Cancer from a Multilevel Perspective:

Tumors as Proto-Organisms?

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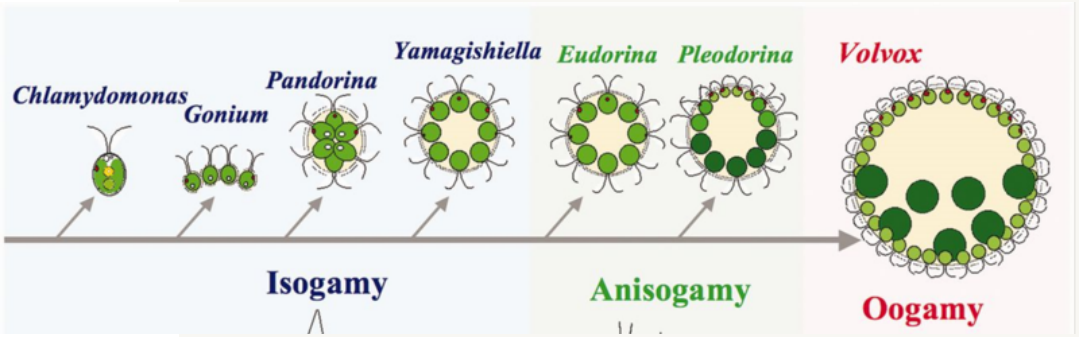
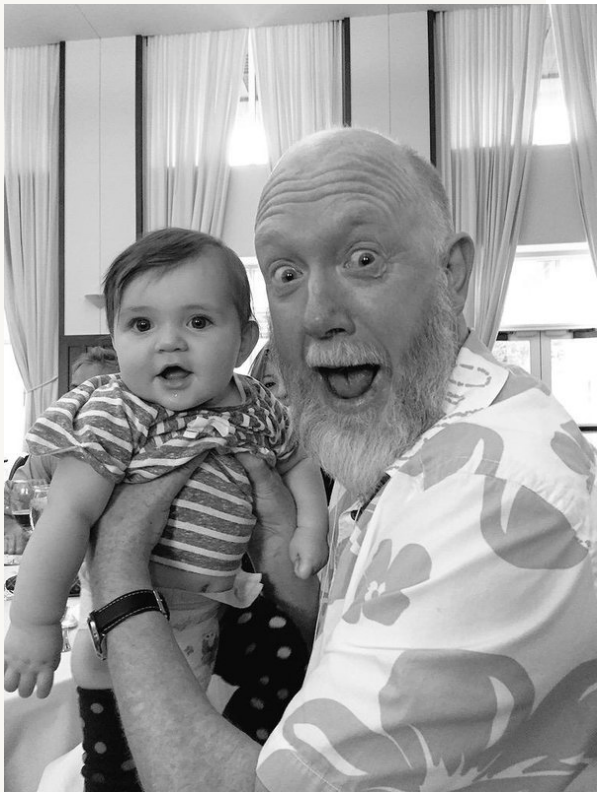
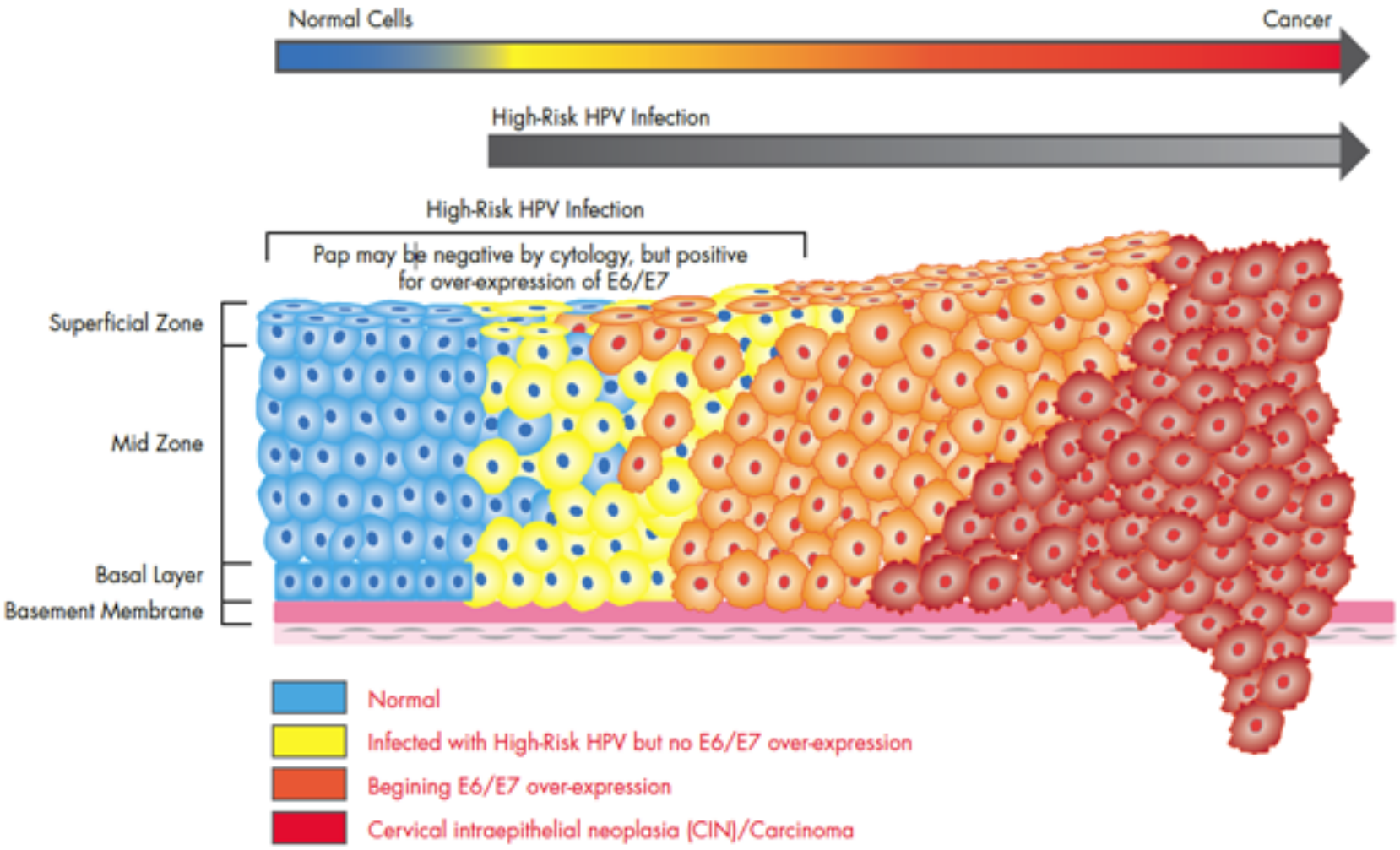


