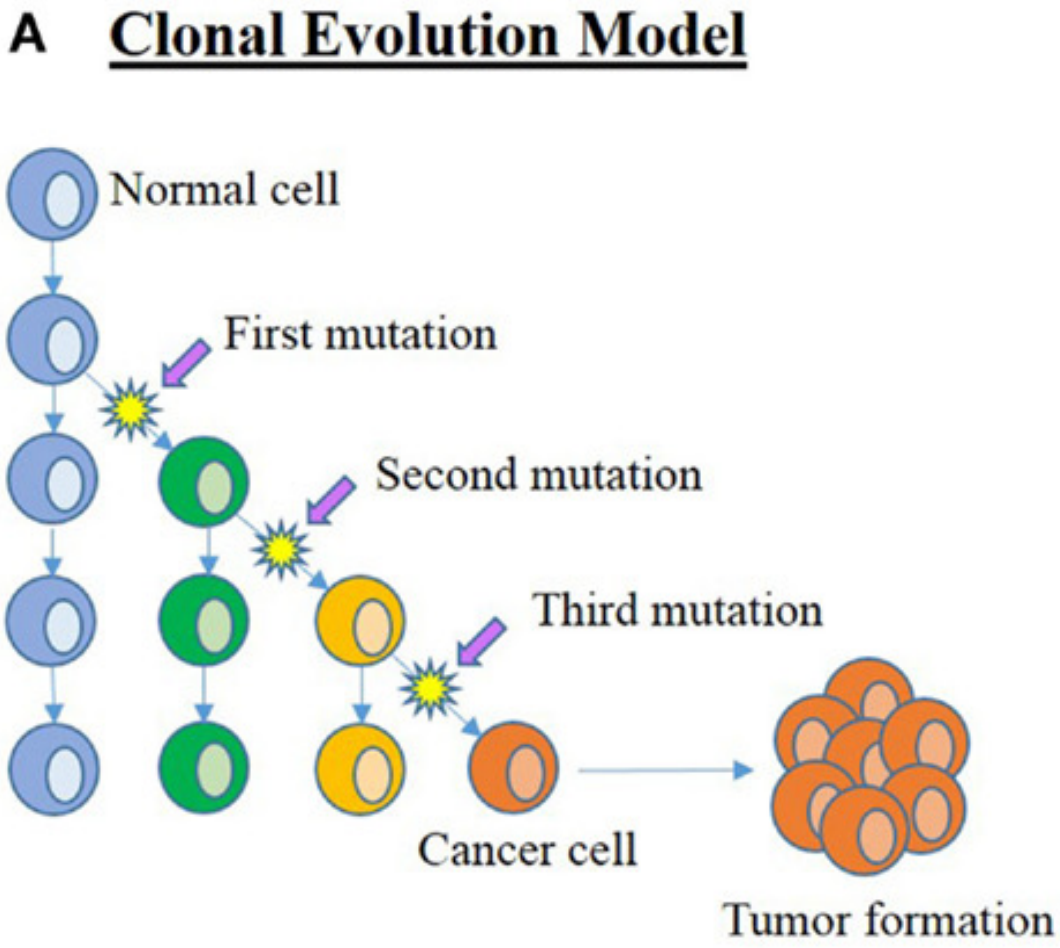
Beyond typical histology of *BAP1*-inactivated melanocytoma☆

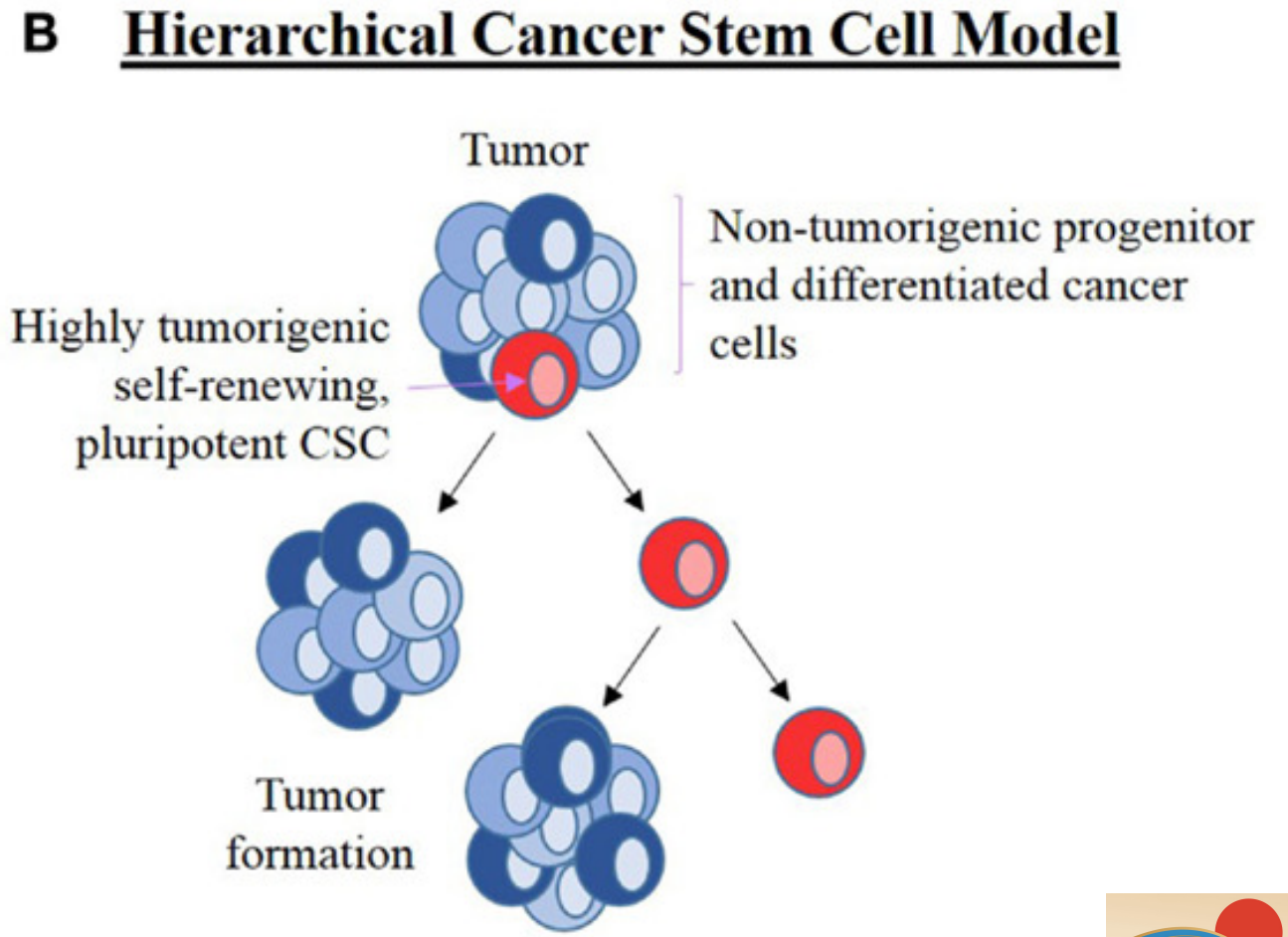
Michele Donati [a,b,*], Dmitry V. Kazakov [c]

[a] *Department of Pathology, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy*
[b] *Department of Pathology, Università Campus Bio-Medico di Roma, Via Alvaro del Portillo, 21 - 00128 Roma, Italy*
[c] *IDP Dermatohistopathologie Institut, Pathologie Institut Enge, Zurich, Switzerland*

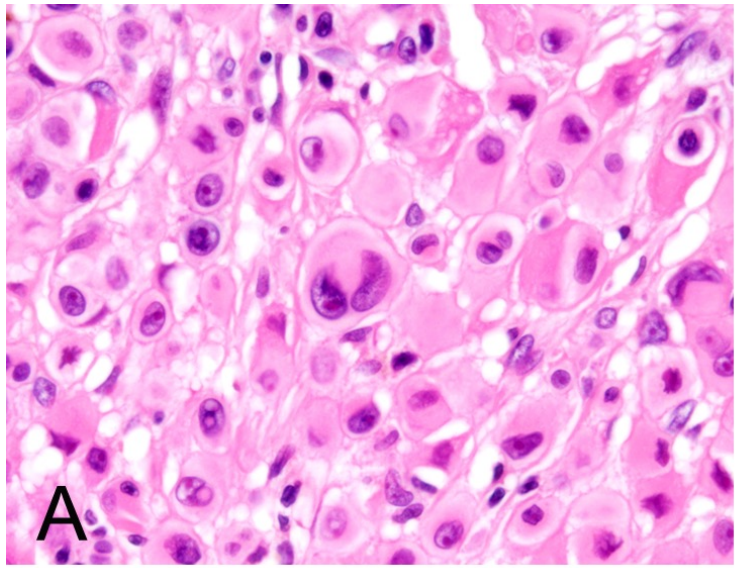


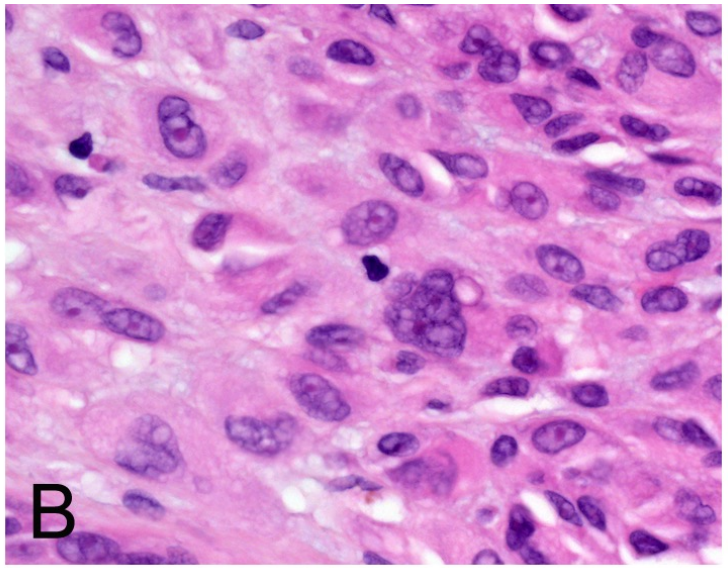

INTRATUMOR CELL HETEROGENEITY

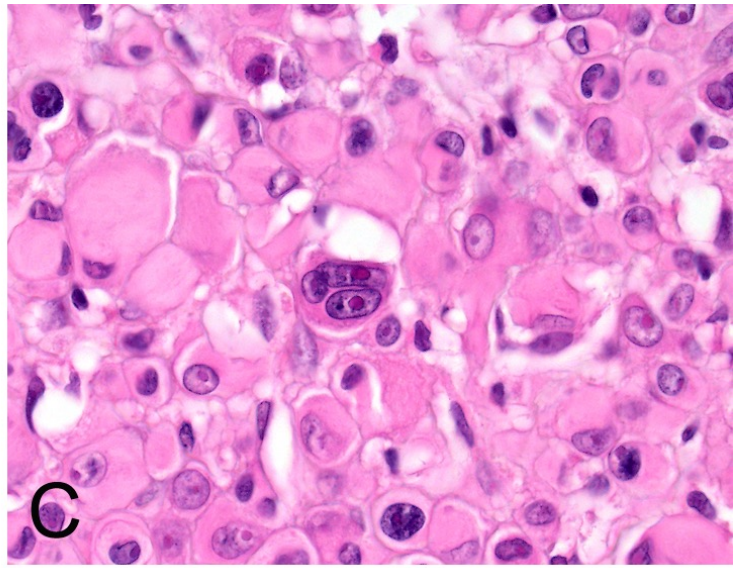

A Clonal Evolution Model
Normal cell
First mutation
Second mutation
Third mutation
Cancer cell
Tumor formation

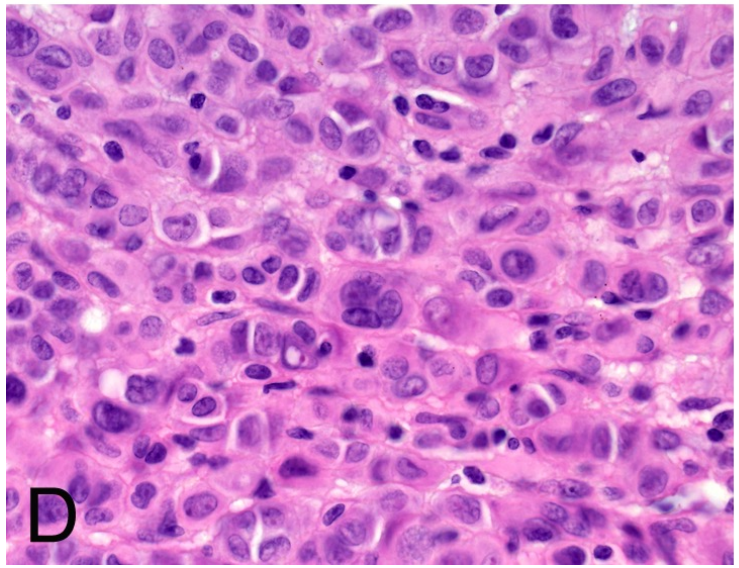

B Hierarchical Cancer Stem Cell Model
Tumor
Non-tumorigenic progenitor and differentiated cancer cells
Highly tumorigenic self-renewing, pluripotent CSC
Tumor formation

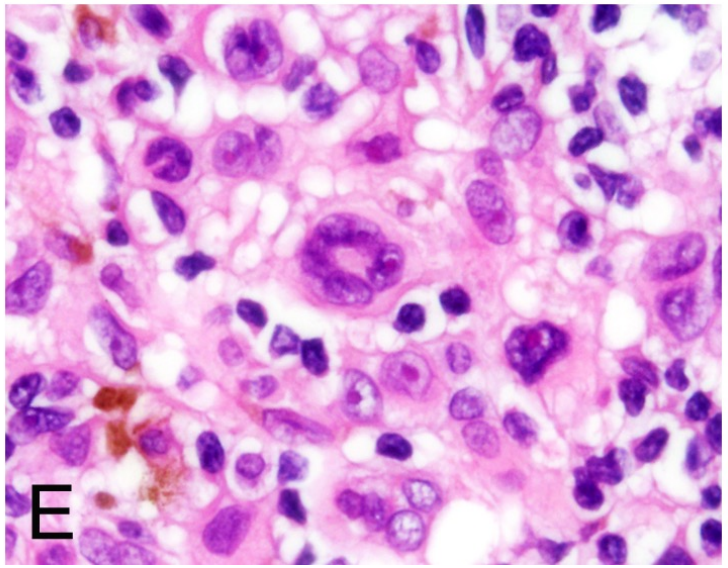
Multinucleation

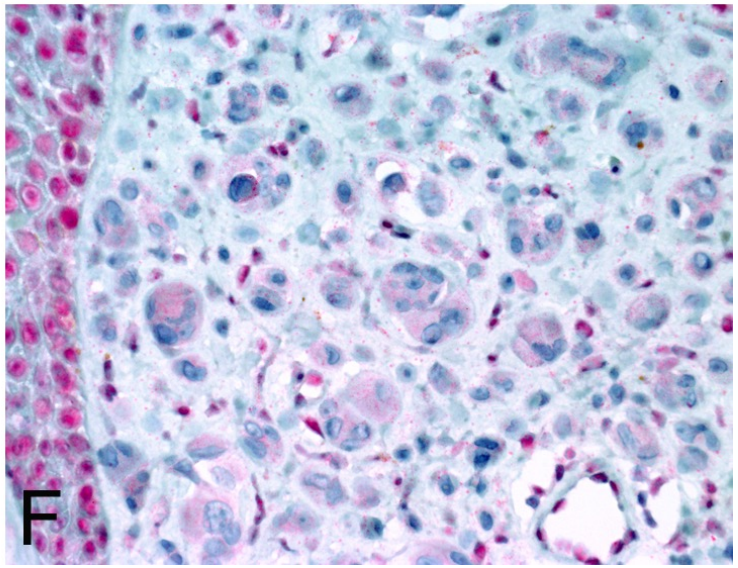








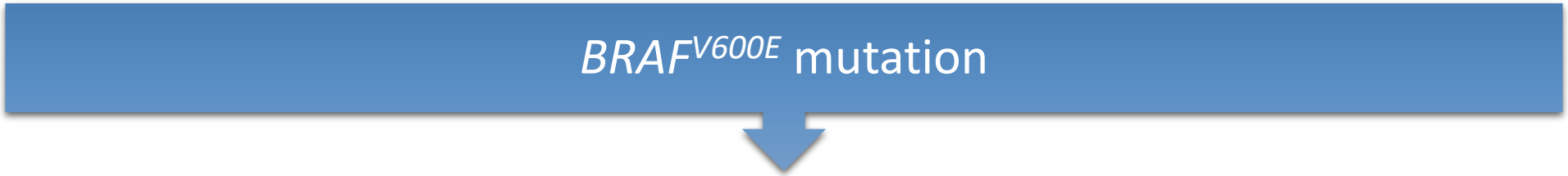




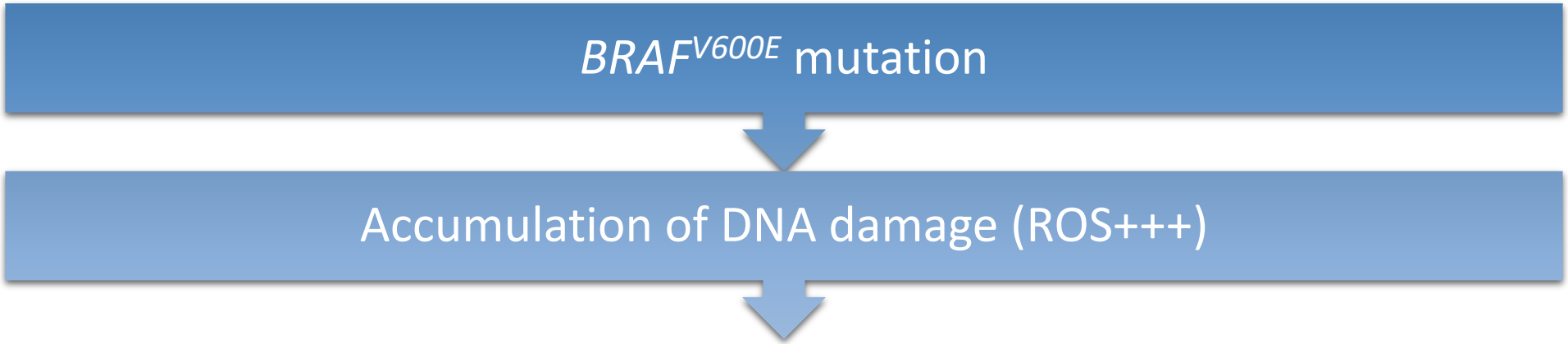
Where do multinucleated melanocytes come from and what do they mean?