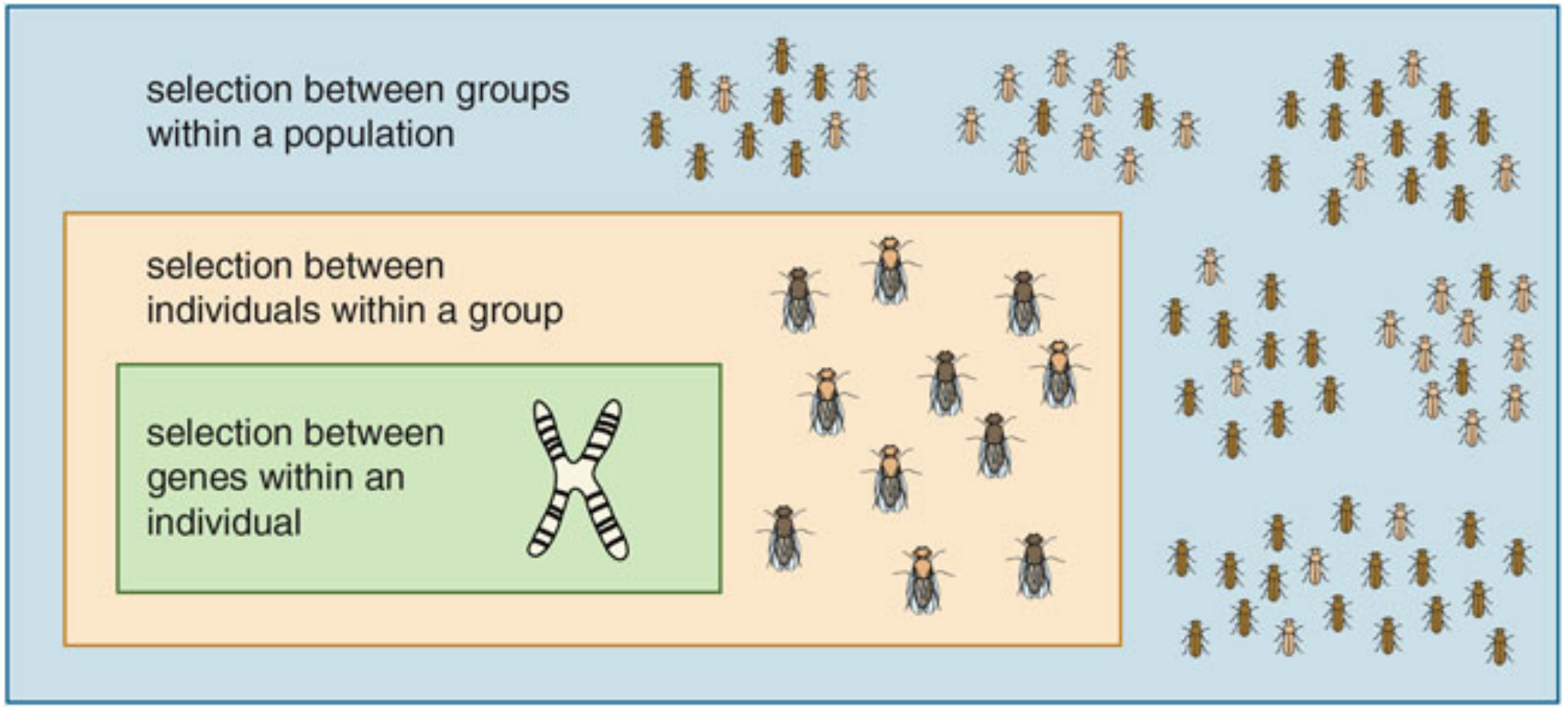


Cancer as breakdown in function?



Plan of argument

- Selection can operate on more than one level of organization, both sequentially, and simultaneously.
- Some traits are, as a consequence, byproducts of selection at other levels of organization.
- Cancer cells coopt organismic adaptations: cell signaling pathways that play roles in wound healing and embryogenesis.
- Cancer progression is a process of selection, at the level of individual cells, and cell lineages (or populations).
- Not all cancers succeed in progression to metastasis; indeed, most fail.
- Those collectives that succeed in progression to invasion and metastasis have capacities are best described as characters of the tumor (collective) as a whole (its parts in interaction), and not simply the additive properties of parts.
- If cooperation In service of adaptation s essential to "organismality," then, tumors may be viewed as proto-organisms.


selection between groups within a population
selection between individuals within a group
selection between genes within an individual

A "Diachronic" Perspective on Multilevel Selection

…the biological hierarchy is *itself* the product of evolution – entities further up the hierarchy, such as multi-cellular organisms, have obviously not been there since the beginning of life on earth… So ideally, **we would like an evolutionary theory which explains how the biological hierarchy came into existence, rather than treating it as a given**… **the levels of selection question is not simply about identifying the hierarchical level(s) at which selection *now* acts**, which is how it was traditionally conceived, **but about identifying the mechanisms which led the hierarchy to evolve in the first place**. (Okasha, 2006 "Multilevel selection and the major transitions in evolution.")