Senescence and multinucleation

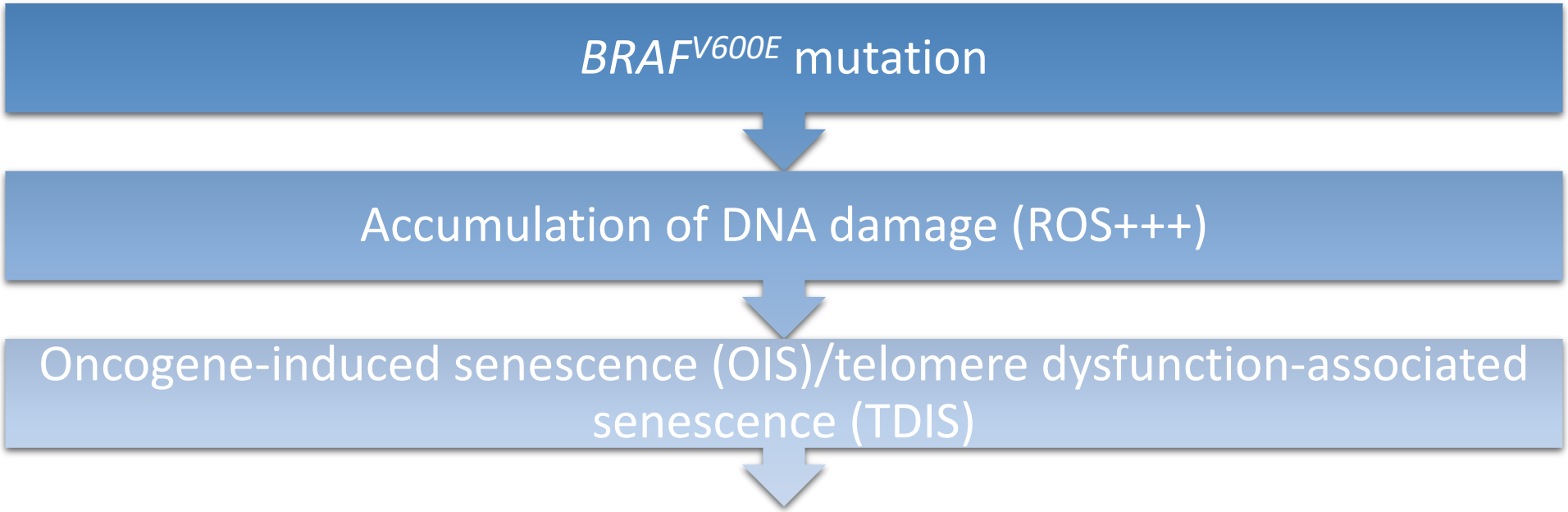
Senescence and multinucleation



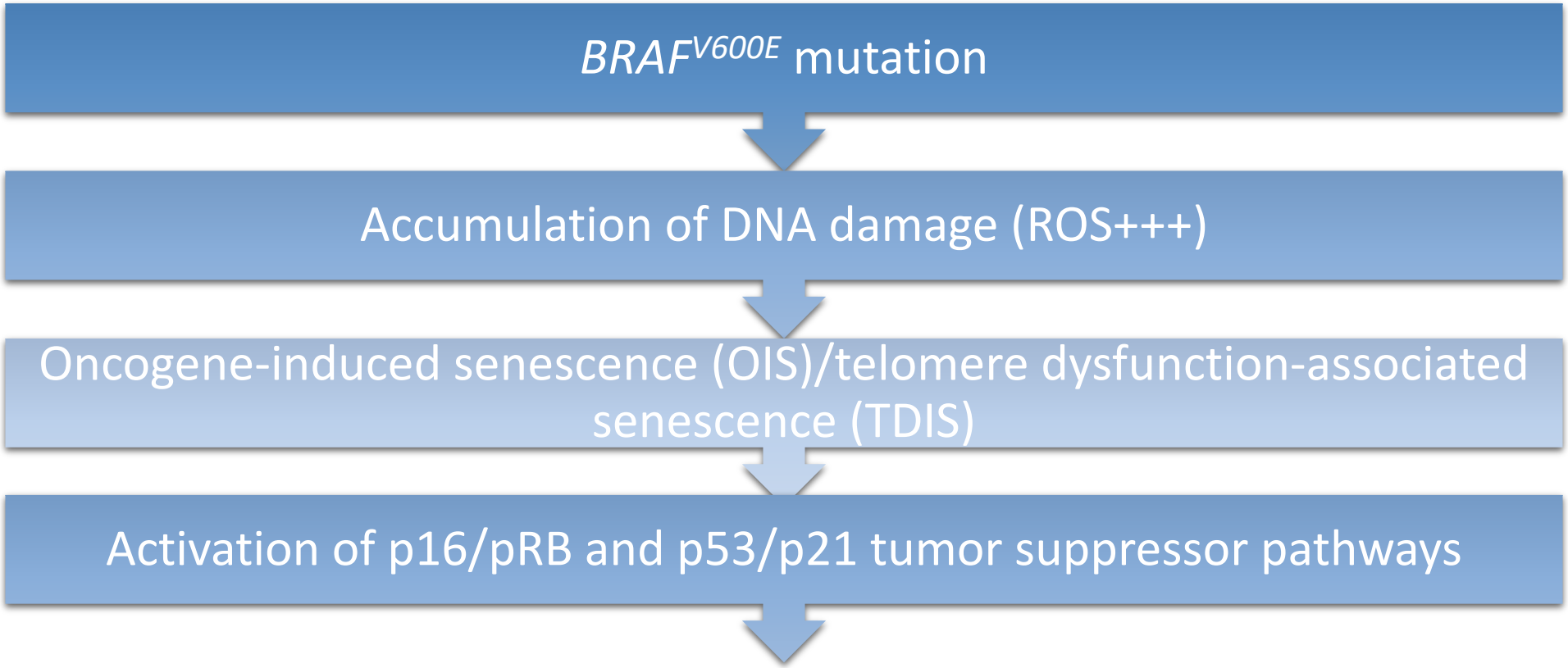
Senescence and multinucleation



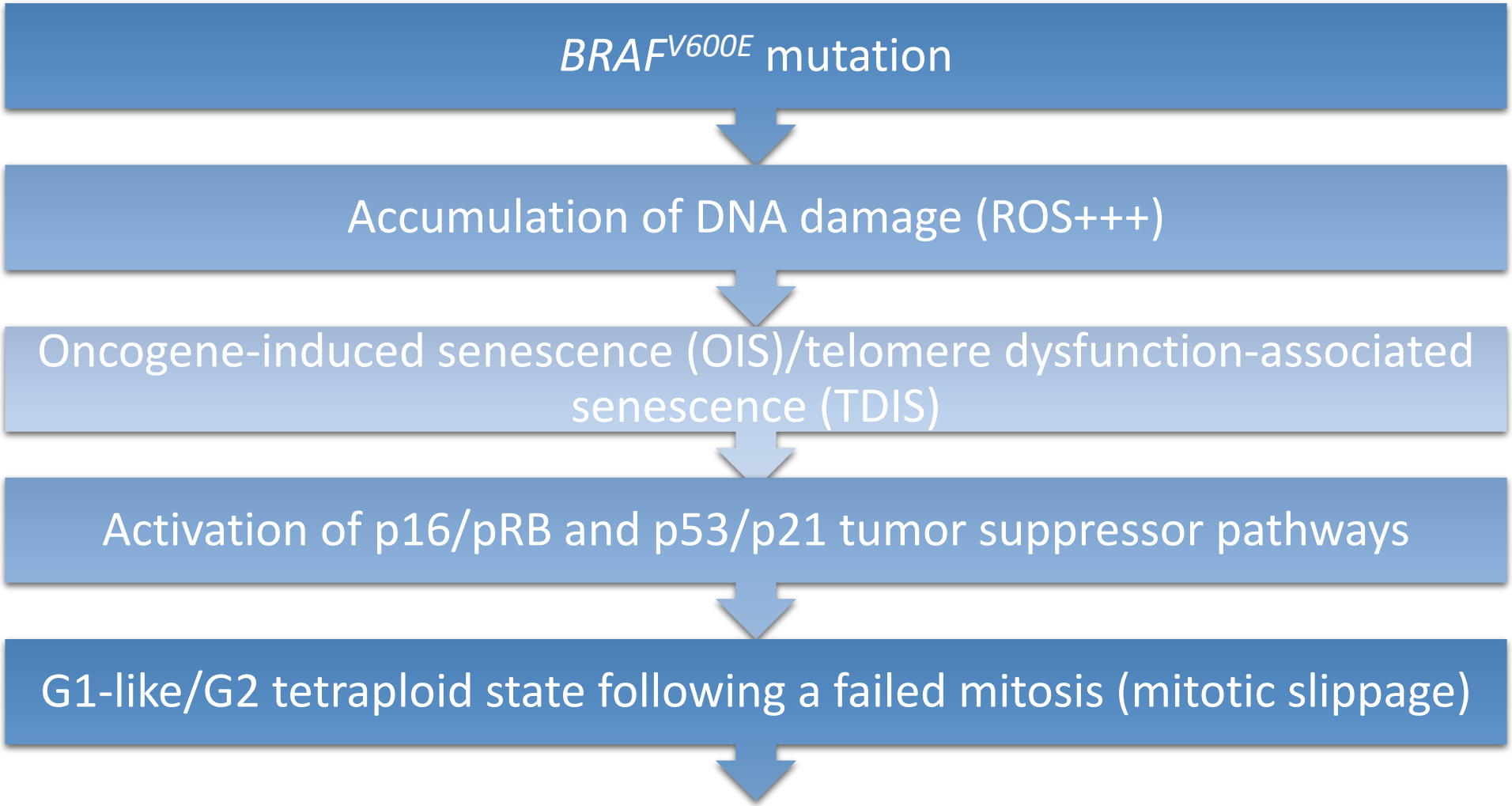
Senescence and multinucleation



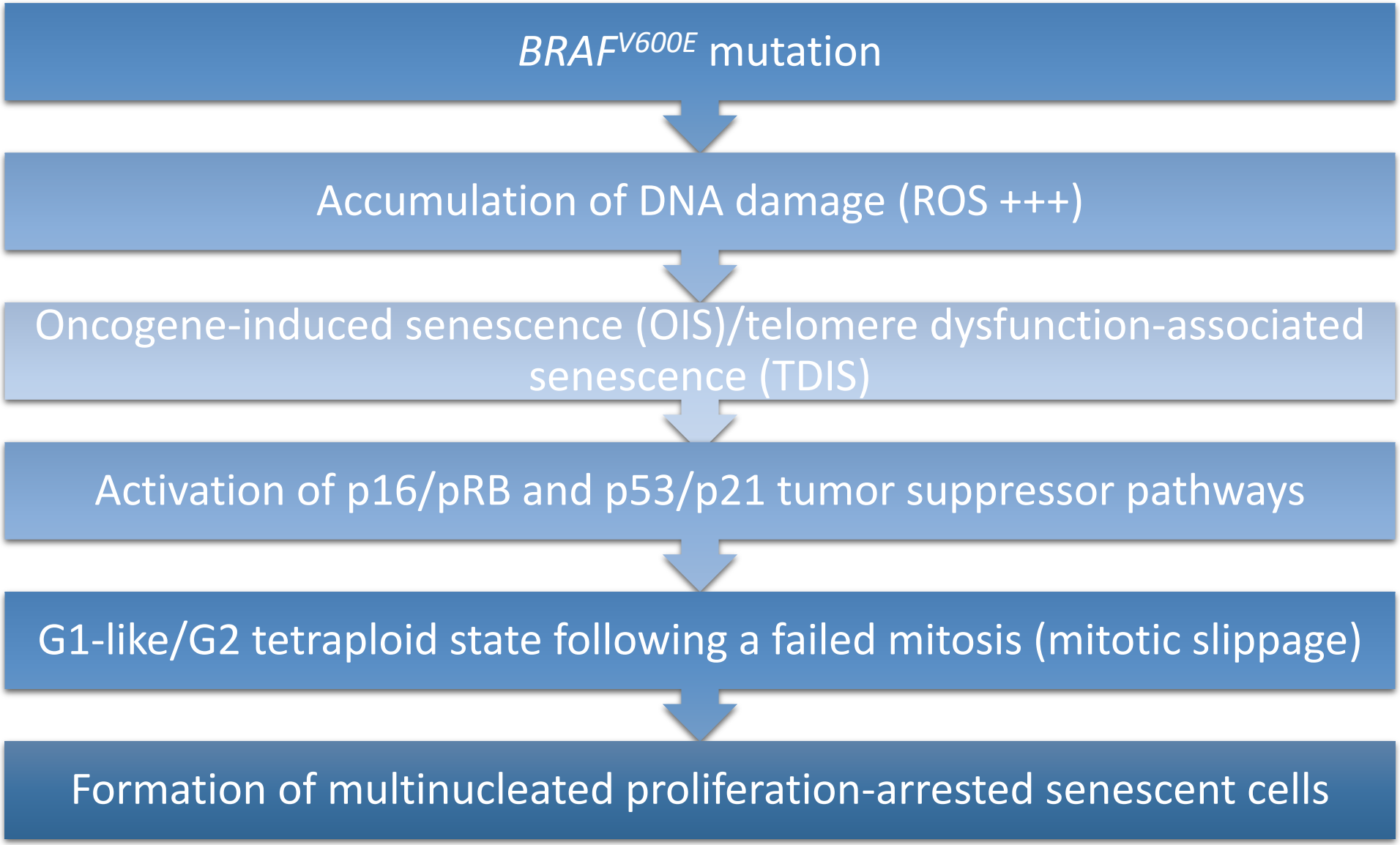
Senescence and multinucleation



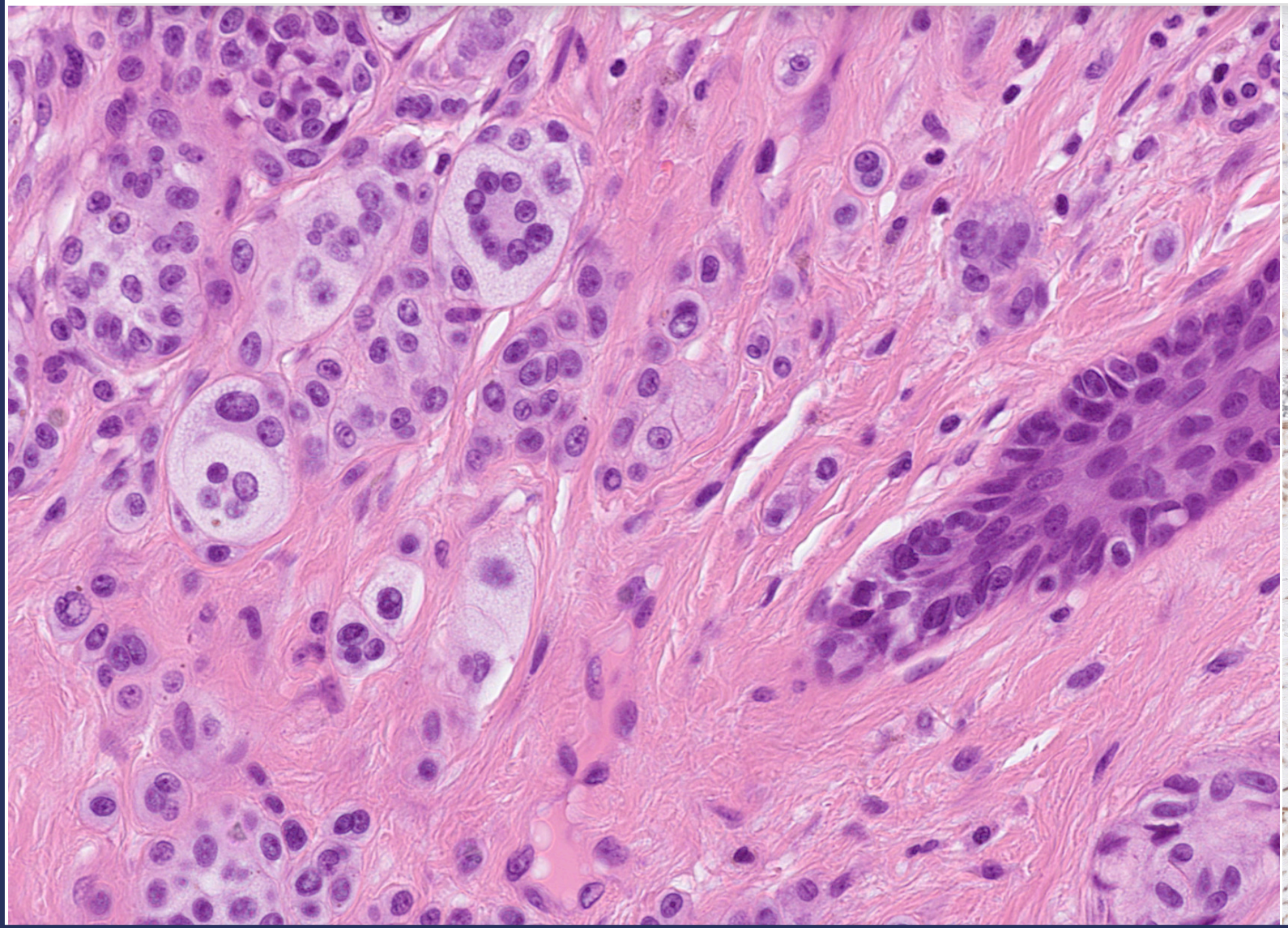
Senescence and multinucleation

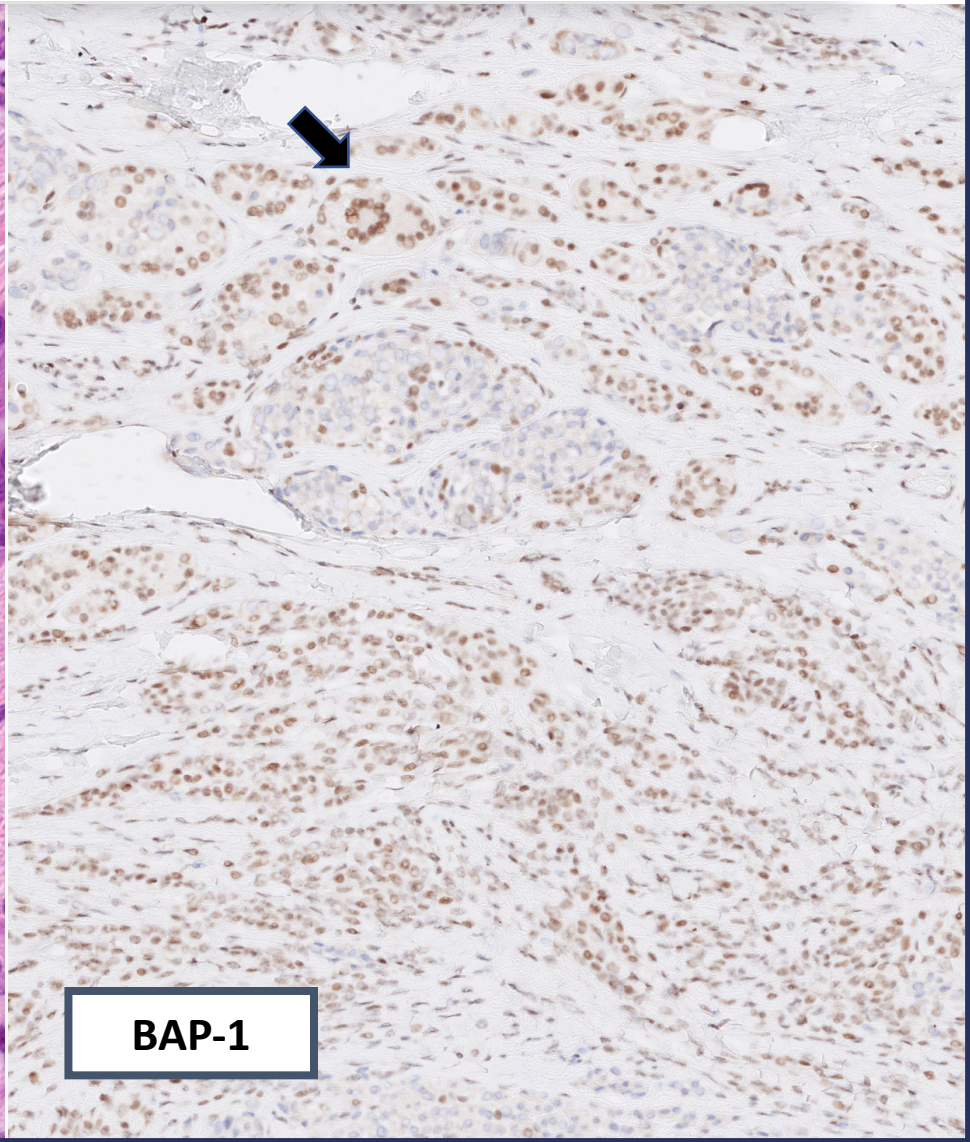


Senescence and multinucleation

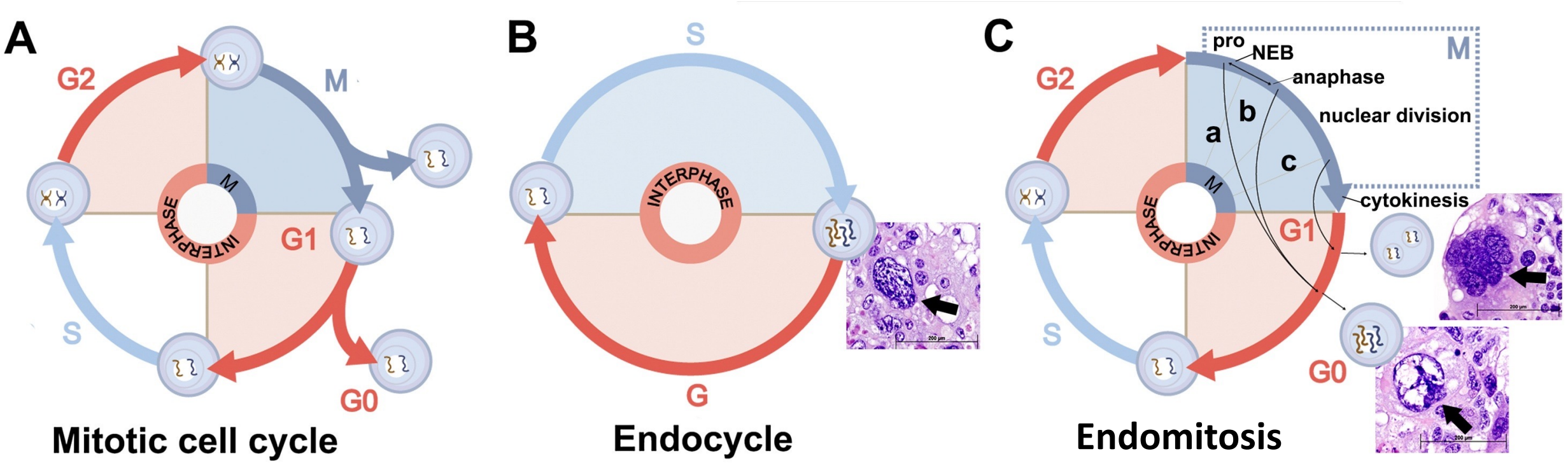


Multinucleated melanocytes in conventional nevus



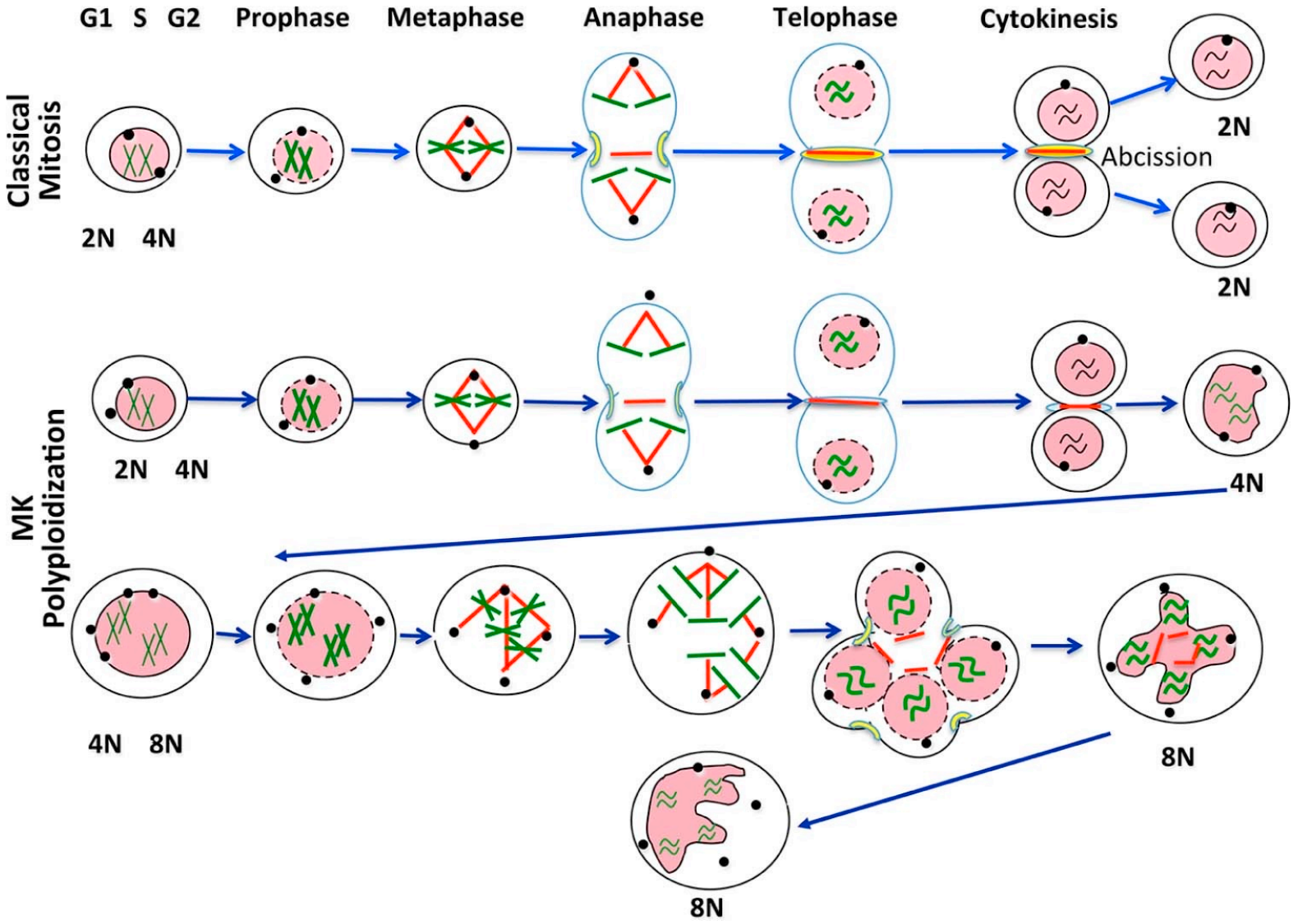


Endoreplication cell cycle



Zhang J, et al. Seminars in Cancer Biology, Volume 81, 2022, Pages 54-63, ISSN 1044-579X, https://doi.org/10.1016/j.semcancer.2021.04.005.