Levels of Organismality & Major Transitions

[there are several] "…levels of organism, and each level was attained by merging formerly separate individuals at a lower level…. Multi-cellular individuals are cooperative groups of cells, eukaryotic cells are cooperative assemblages of multiple prokaryotic lineages and prokaryotic cells must have emerged by assembly of formerly independent replicators. These major transitions in evolution construct new levels of organism out of separate individuals."

(Queller & Strassman, 2009)

Features of "organismality" (cf. Queller and Strassman)

- physical contiguity
- development from a single cell
- short term and long-term genetic cotransmission
- germ-soma separation
- membership of the same species
- near unanimous cooperation

Multilevel selection (Damuth and Haisler, 1988)	MLS1	MLS2
"Group selection" refers to:	Change in frequency of individuals, where group membership has an effect on individual fitness	Change in frequencies of different kinds of groups
Fitnesses are properties of:	Individuals	Groups
Characters are values attributed to:	Individuals (e.g. altruism)	Groups (e.g., group mean, population density, proportion of different phenotypes)
Appropriate for investigation of:	Evolution of characters of individuals likely affected by group membership	Changing proportions of different types of groups; different propensities to go extinct or to found new groups

Michod and Nedelcu, 2003. "On the reorganization of fitness during evolutionary transitions in individuality." *Integr. Comp. Biology*. 43(64-73)

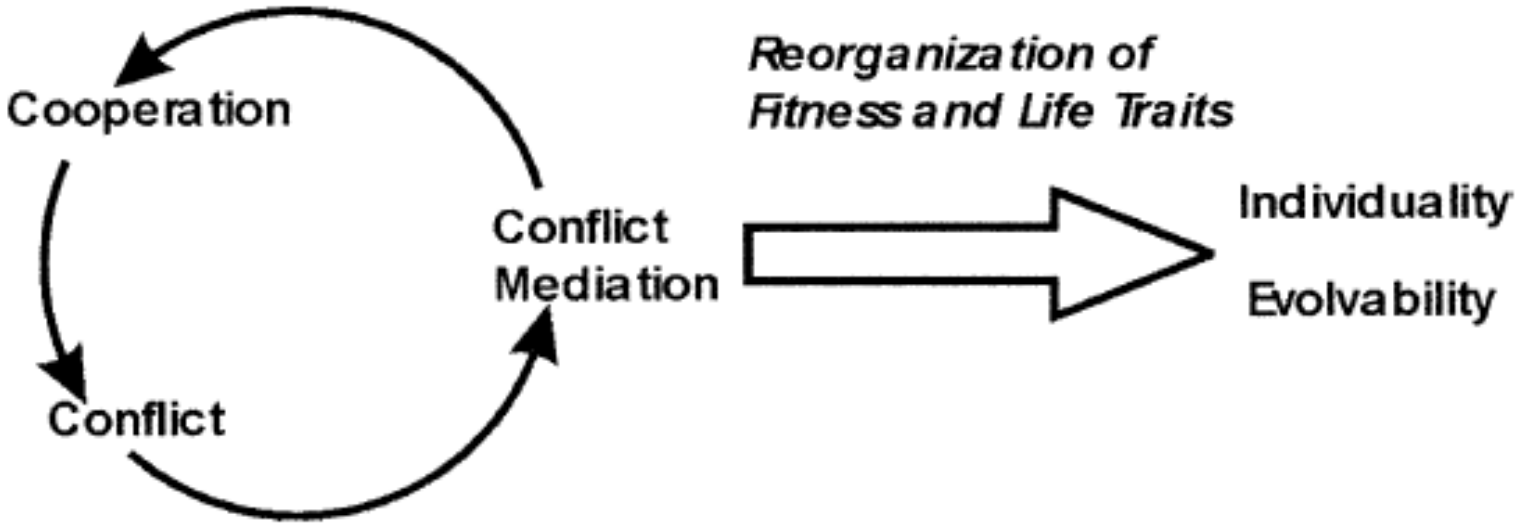
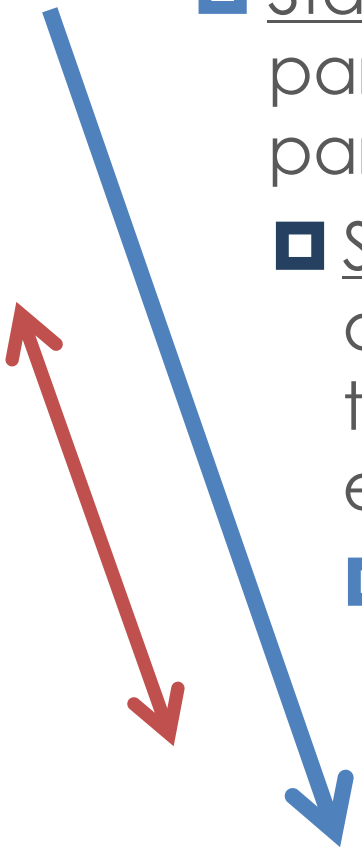