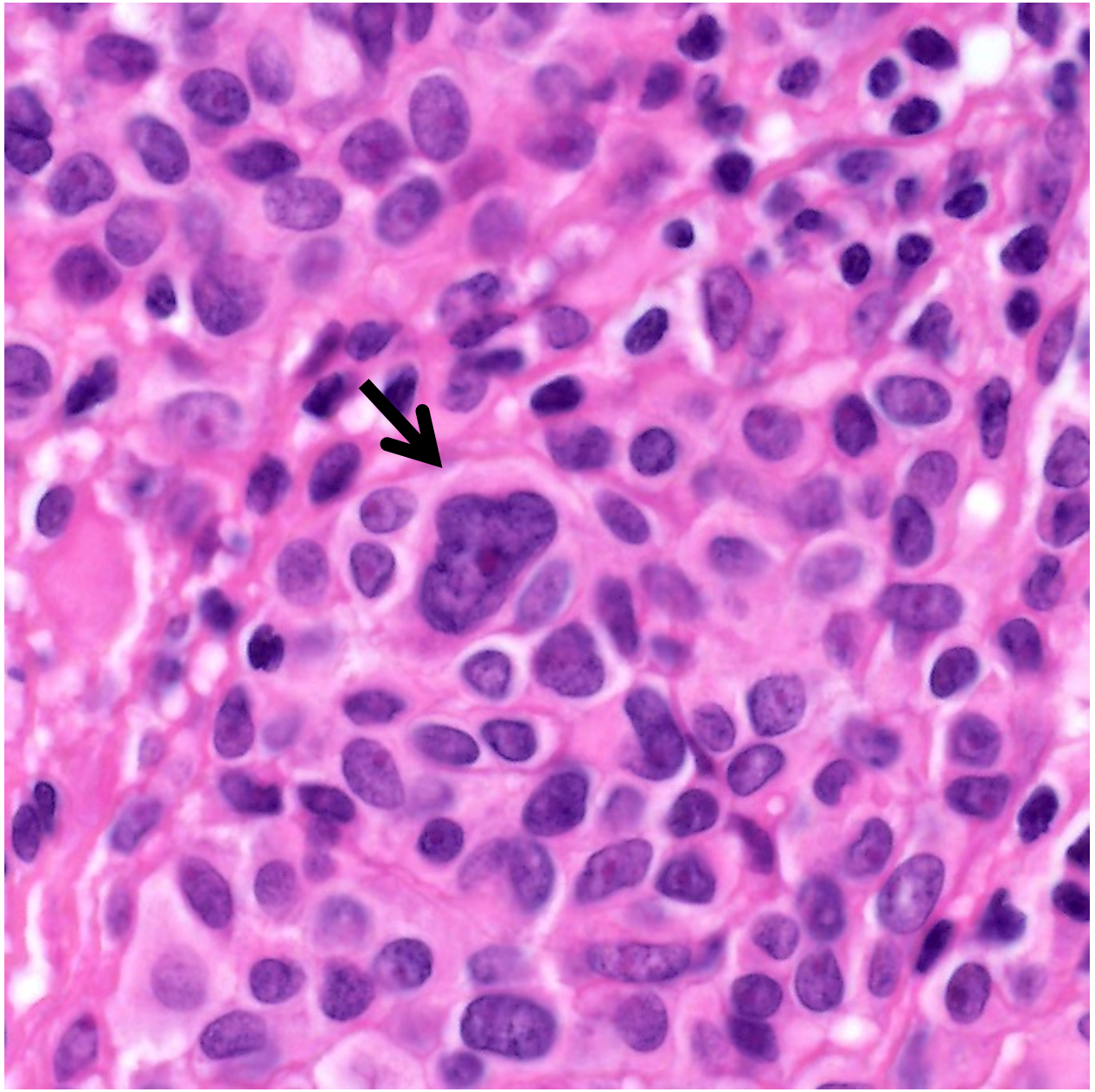
Endoreplication in human megakaryocytes



Senescence-related features

Table 2
Selected histological features in 50 *BAP1*-inactivated melanocytomas.

Histological features	Cases (%)
Nuclear blebbing	49 (98%)
Nuclear budding	49 (98%)
Micronuclei	40 (80%)
Multinucleated cells	49 (98%)
Cytoplamic vacuolization	35 (70%)
Nuclear pseudoinclusions	28 (56%)



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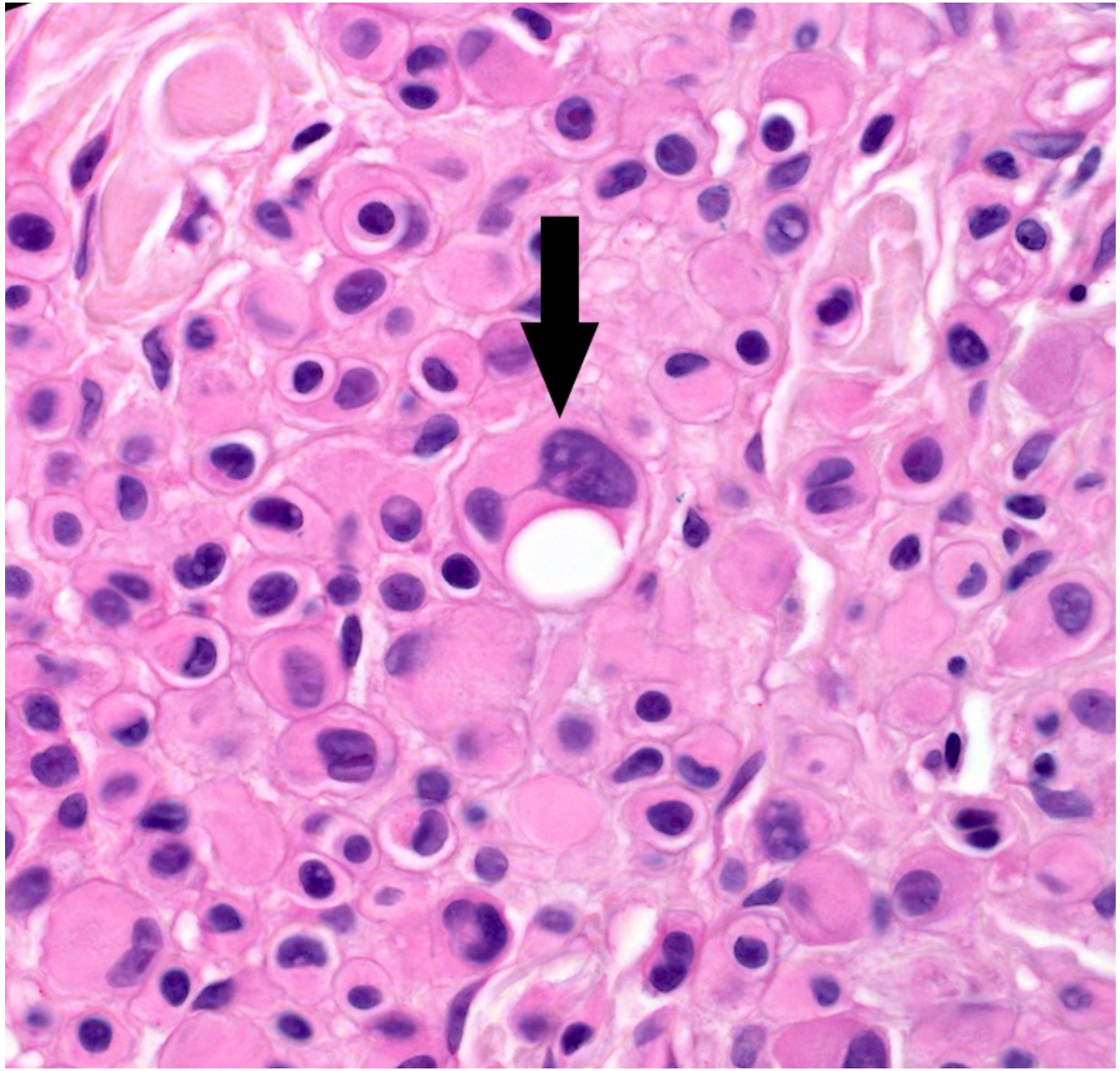

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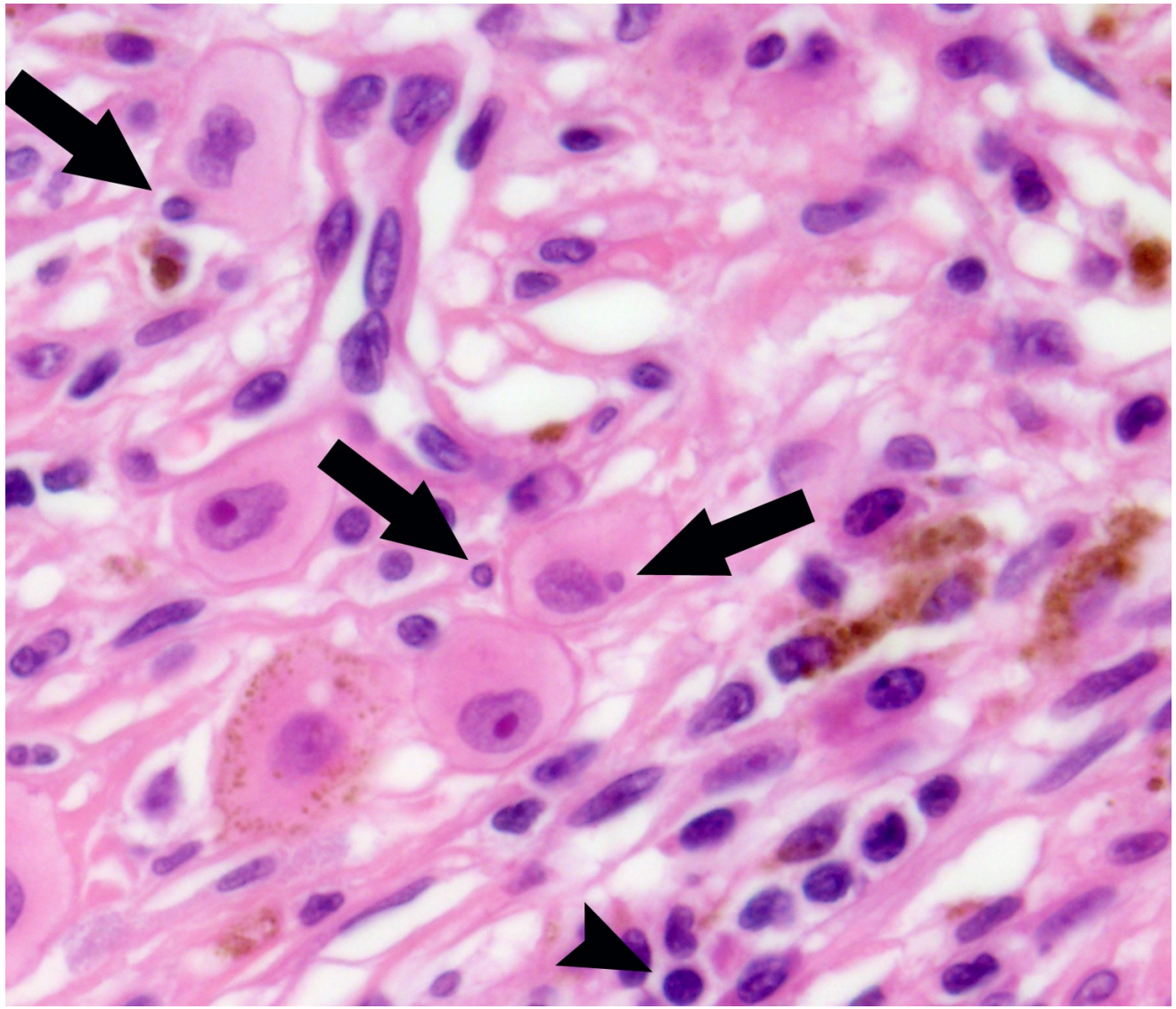

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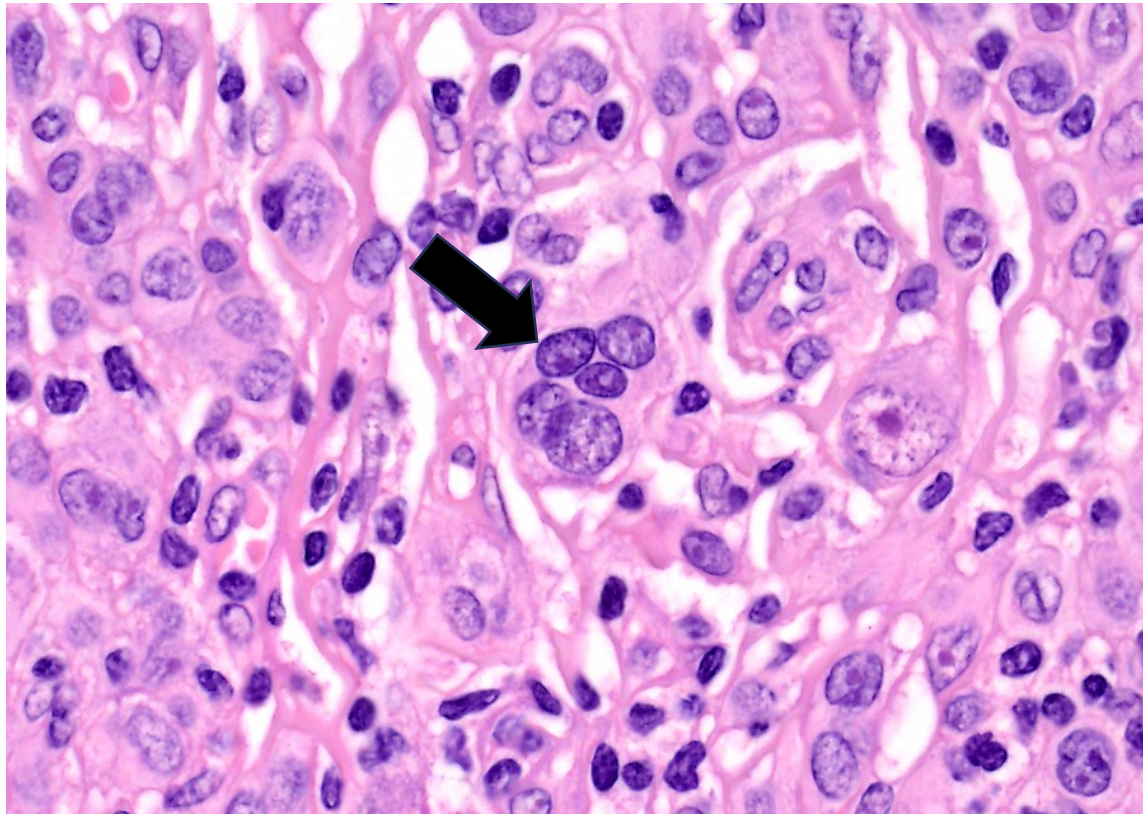