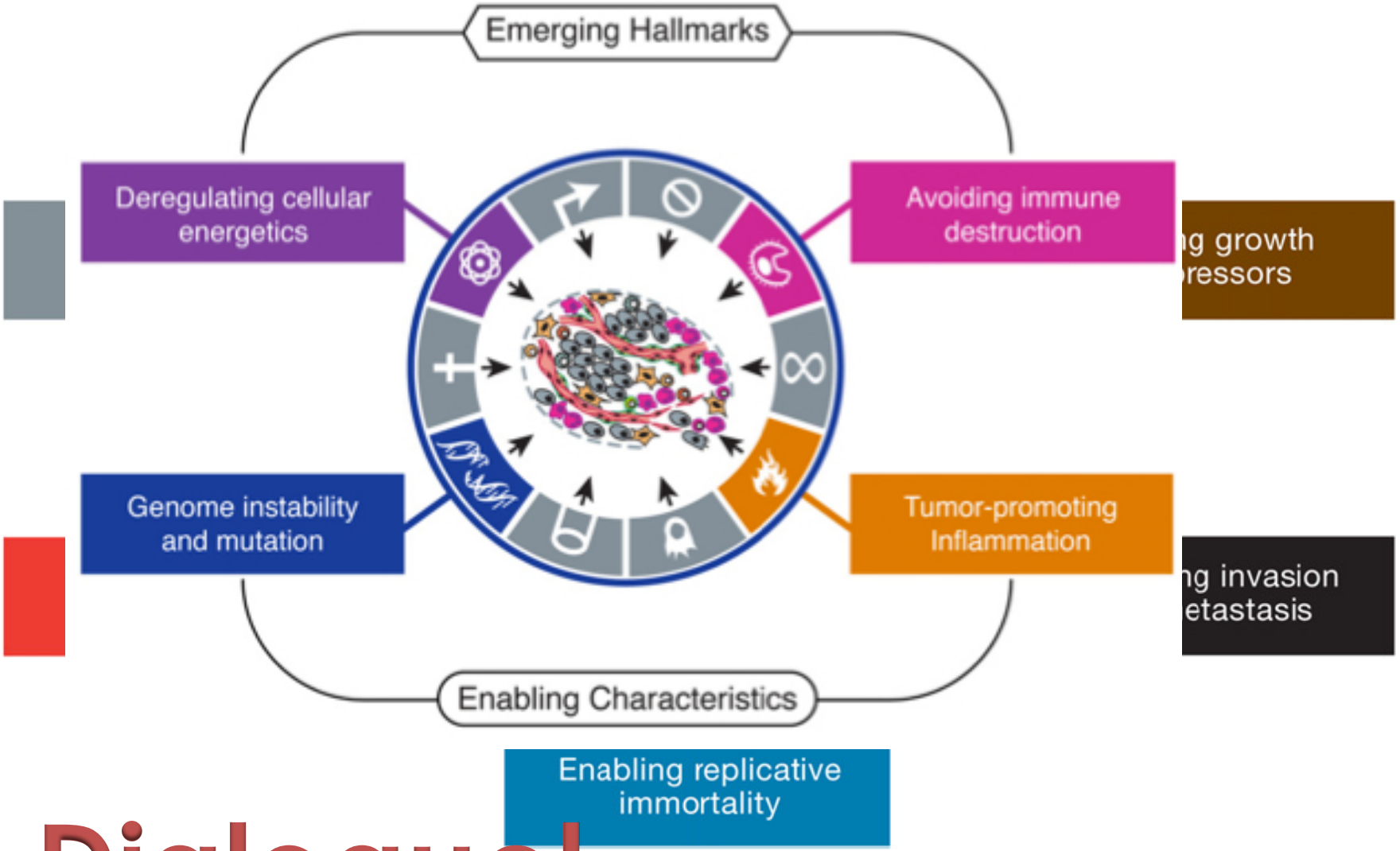
FIG. 1. Conflict and conflict mediation in evolutionary transitions. Stability of the group, and ultimately the emergence of individuality at a higher level, requires the mediation of conflict. Conflict may arise directly in response to cooperation as defection spreads within the group. Conflict mediation through the re-organization of fitness components (survival and reproduction) and general life-traits (immortality and totipotency) ads to further increases in cooperation and individuality at the group level. A successful mediation reflects in the continued evolvability of the new higher-level unit, which is fueled by new modes of cooperation and new ways to mediate conflict among component entities leading to new adaptations at the higher-level.

Major Transitions (cf. Okasha, 2006)



- Stage 1: collective fitness defined as average particle fitness (co-operation spreads among particles)
  - Stage 2: collective fitness not *defined* as average particle fitness, but still *proportional* to average particle fitness (collectives start to emerge as entities in their own right)
    - Stage 3: collective fitness neither defined as nor proportional to average particle fitness (collectives have fully emerged; fitnesses are decoupled)

From Monologue...



To Dialogue!

From "Monologue" to Dialogue

- …non-neoplastic cells are active, indeed essential **collaborators** of the neoplastic epithelial cells within tumor masses…
- during the course of tumor progression, stromal cells become **increasingly adept at helping their epithelial neighbors to survive and proliferate**…
- stromal cells co-evolve with their neoplastic neighbors during these long periods of tumor development by altering their genomes in order to adapt to the physiological stresses present within tumors. (Weinberg, 2014. *The Biology of Cancer*, 2nd ed. (pp. 585, 601, 603)

Interactions that Facilitate Invasion & Metastasis

- Carcinomas recruit stromal cells through heterotypic signaling, attracting:
  - EPCs (endothelial percursor cells) from the blood marrow, which differentiate into blood vessels
  - Platelets, which release PDGF (platelet derived growth factor) increase permeability of blood vessels, and attract fibroblasts.
  - Fibroblasts and myofibroblasts degrade the extracellular matrix
  - Monocytes, neutrophils, mast cells, play a role in activating growth, assist in angiogenesis
  - MMPs (metrix metalloproteinases) remodel the extracellular matrix, release factors that activate EMT (epithelial-mesenchymal transition), imparting motility and invasiveness.

Collaboration as Co-option

Schäfer and Werner, 2008. "Cancer as an overhealing wound: an old hypothesis revisited." *Nature Reviews Molecular Cell Biology*. 9:628-638.

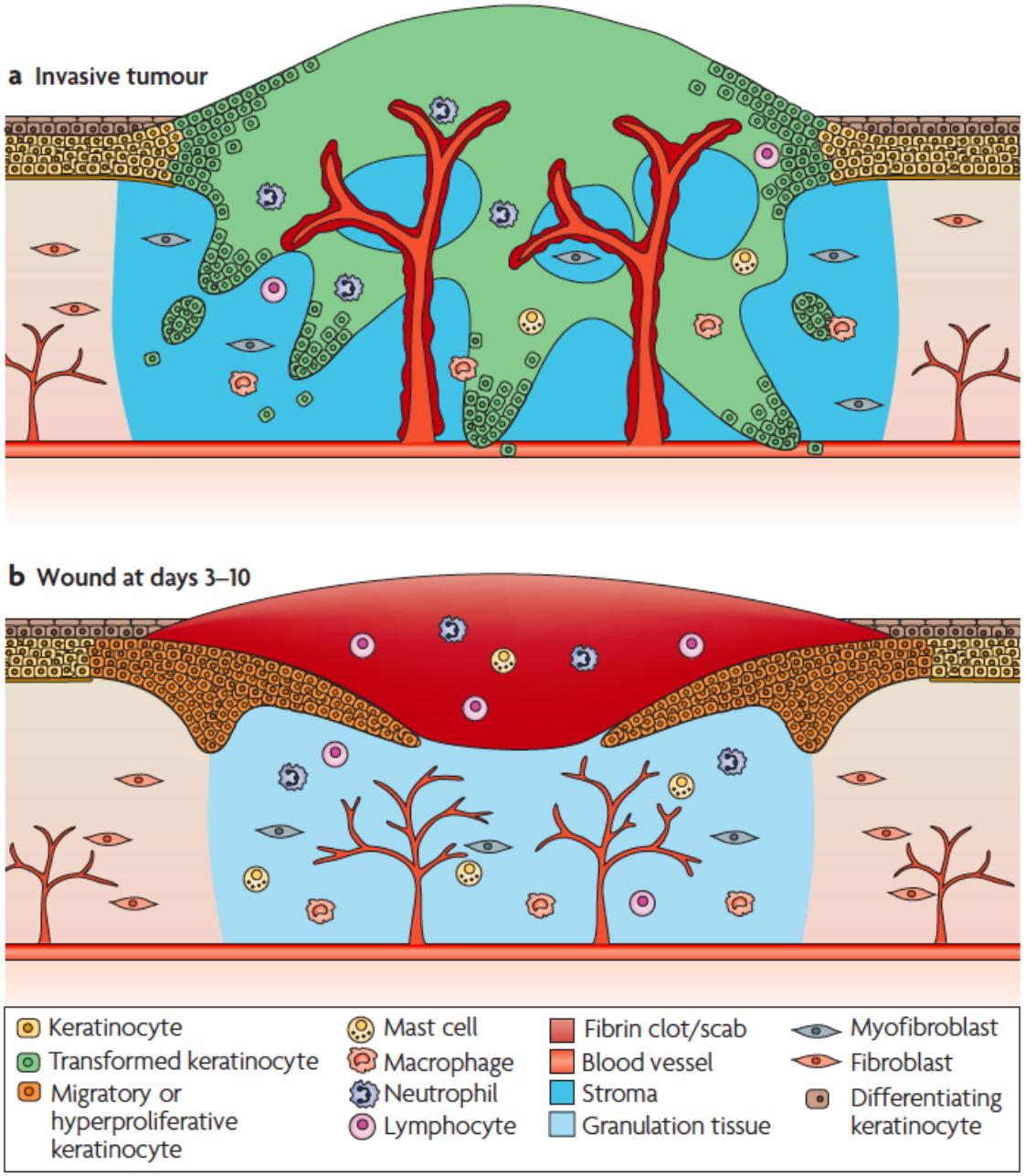
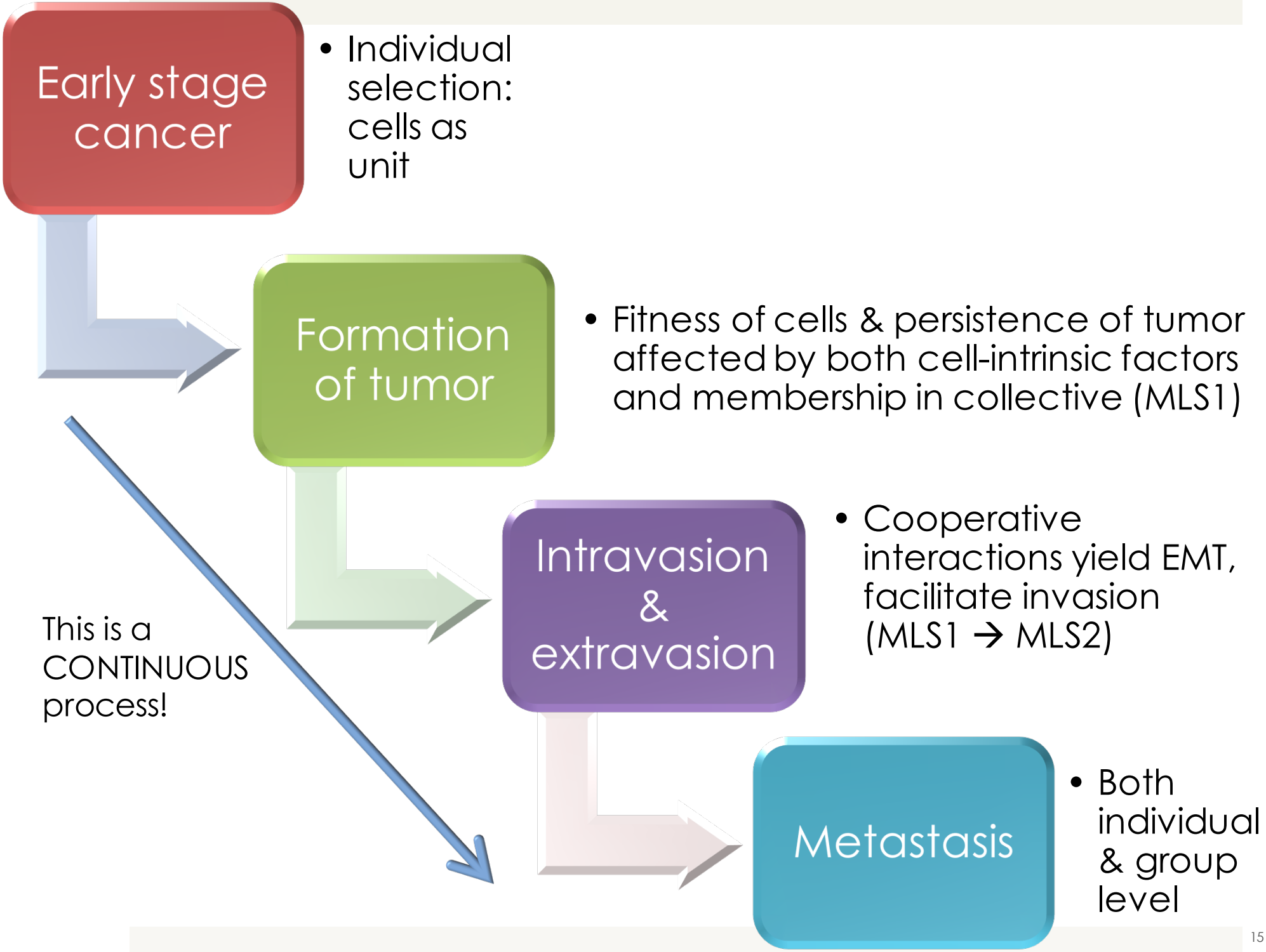