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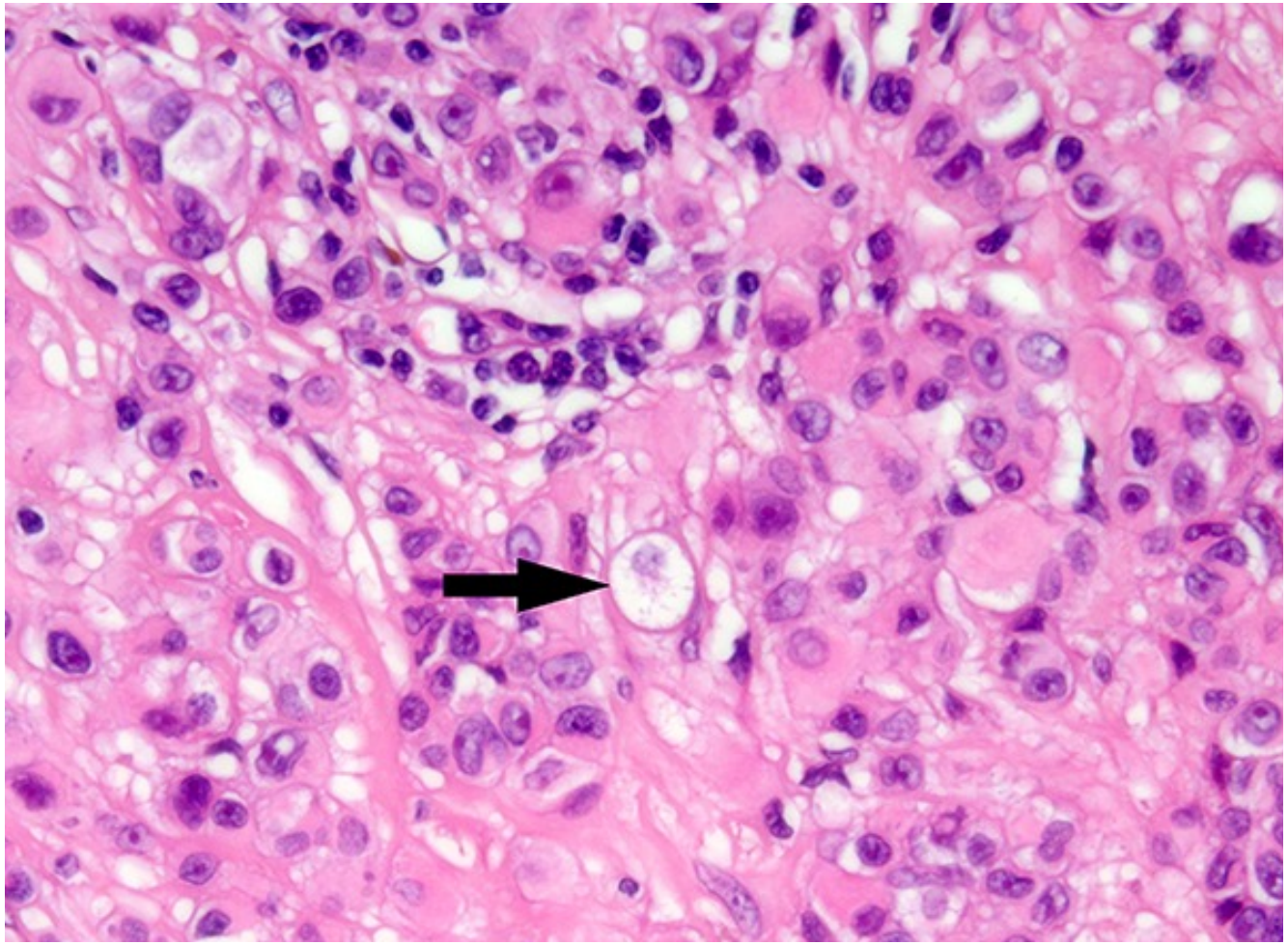
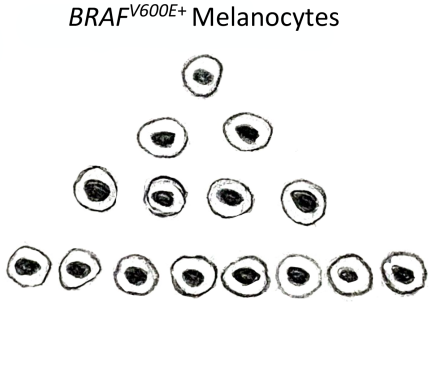


1) **Oncogenic driver mutation**

MAPK activation → MEK → ERK

proliferation
cell growth
survival



CONVENTIONAL MELANOCYTIC NEVUS

Clonal expansion through mitosis

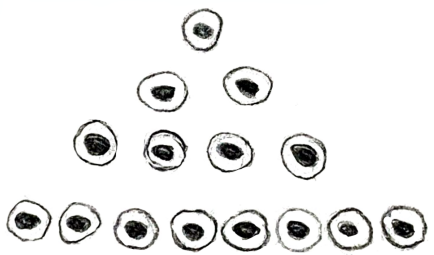
1) **Oncogenic driver mutation**

MAPK activation → MEK → ERK

↓

{ proliferation
cell growth
survival

BRAF^{V600E+} Melanocytes



CONVENTIONAL MELANOCYTIC NEVUS

Clonal expansion through mitosis

2) **Oncegene induced senescence (OIS)**

{ ROS +
DNA damage +
p16/p53 activation

BRAF^{V600E+} Melanocytes

SENESCENT CONVENTINAL MELANOCYTIC NEVUS

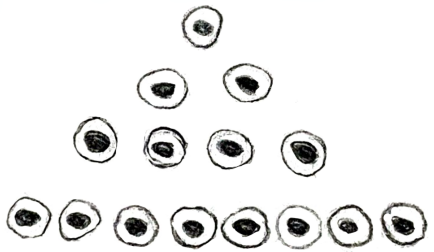
Proliferation arrest

1) **Oncogenic driver mutation**

MAPK activation → MEK → ERK

proliferation
cell growth
survival

BRAF^{V600E+} Melanocytes



CONVENTIONAL MELANOCYTIC NEVUS
Clonal expansion through mitosis

2) **Oncegene induced senescence (OIS)**

ROS +
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p16/p53 activation

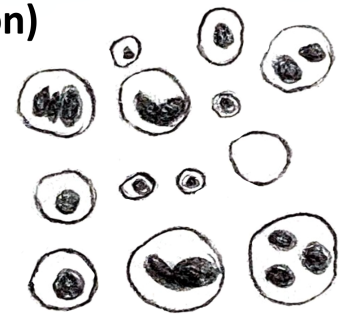
BRAF^{V600E+} Melanocytes

SENESCENT CONVENTINAL MELANOCYTIC NEVUS
Proliferation arrest

3) **Second molecular event (*BAP1*-inactivation)**

Endocycling/endoreplication
Polyploidization
Global transcription reprogramming

BRAF^{V600E+}/ *BAP1*^{loss} Melanocytes



***BAP1*-INACTIVATED MELANOCYTOMA**
Further accumulation of DNA damage
Enhanced shift to endoreplication

OPEN

Citation: Cell Death and Disease (2015) 6, e1711; doi:10.1038/cddis.2015.71

www.nature.com/cddis

In vitro evidence for senescent multinucleated melanocytes as a source for tumor-initiating cells

C Leikam[1], AL Hufnagel[1], C Otto[2], DJ Murphy[3], B Mühling[2], S Kneitz[1], I Nanda[4], M Schmid[4], TU Wagner[1], S Haferkamp[5], E-B Bröcker[6], M Schartl[1,7] and S Meierjohann*[,1,7]

Oncogenic signaling in melanocytes results in oncogene-induced senescence (OIS), a stable cell-cycle arrest frequently characterized by a bi- or multinuclear phenotype that is considered as a barrier to cancer progression. However, the long-sustained conviction that senescence is a truly irreversible process has recently been challenged. Still, it is not known whether cells driven into OIS can progress to cancer and thereby pose a potential threat. Here, we show that prolonged expression of the melanoma oncogene N-RAS^{61K} in pigment cells overcomes OIS by triggering the emergence of tumor-initiating mononucleated stem-like cells from senescent cells. This progeny is dedifferentiated, highly proliferative, anoikis-resistant and induces fast growing, metastatic tumors. Our data describe that differentiated cells, which are driven into senescence by an oncogene, use this senescence state as trigger for tumor transformation, giving rise to highly aggressive tumor-initiating cells. These observations provide the first experimental *in vitro* evidence for the evasion of OIS on the cellular level and ensuing transformation.
Cell Death and Disease (2015) **6,** e1711; doi:10.1038/cddis.2015.71; published online 2 April 2015

Seminars in Cancer Biology 60 (2020) 380–397

Contents lists available at ScienceDirect

Seminars in Cancer Biology

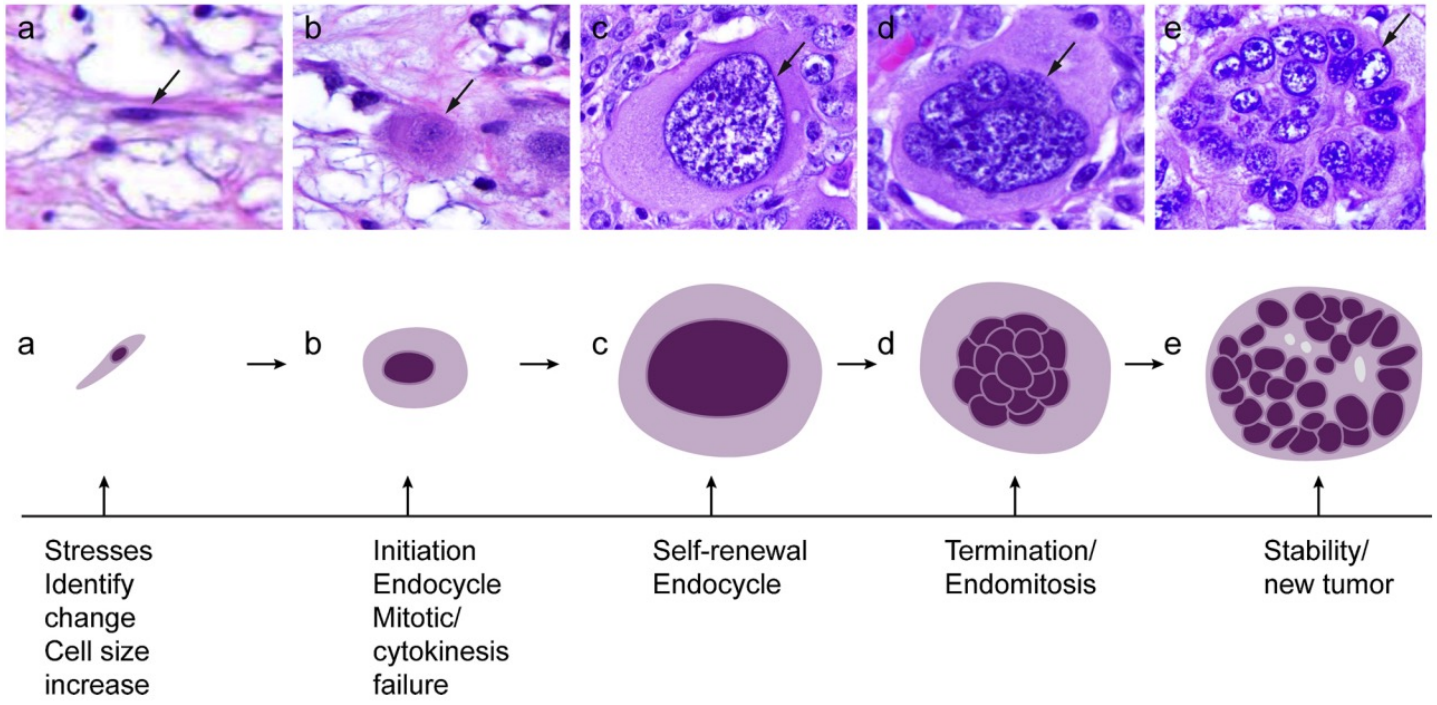
journal homepage: www.elsevier.com/locate/semcancer

Review

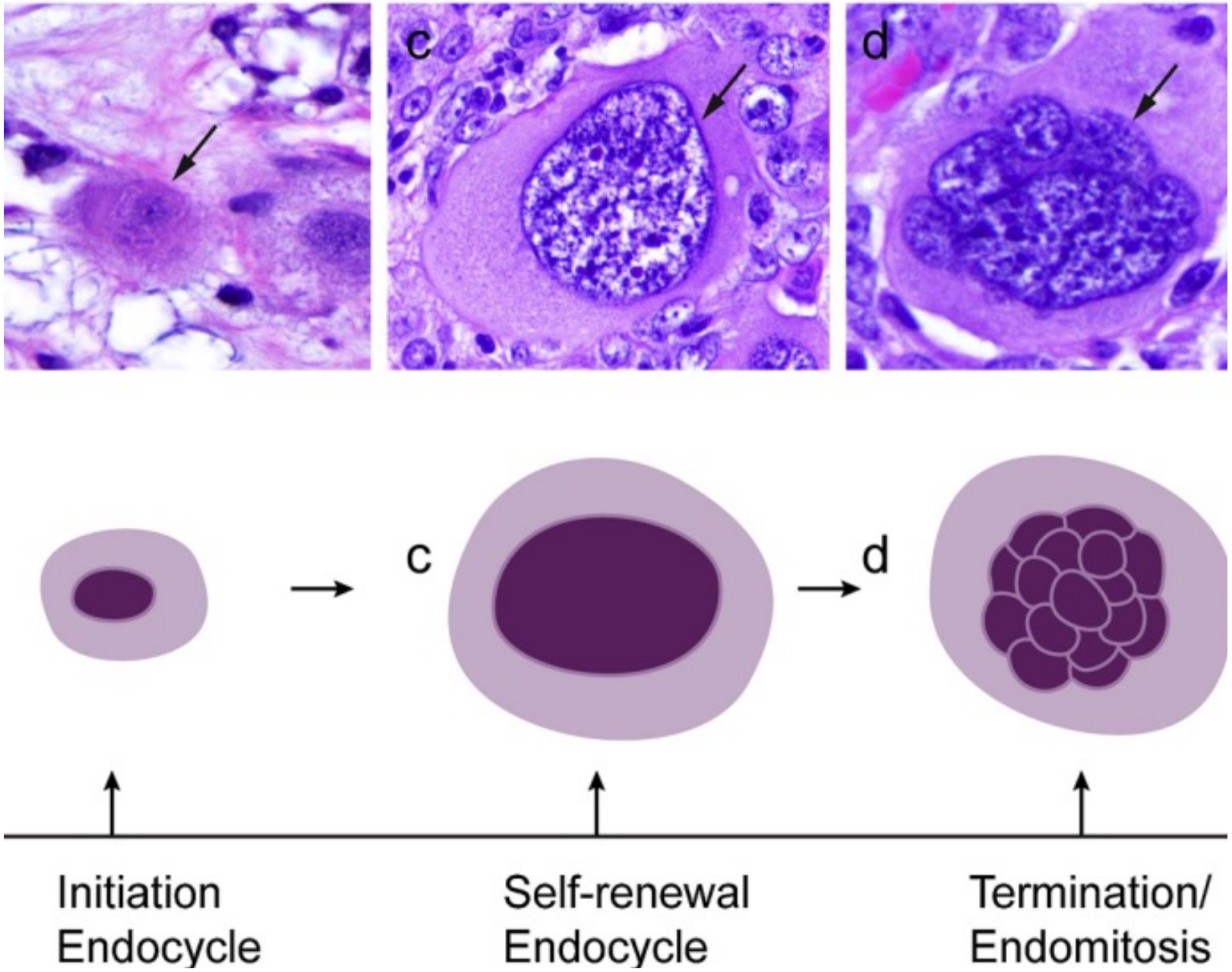
The “life code”: A theory that unifies the human life cycle and the origin of human tumors

Jinsong Liu

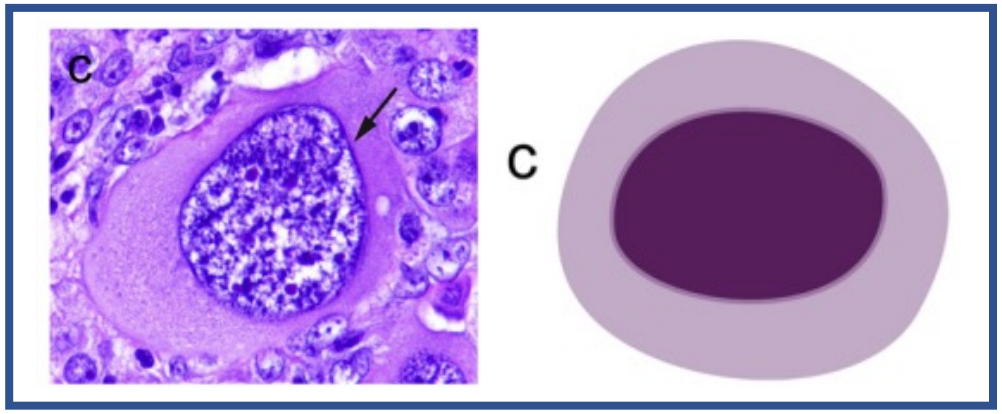
Department of Anatomic Pathology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX, 77030, United States