Figure 2 | **Cellular parallels between a tumour and a skin wound.** Schematic


Early stage cancer
• Individual selection: cells as unit
Formation of tumor
• Fitness of cells & persistence of tumor affected by both cell-intrinsic factors and membership in collective (MLS1)
Intravasion & extravasion
• Cooperative interactions yield EMT, facilitate invasion (MLS1 → MLS2)
Metastasis
• Both individual & group level
This is a CONTINUOUS process!

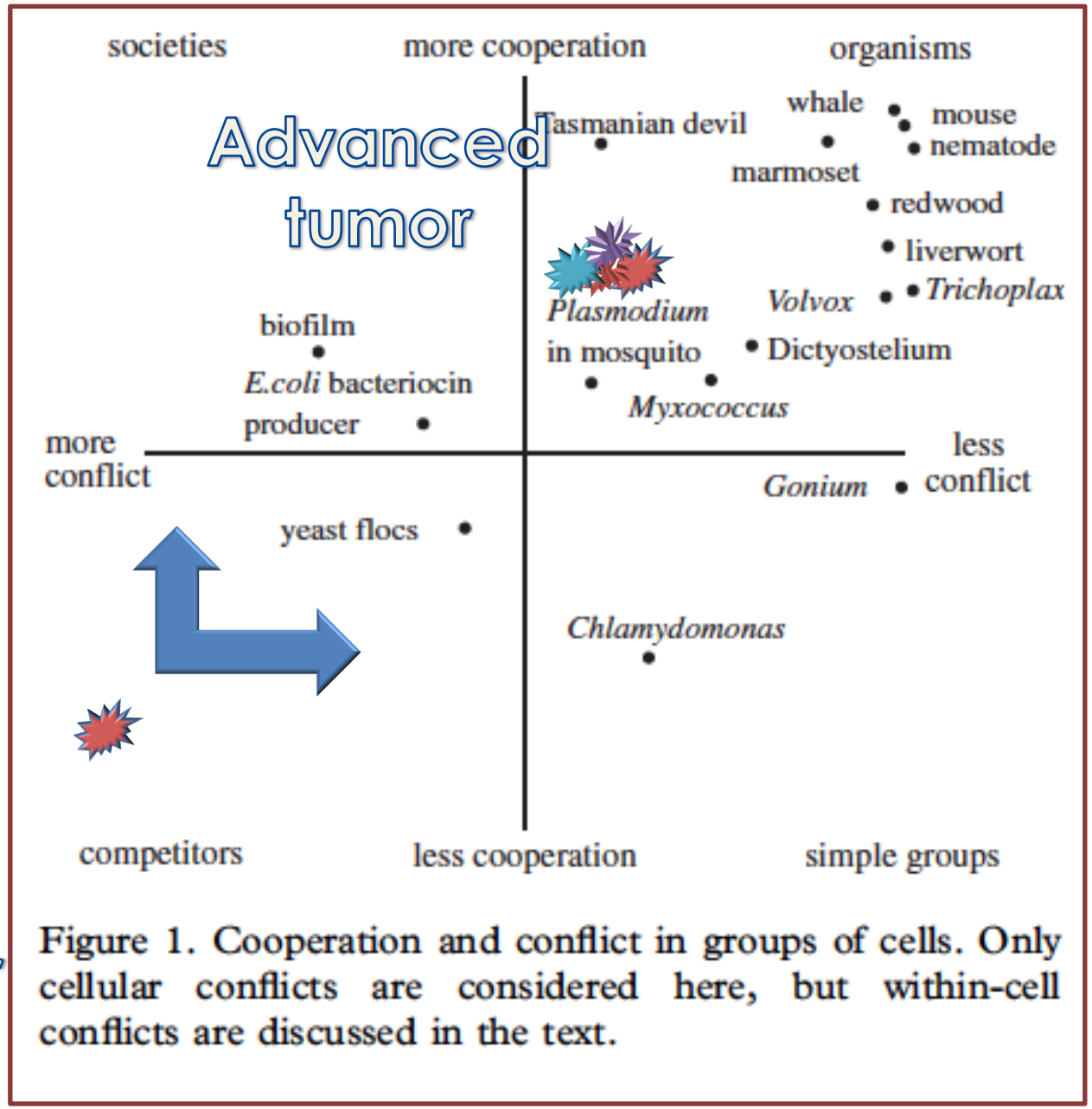
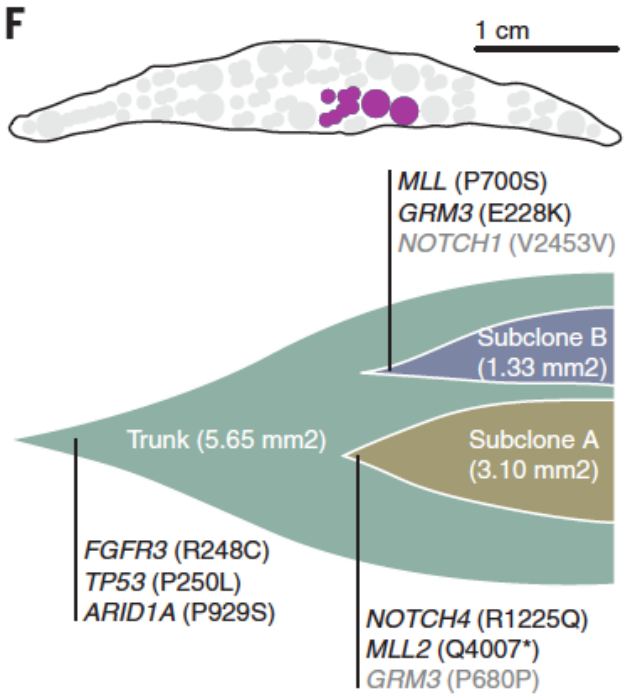


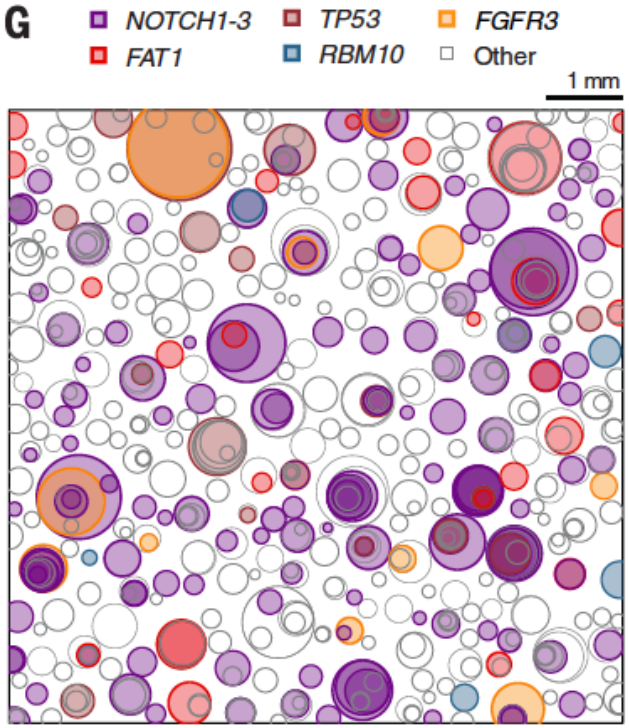
Figure 1. Cooperation and conflict in groups of cells. Only cellular conflicts are considered here, but within-cell conflicts are discussed in the text.

Queller & Strassman, 2009. "Beyond society: the evolution of organismality. Phil. Trans. R. Soc. B 364, 3143–3155.

How is this MLS1?

- Most cancerous cells do not progress to an invasive and metastatic tumor, but are destroyed by immune response, lack of access to blood supply, etc. (see, e.g., Martinocerena, et. al., 2015)
- The relative success of a population of cancer cells depends not only upon the individual cells' properties, **but on membership in a collective successful at recruiting non-cancer stromal cells, which are active participants in tumor progression**, resisting immune response, attracting blood supply, etc.