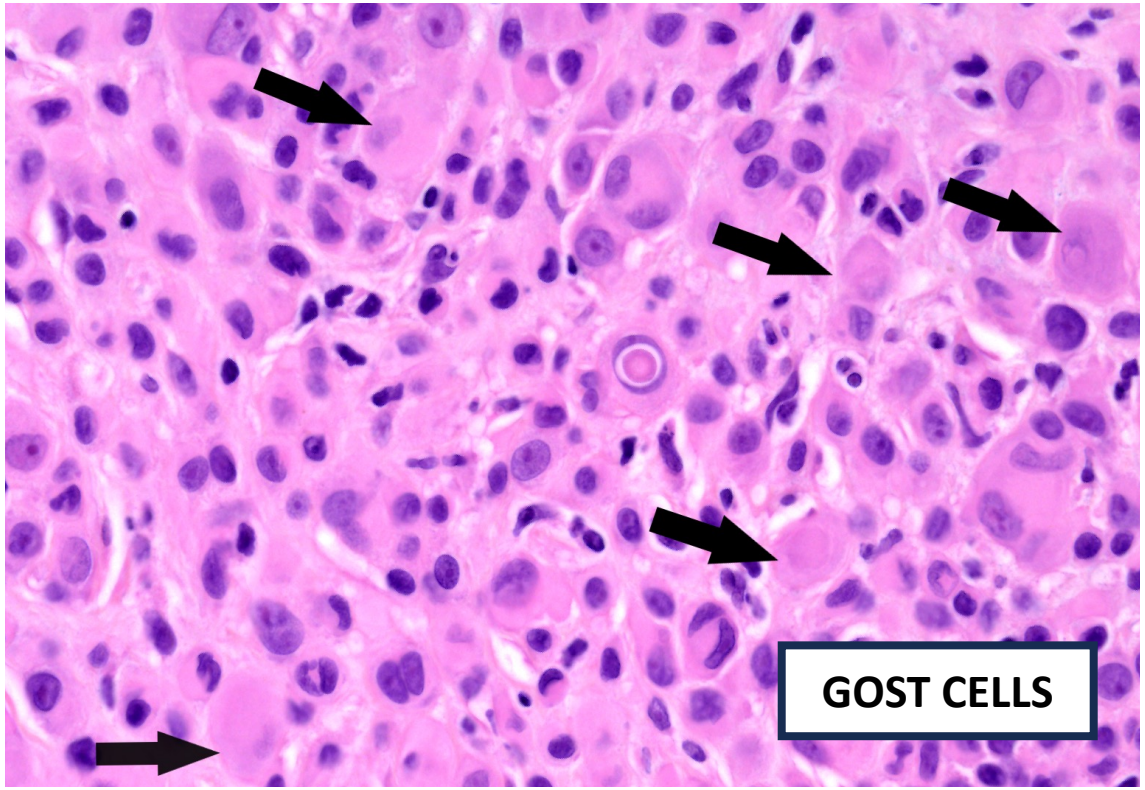


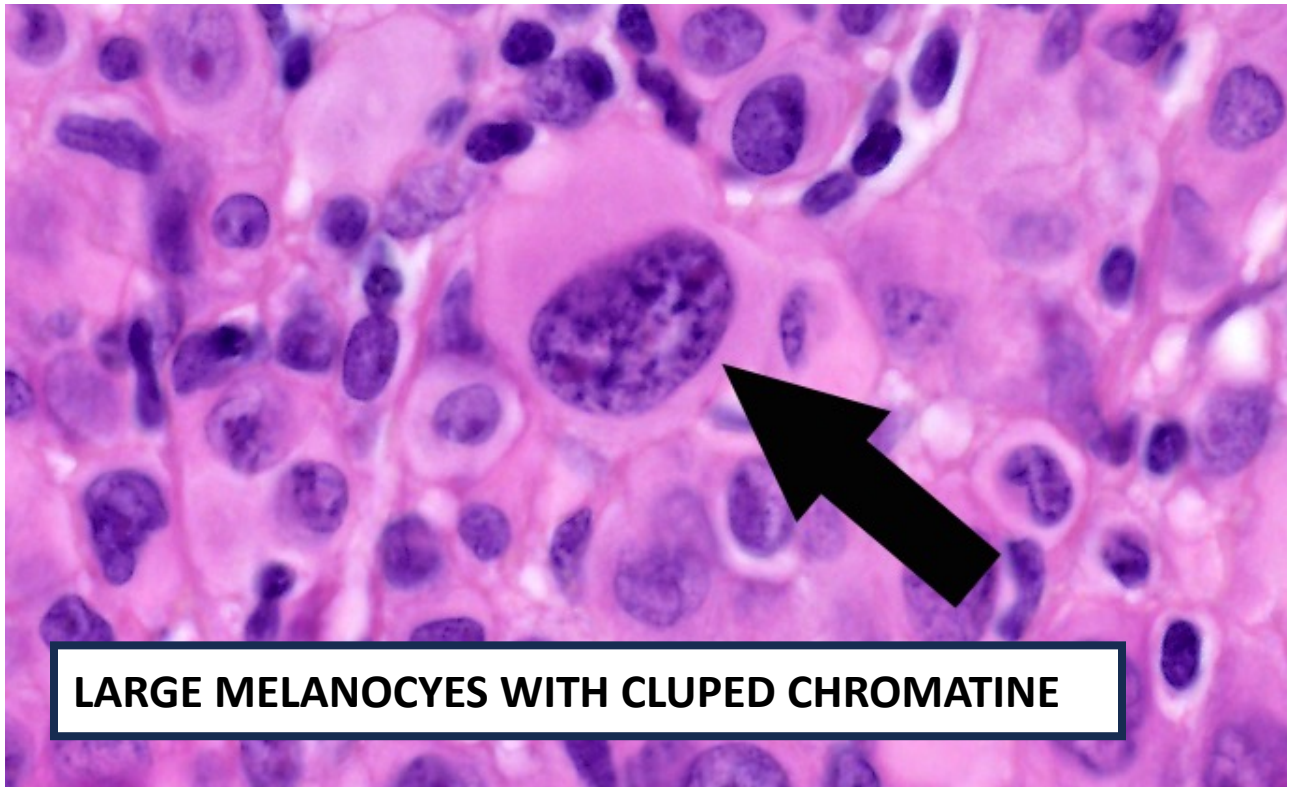
Morphological features related to endoreplication



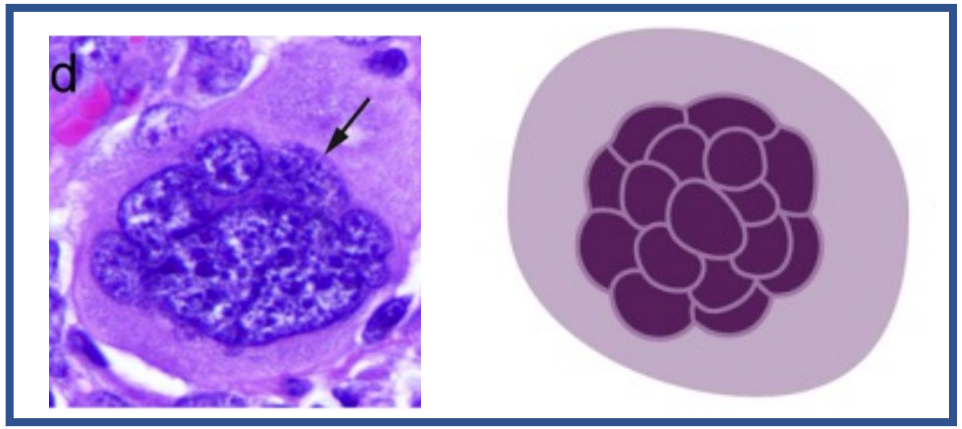
Endocycling

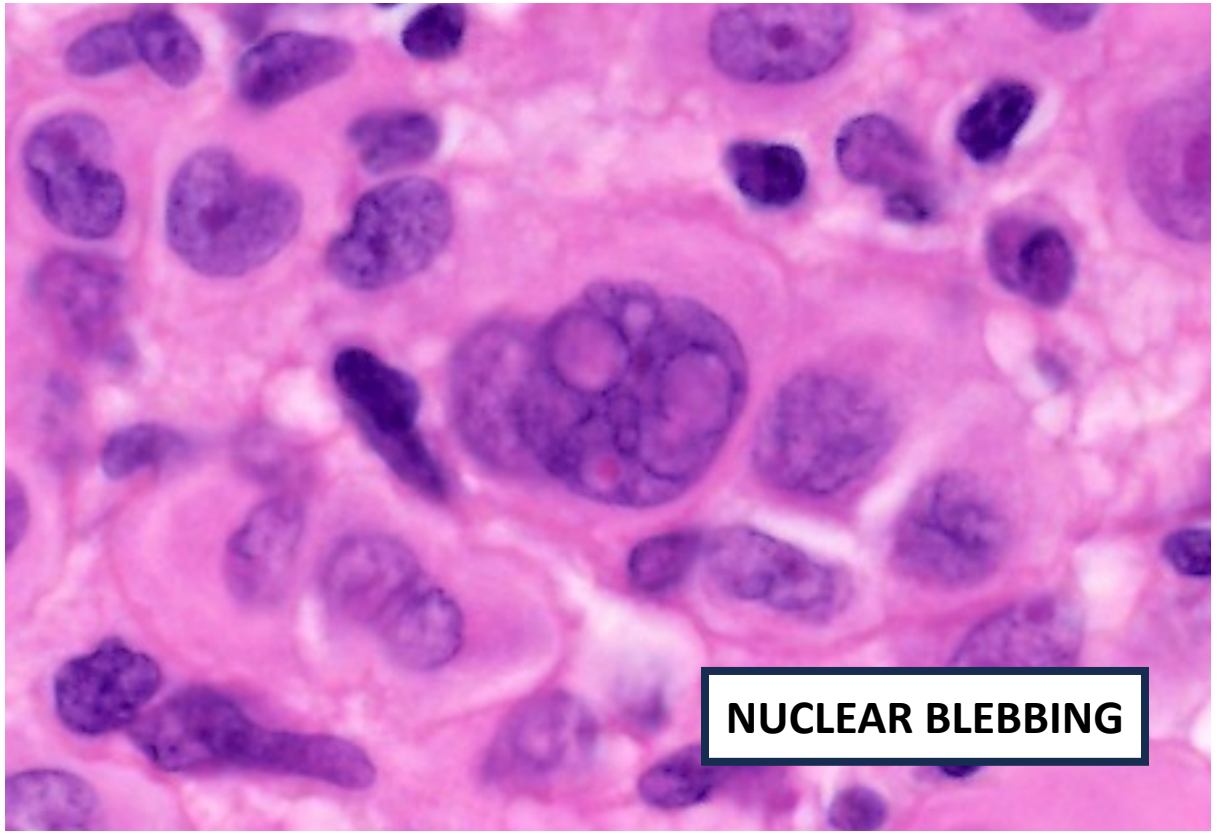


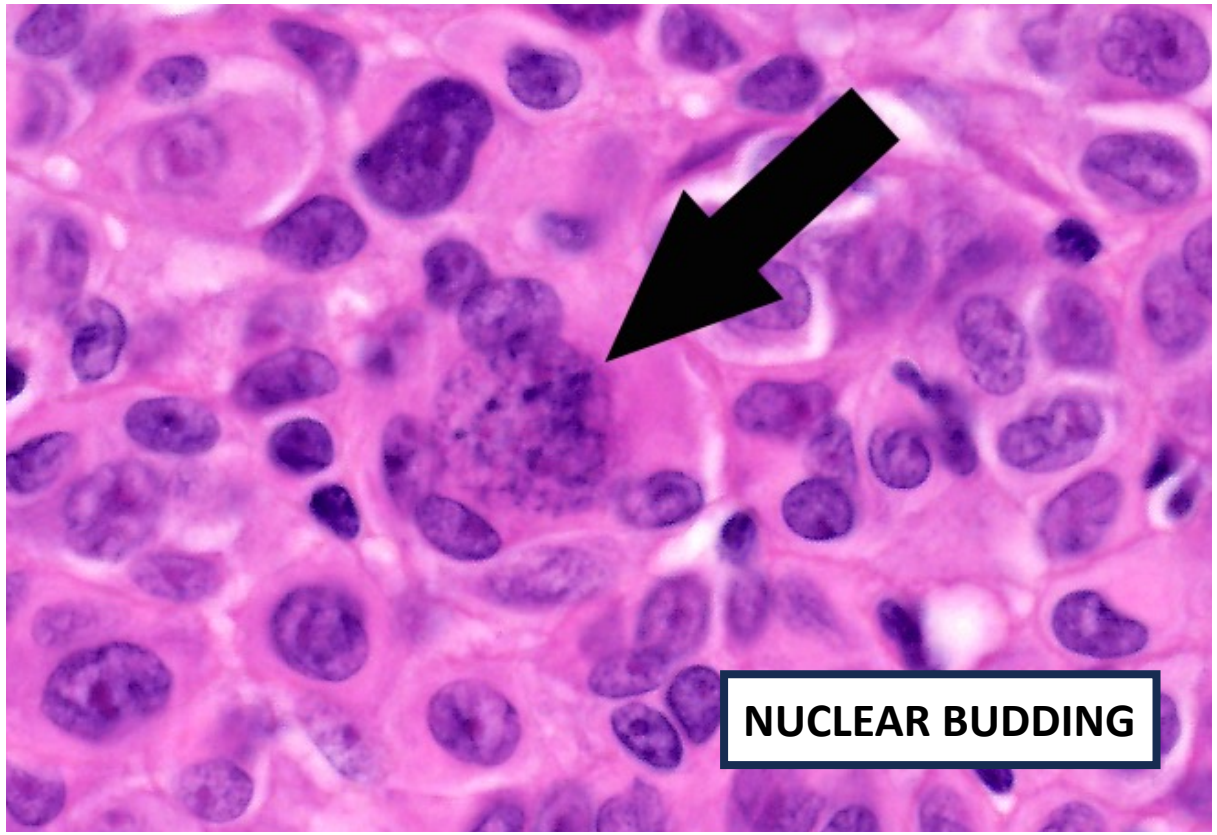




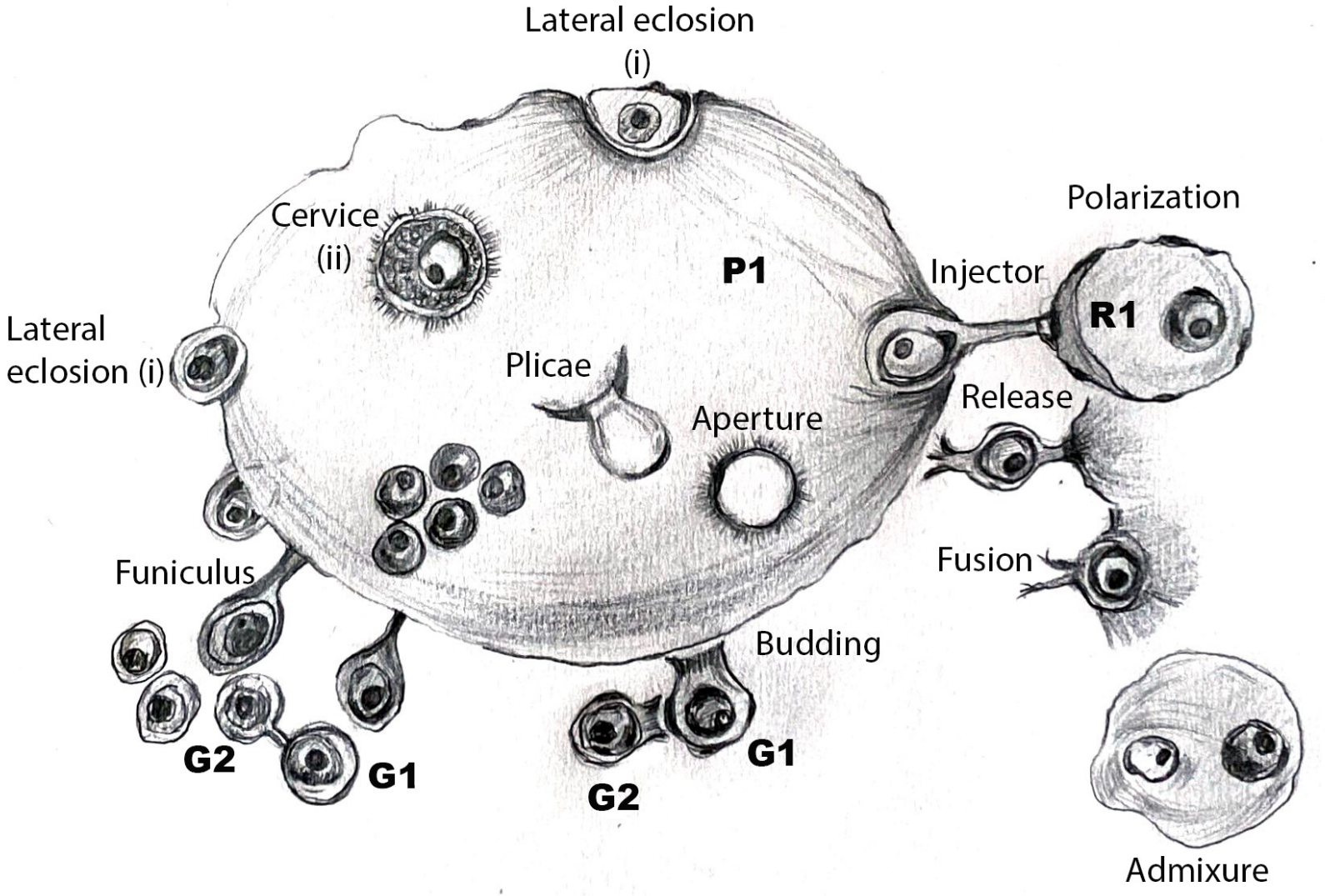
Endomitosis



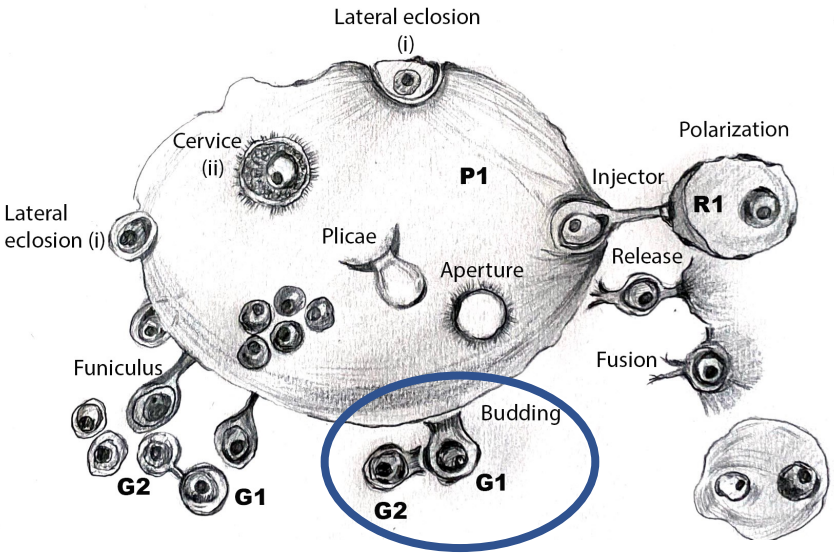


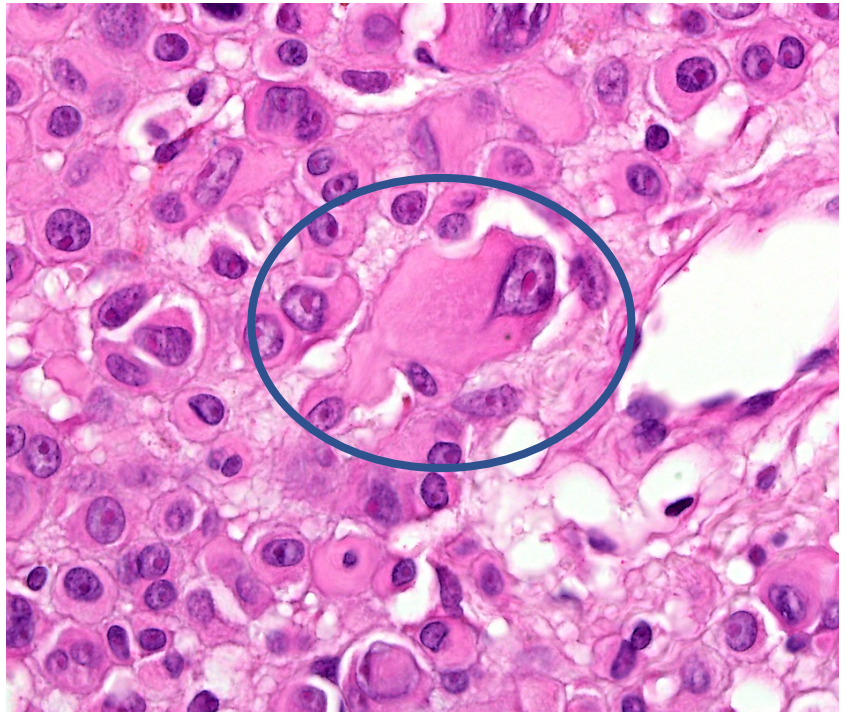


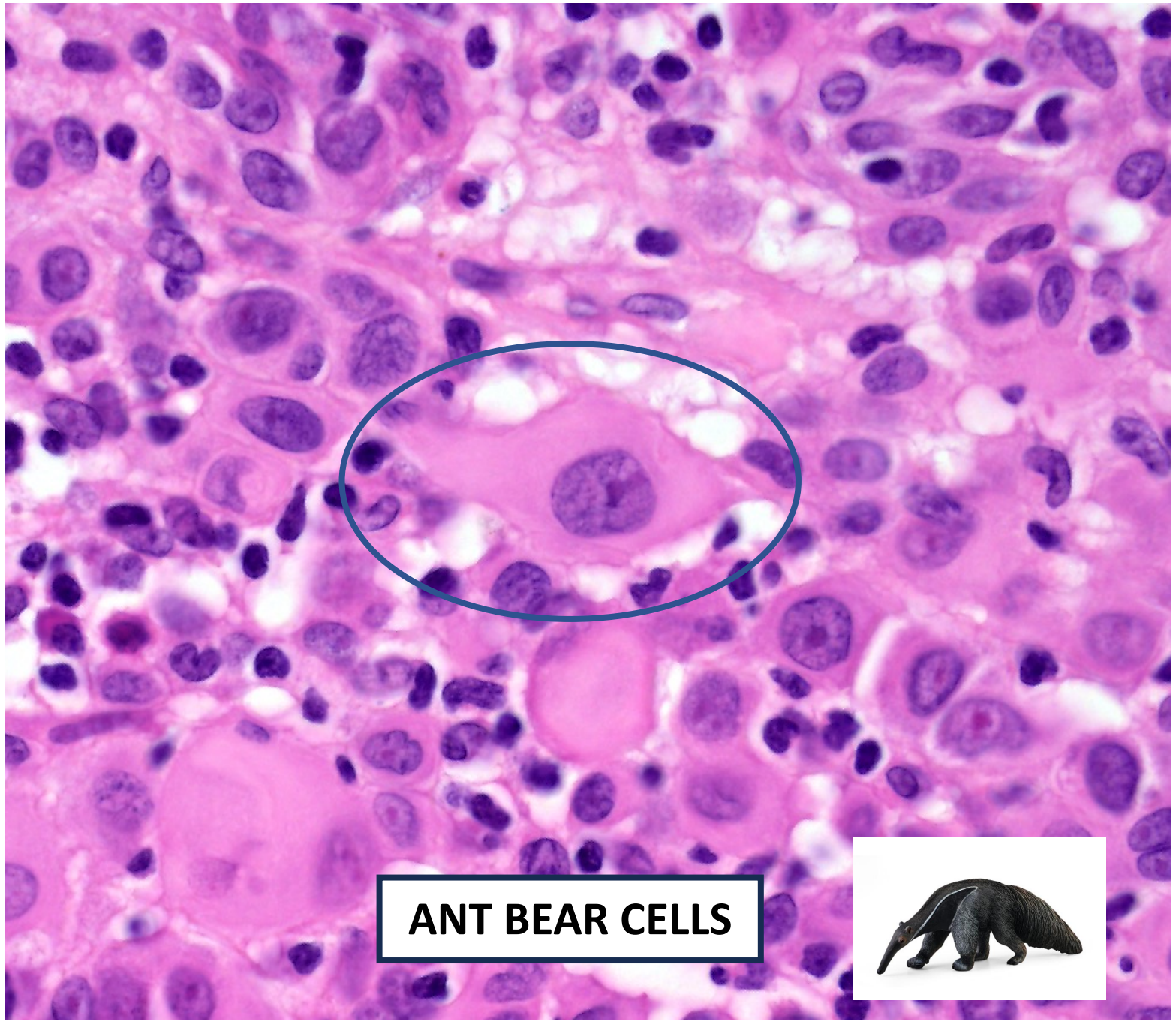
Polyploid multinucleated cell life cycle

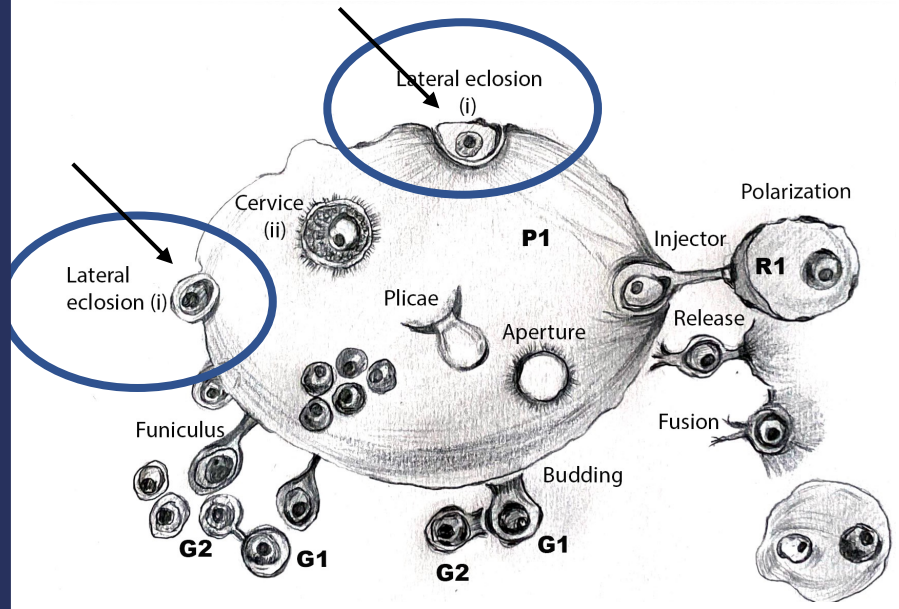


Díaz-Carballo et al. A Distinct Oncogenerative Multinucleated Cancer Cell Serves as a Source of Stemness and Tumor Heterogeneity. Cancer Res. 2018 May 1;78(9):2318-2331. doi: 10.1158/0008-5472.CAN-17-1861.


Lateral eclosion
(i)
Cervice
(ii)
P1
Polarization
Injector
R1
Lateral
eclosion (i)
Plicae
Aperture
Release
Fusion
Funiculus
Budding
G2
G1
G2
G1




ANT BEAR CELLS


Lateral eclosion
(i)
Cervice
(ii)
P1
Polarization
Injector
R1
Lateral
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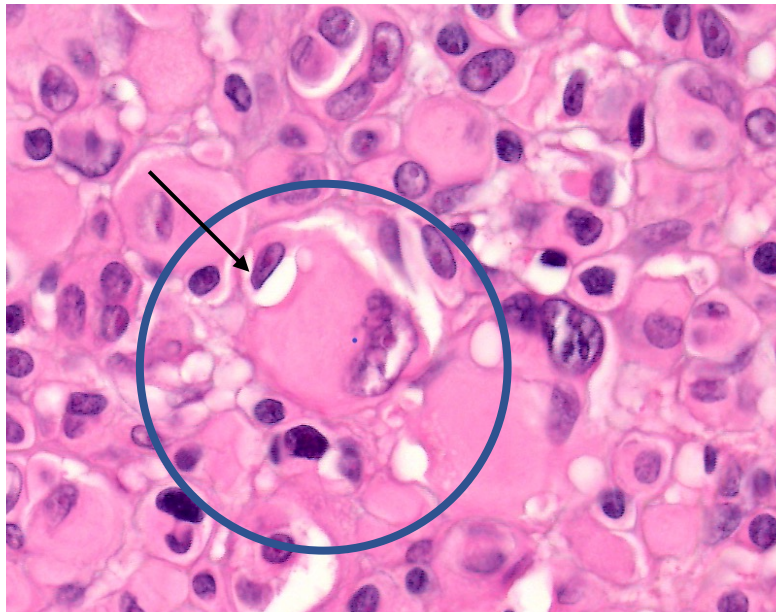
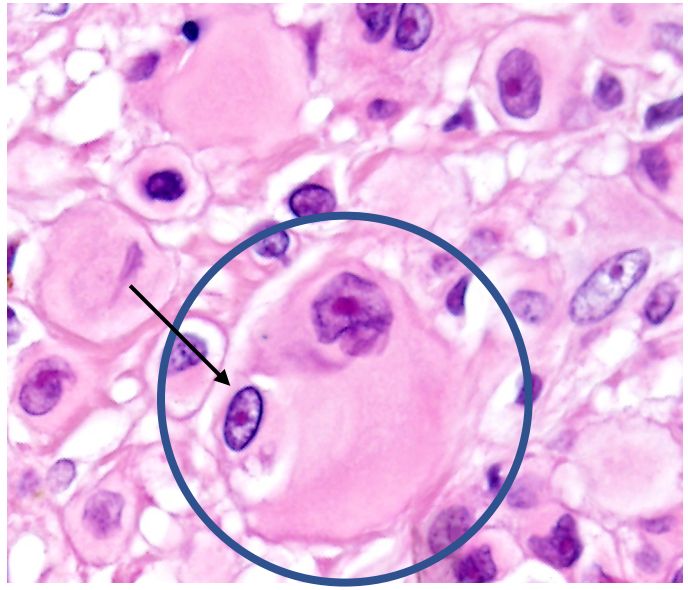
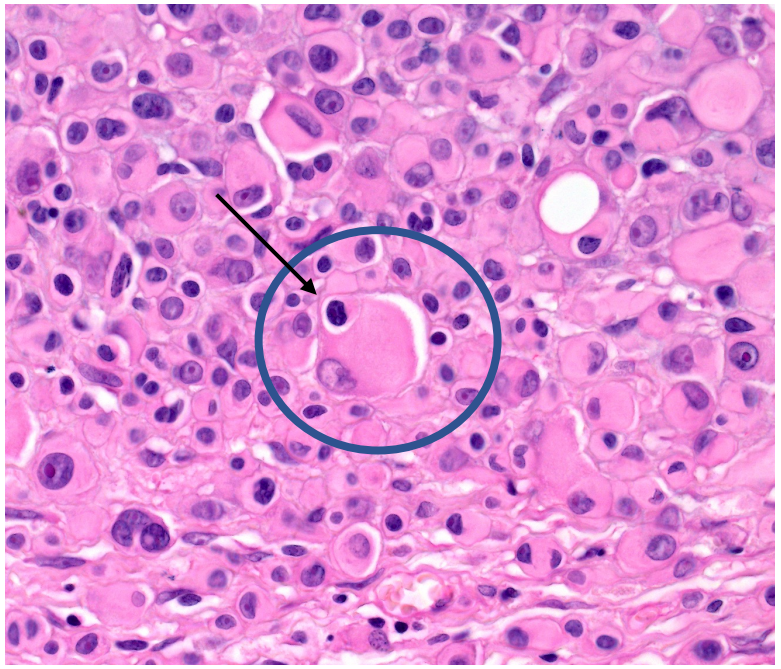
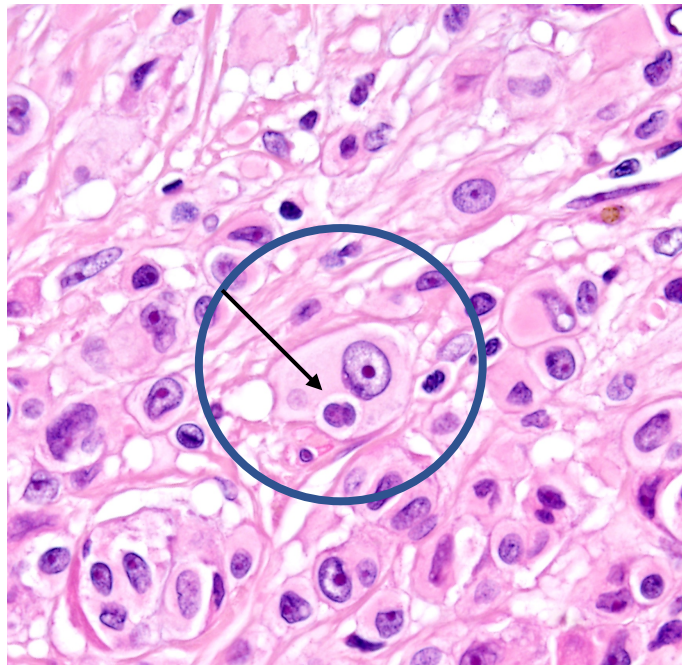
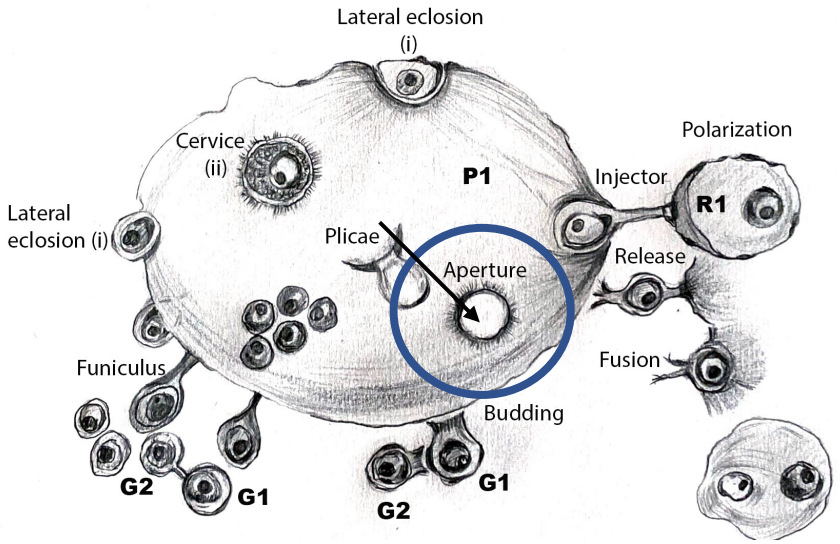
Plicae
Aperture
Release
Fusion
Funiculus
Budding
G2
G1
G2
G1

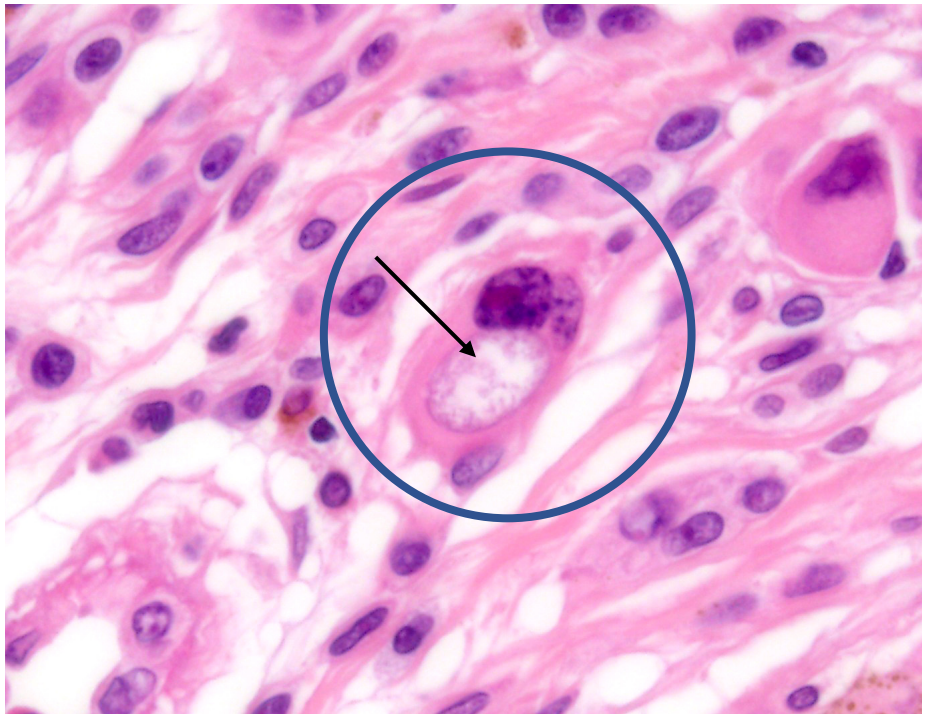


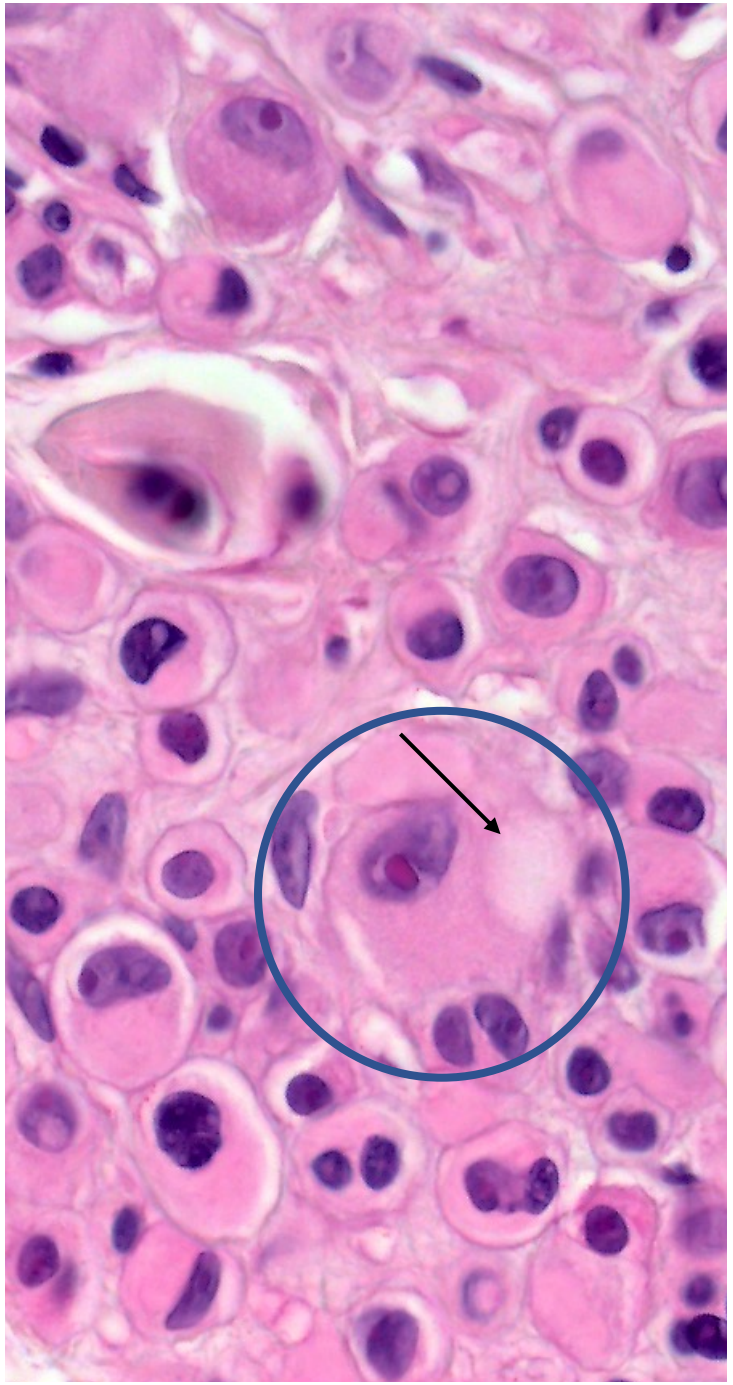


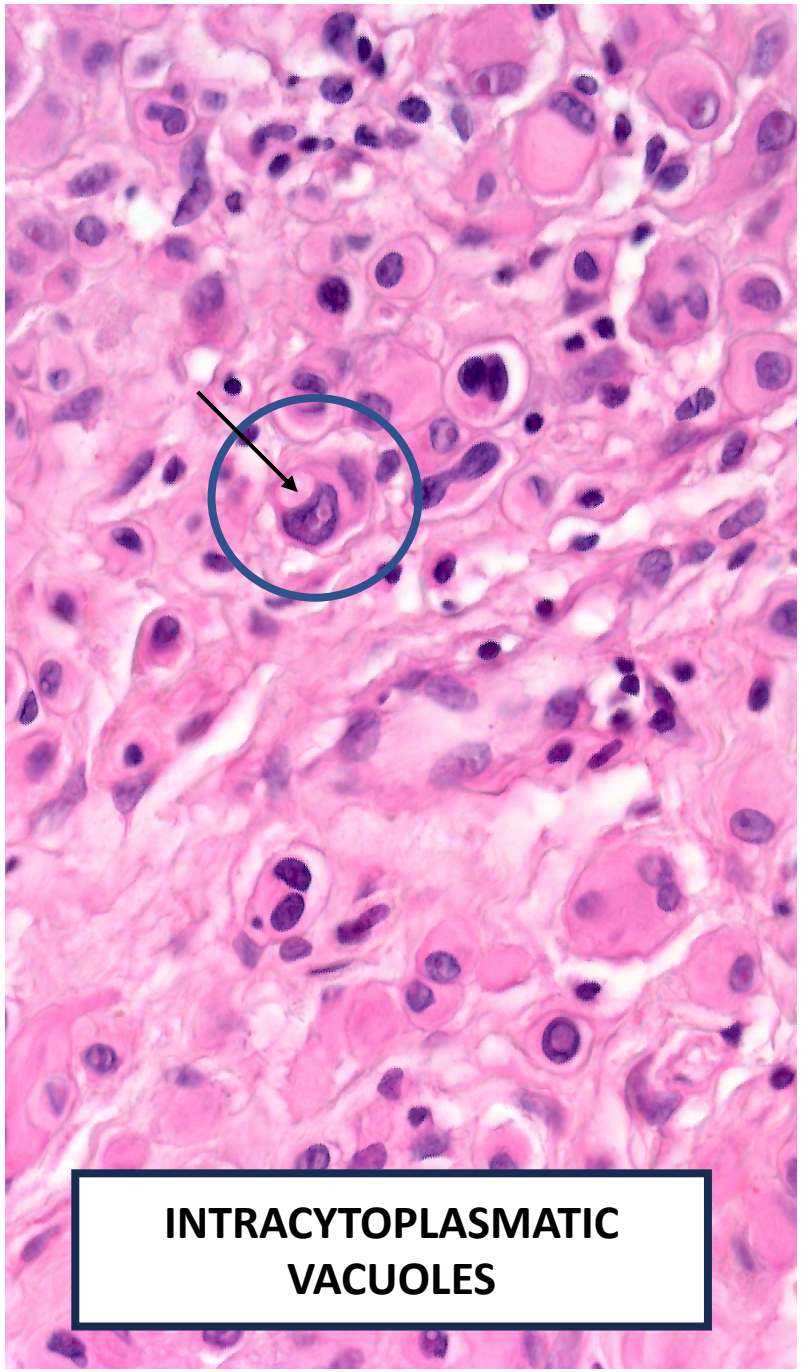


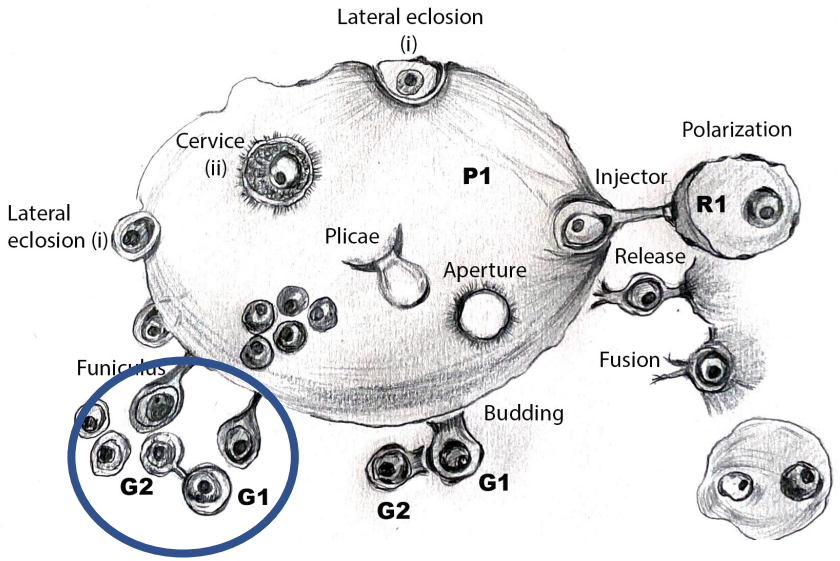


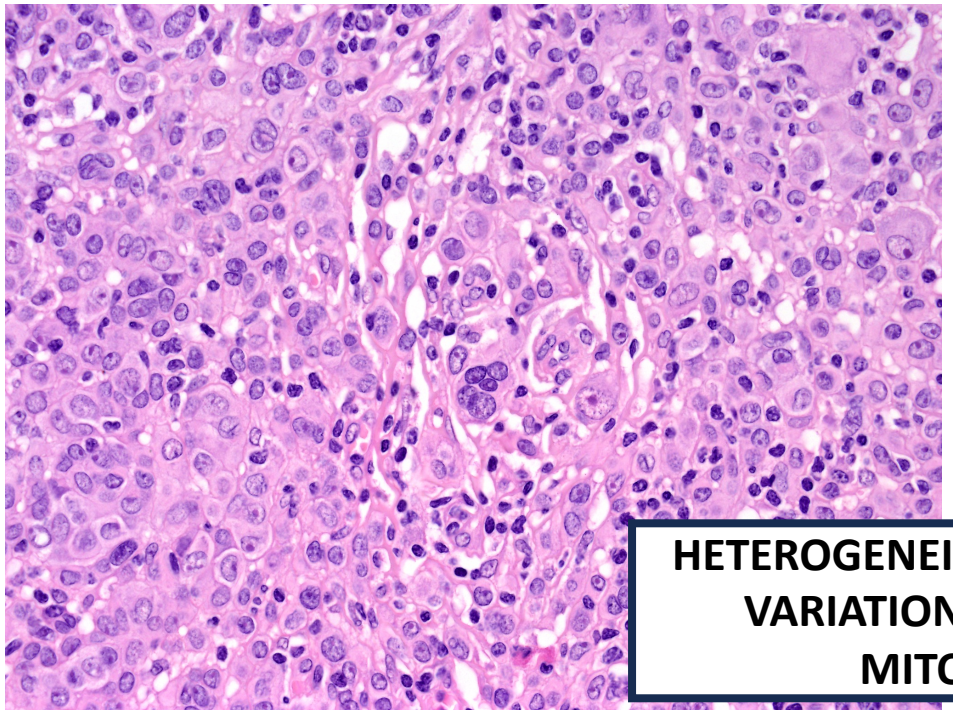

Lateral eclosion
(i)
Cervice
(ii)
P1
Polarization
Injector
R1
Lateral
eclosion (i)
Plicae
Aperture
Release
Fusion
Funiculus
Budding
G2
G1
G2
G1

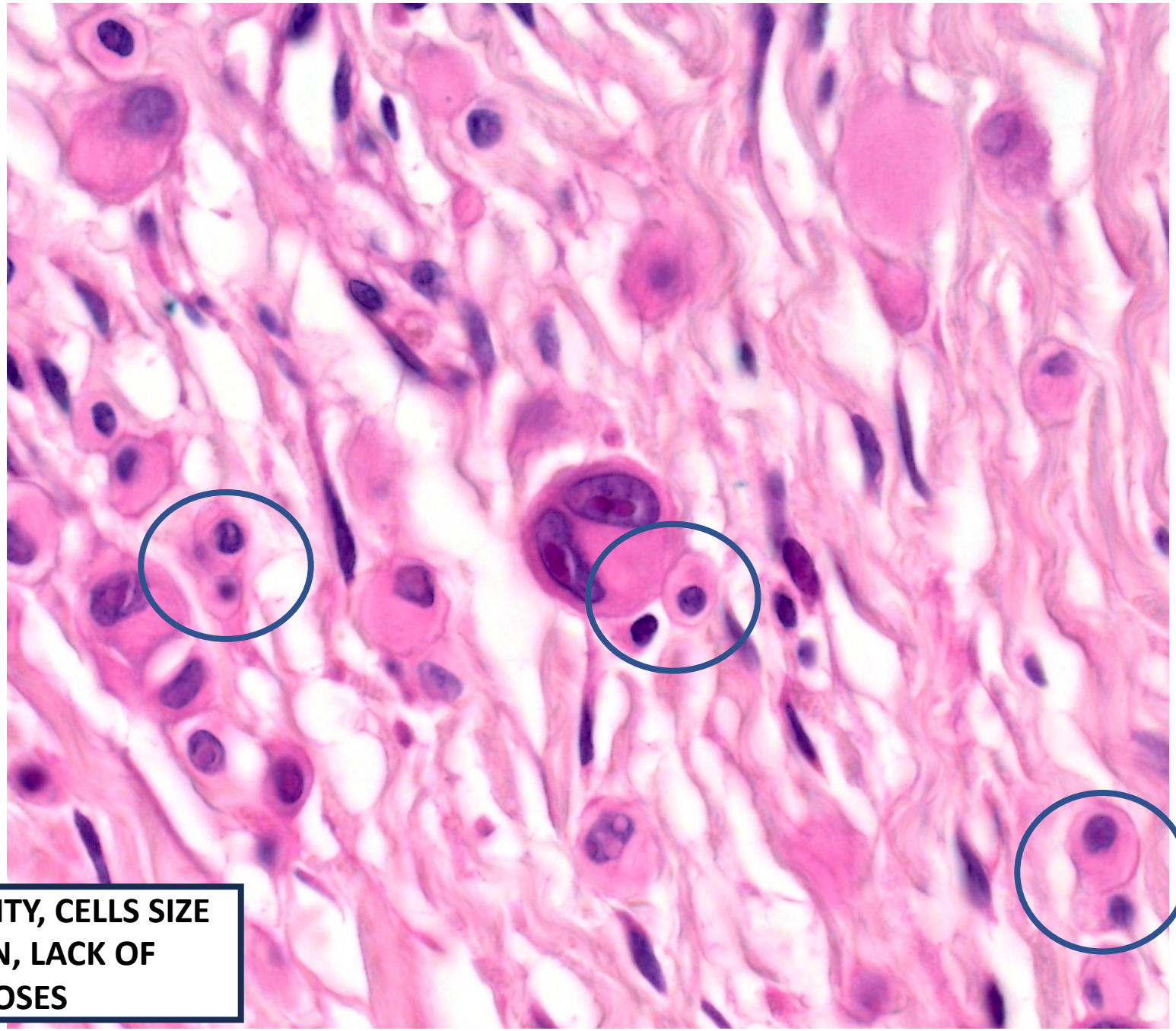





INTRACYTOPLASMATIC
VACUOLES

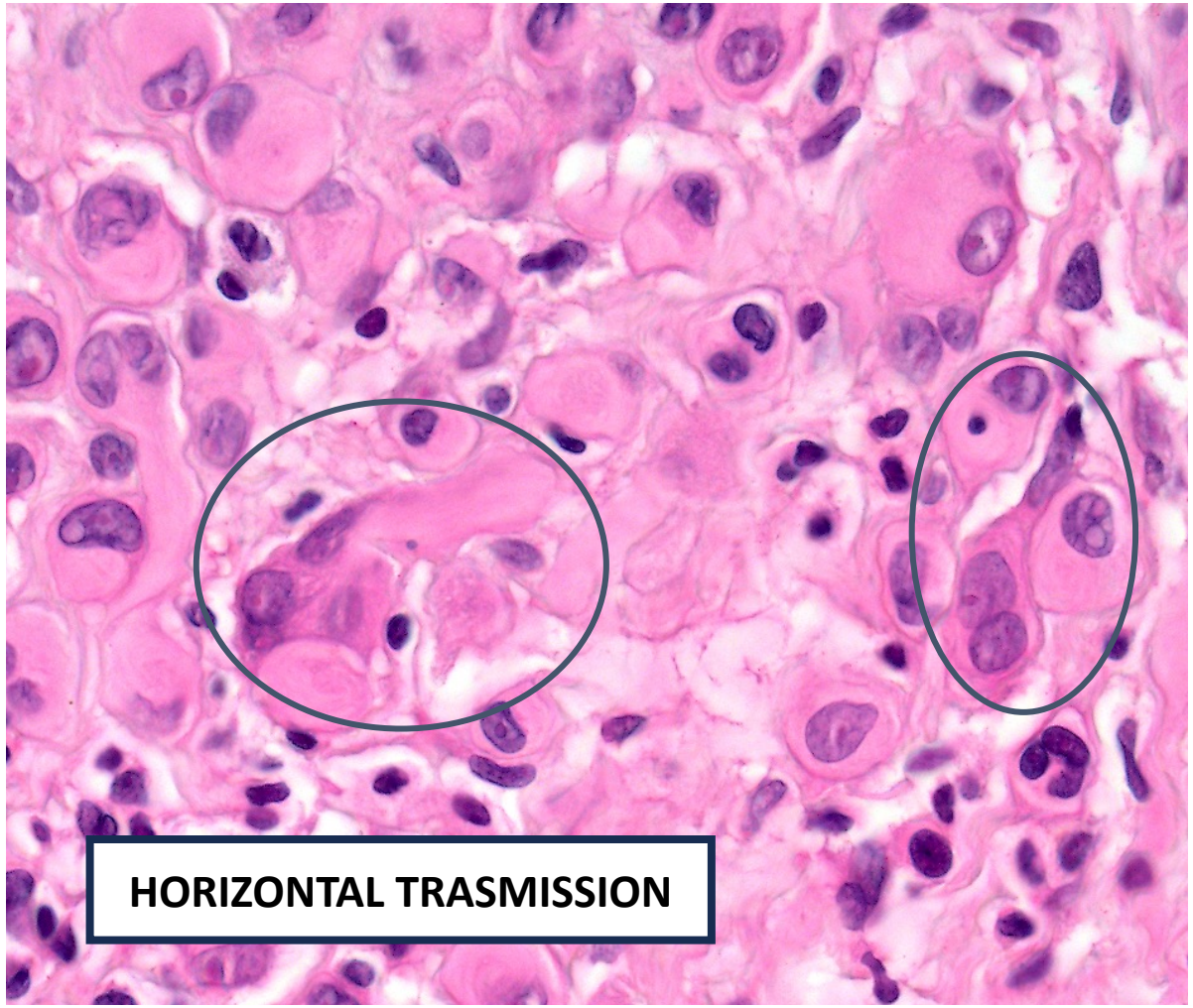


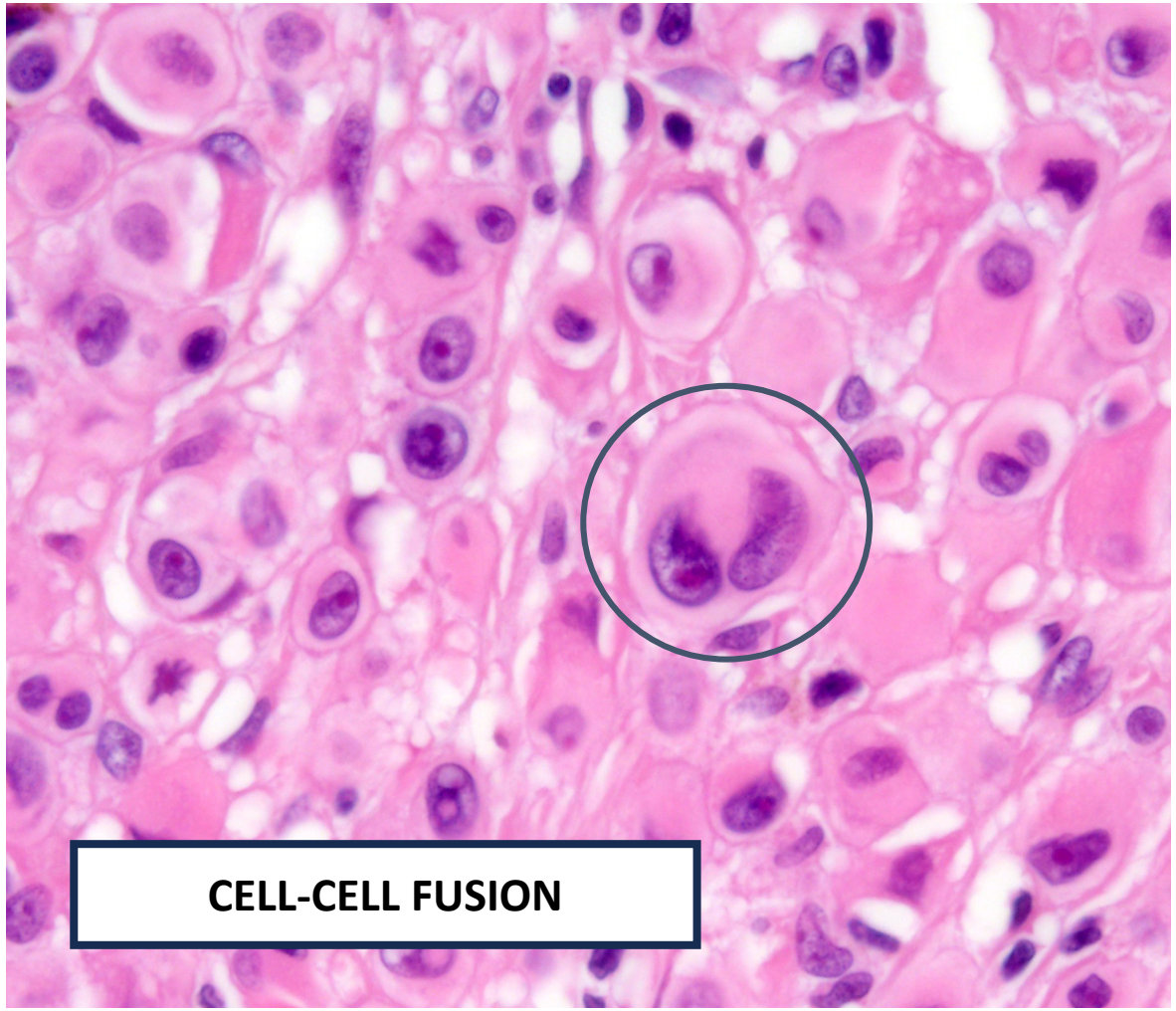


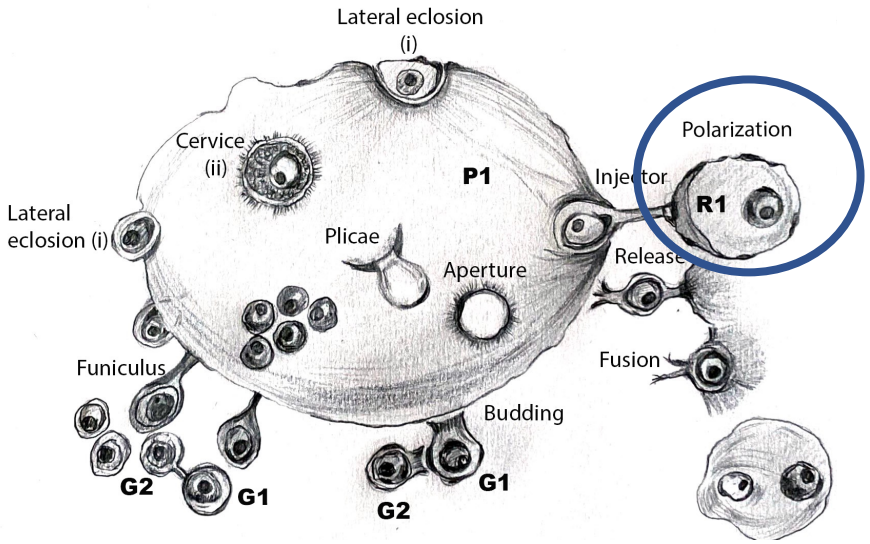


HETEROGENEITY, CELLS SIZE VARIATION, LACK OF MITOSES

Other suggested mechanisms to polyploidy and multinucleation



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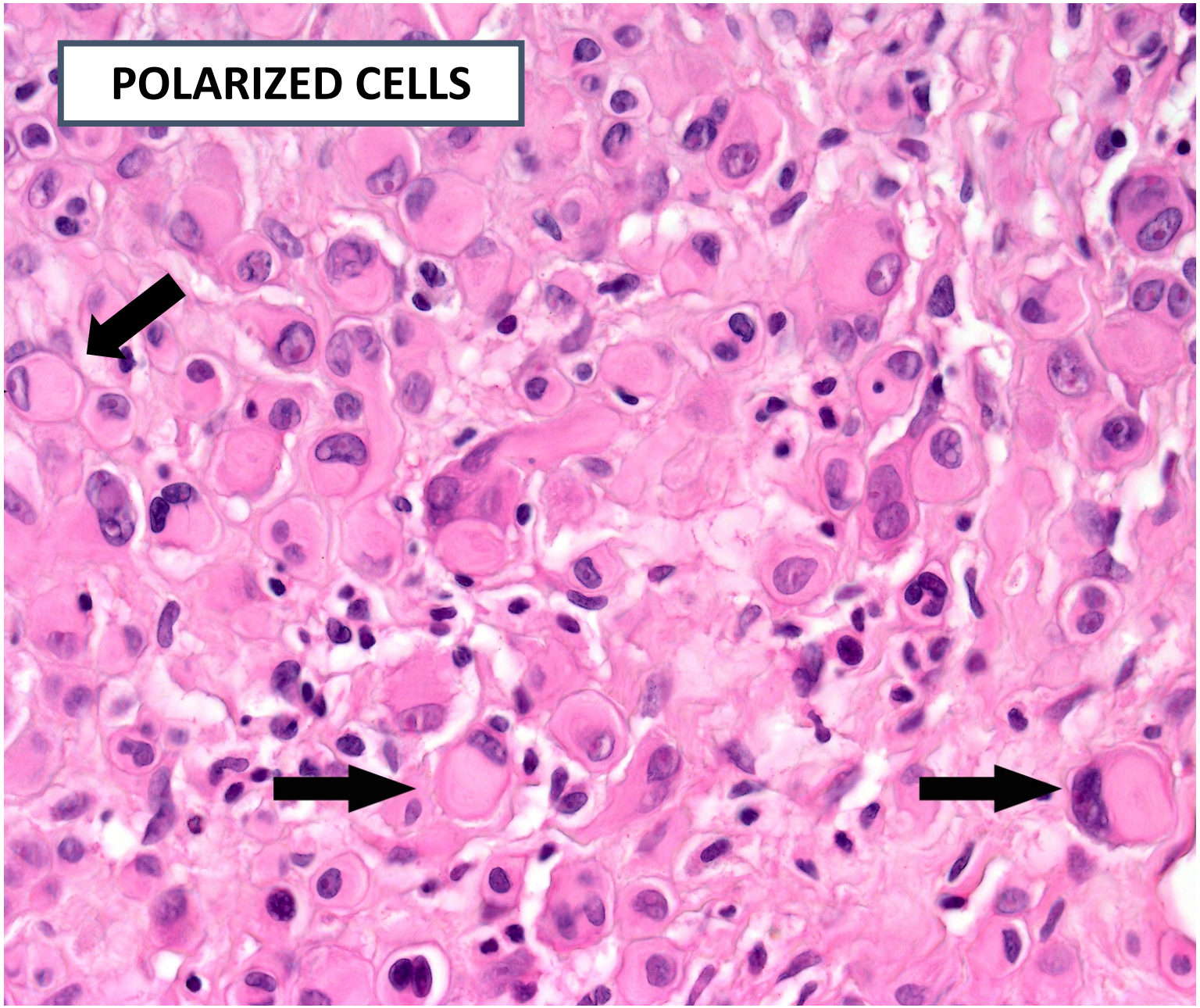
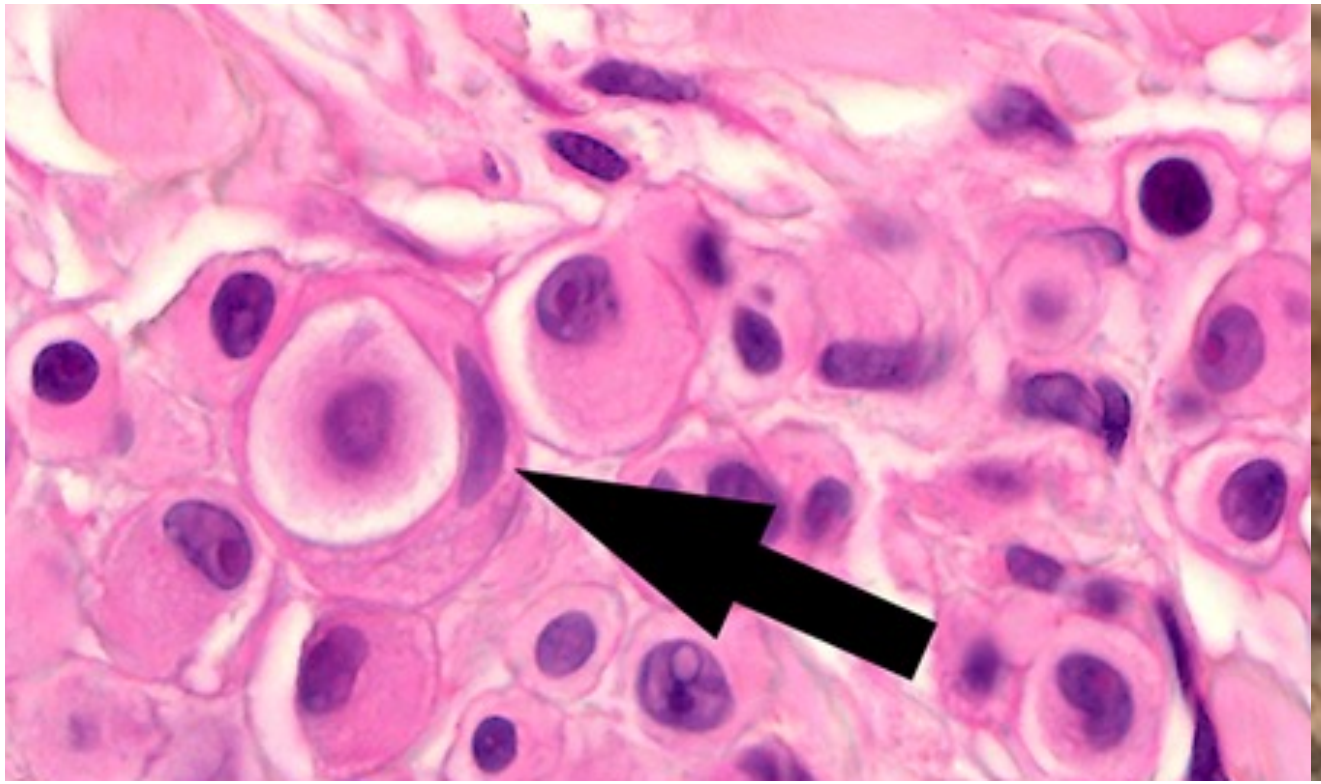
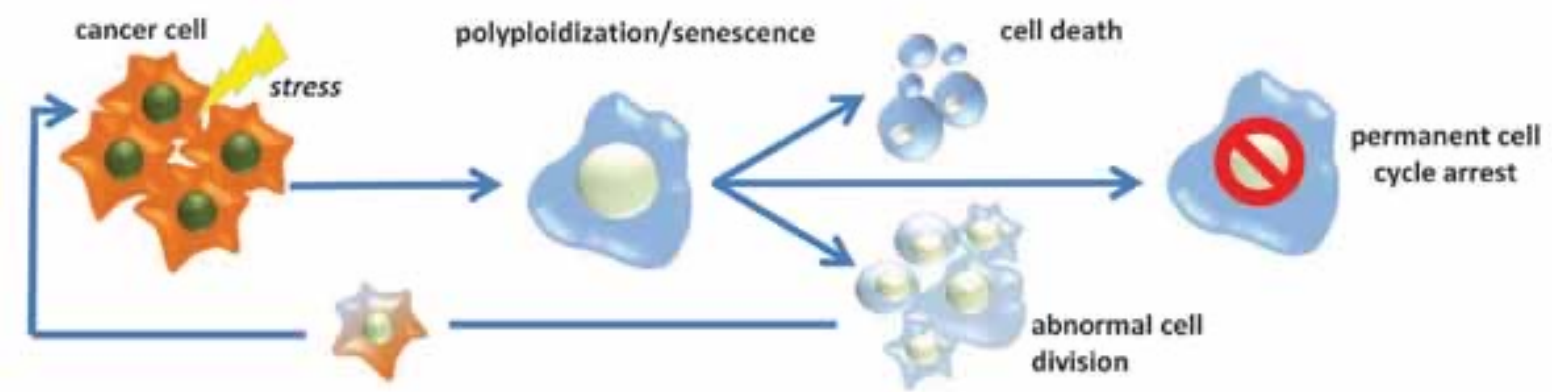

POLARIZED CELLS

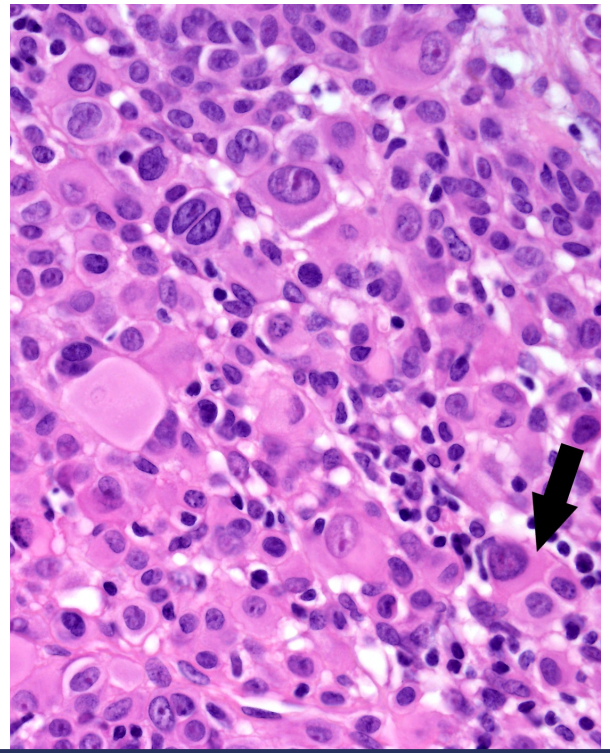
ENTOSIS

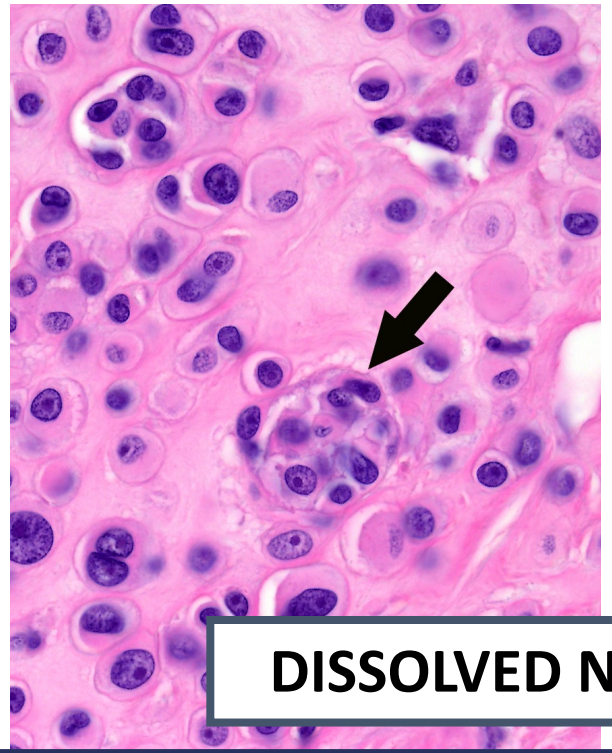
- Cell-in-cell structures
- Outer cell internalizing inner cell
- Tumor cell with a crescent-shaped nucleus containing another cell
- ‘Bird’s-eye cells’ morphology

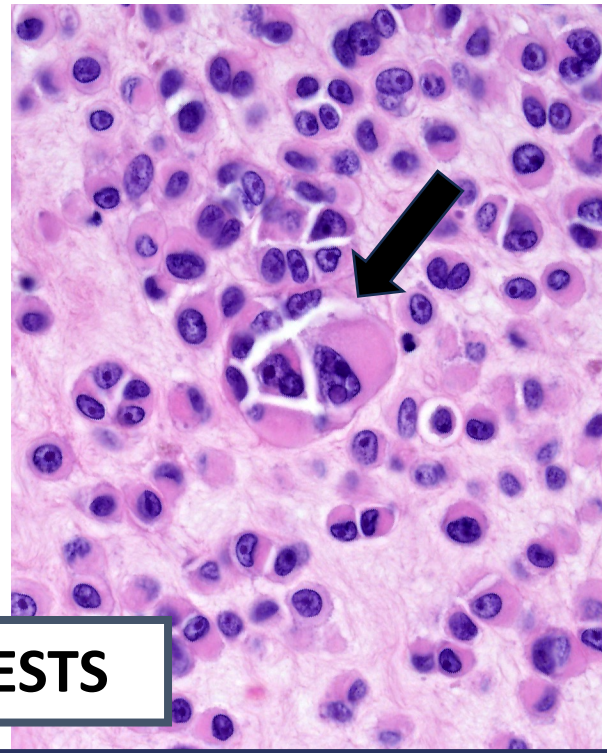


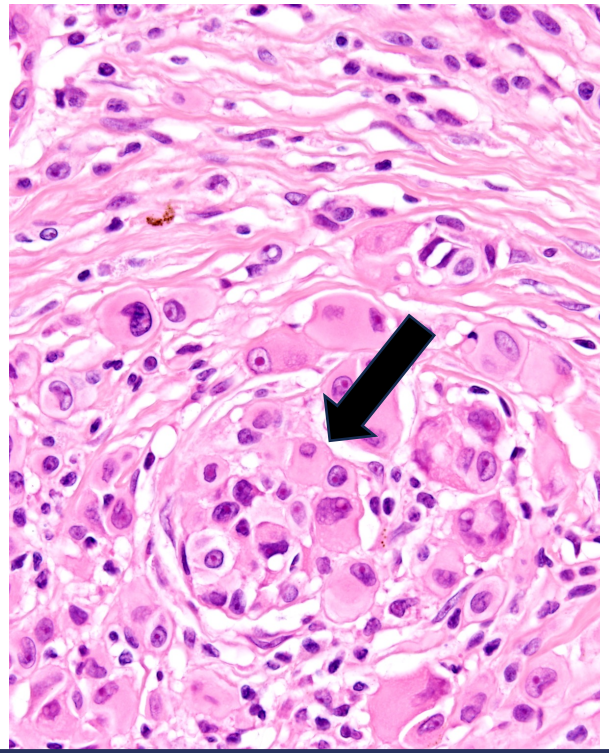
Simultaneous asymmetric cytokinesis











DISSOLVED NESTS

POLYPLOID MULTINUCLEATED CELLS

Capability of self-renewal

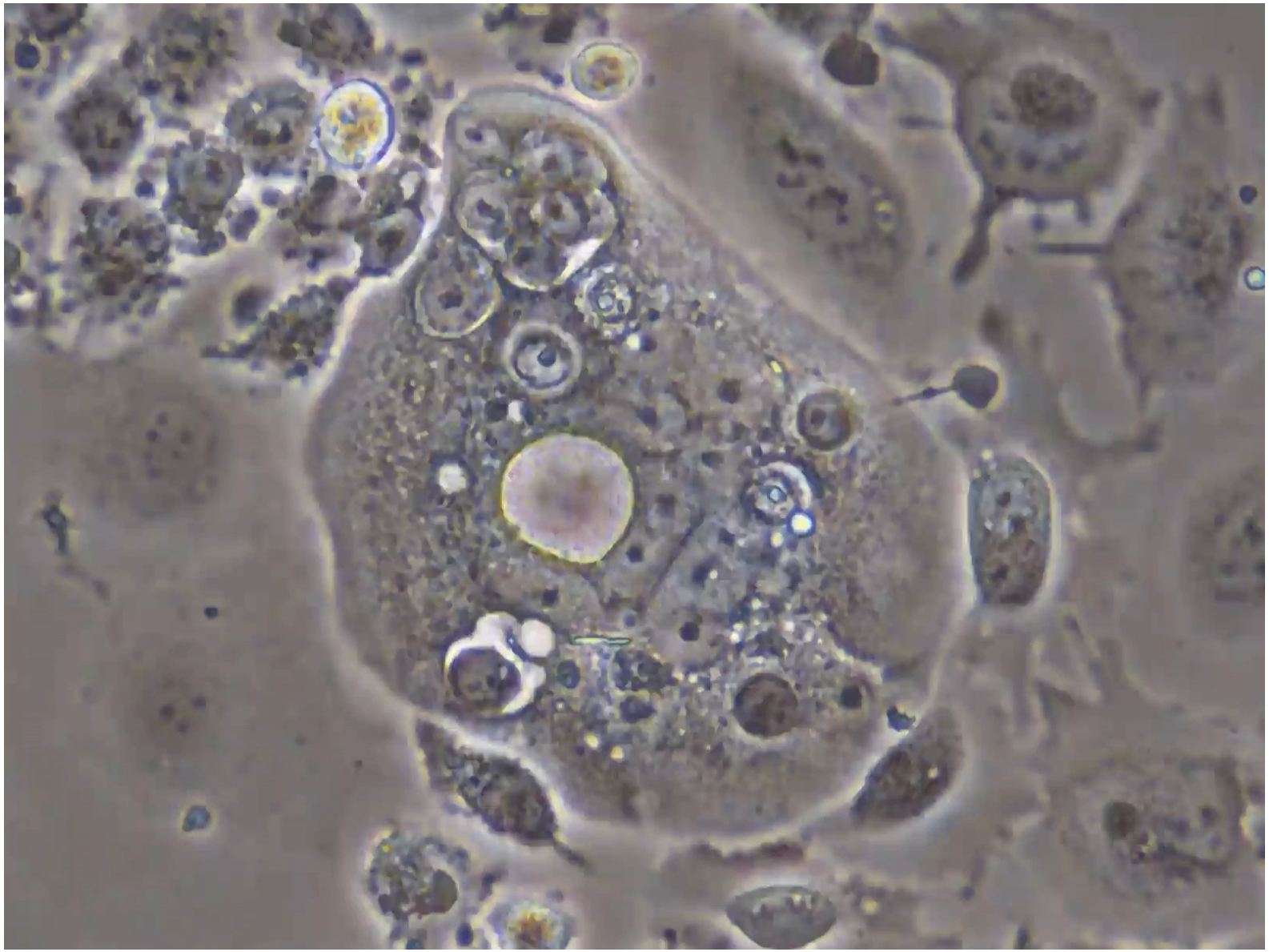
Stemness

Source of tumor heterogeneity

Observed in several tumors

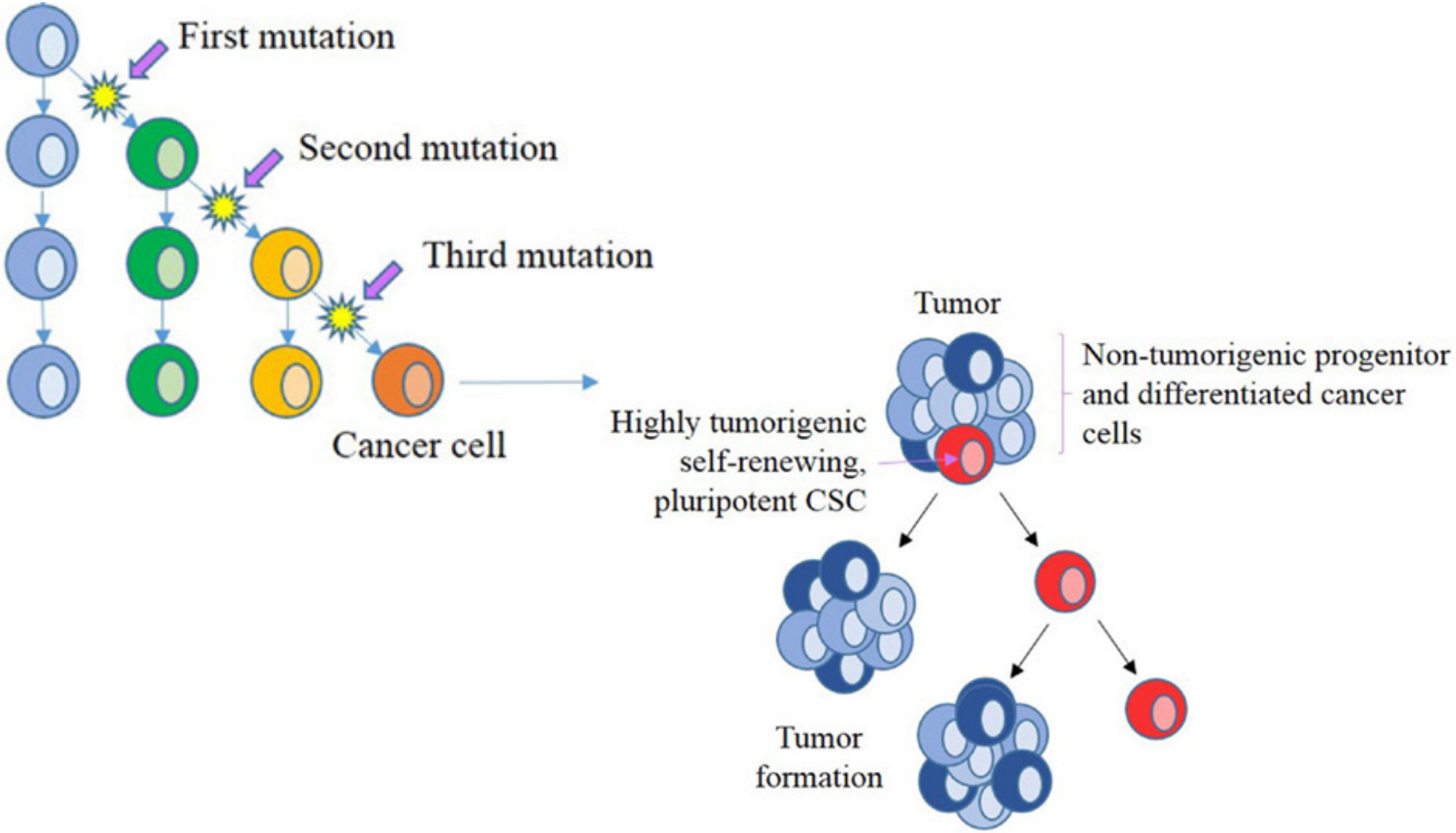
Resistance to conventional treatment

TIME LAPS



Díaz-Carballo et al. Cancer Res. 2018 May 1;78(9):2318-2331. doi: 10.1158/0008-5472.CAN-17-1861.

Polyploid multinucleated cells unify the two models



Thanks for your attention