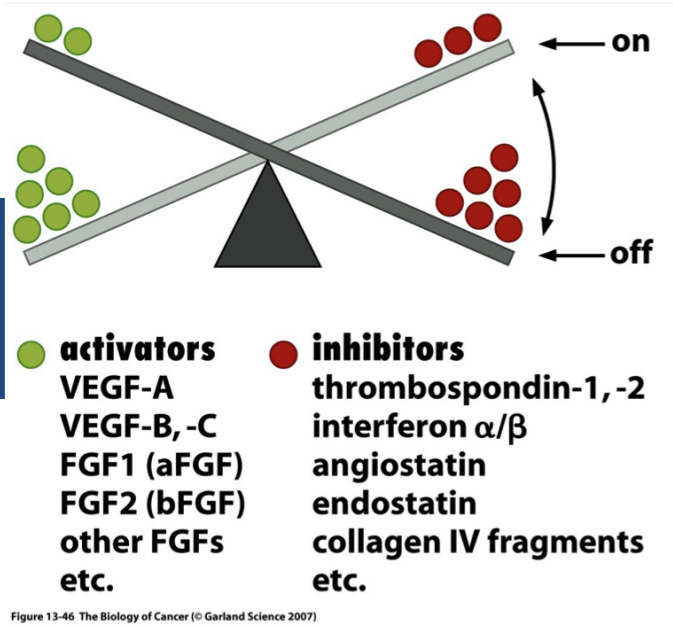


Do we all have cancer?

Tissue architecture, the tissue microenvironment – inflammatory and immune response, the extracellular matrix – play an essential role in preventing most population of proto-cancer cells from becoming invasive cancer. Thank goodness! (see, e.g., Bissell and Hines, 2011)

Martincorena, et. al., 2015, "High Burden and Pervasive Positive Selection of Somatic Mutations in Human Skin." *Science*. Vo. 348: 6237.

Critical Mass

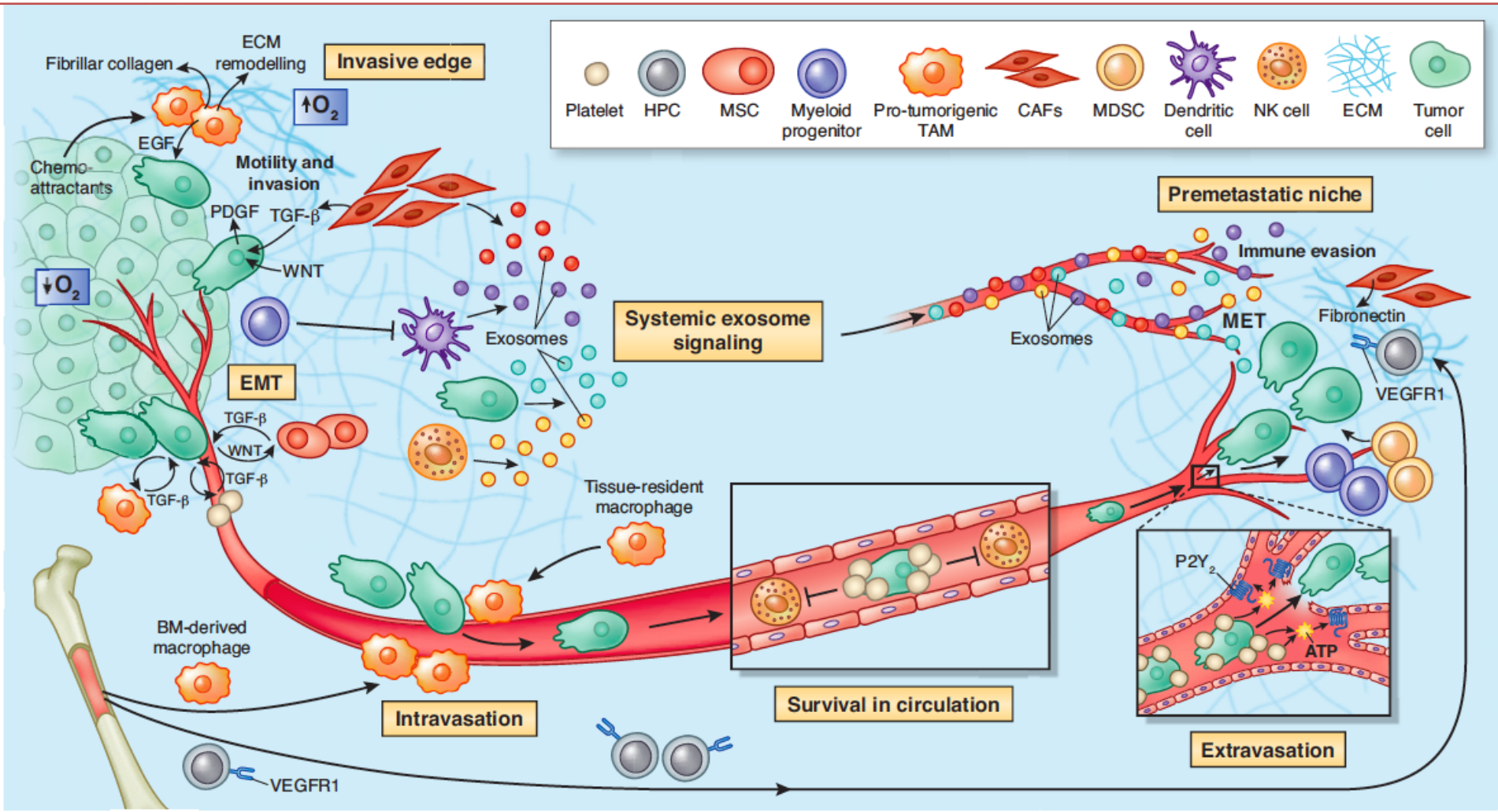


- You need **critical mass = a combination of cancer and stromal cells** to:
  - "trip the angiogenic switch" (attract a blood supply)
  - "remodel" (break down the extracellular matrix, to enable invasion of the basement membrane)
  - Grow (Heterotypic signaling promotes angiogenesis and growth of cells: carcinoma cells release growth factors orchestrate an inflammatory response, which in turn stimulates the proliferation of epithelial cells and the process of angiogenesis in the tumor stroma.)
- **I.e., the relative success of tumor cells depends upon their membership in a collective… MLS1**

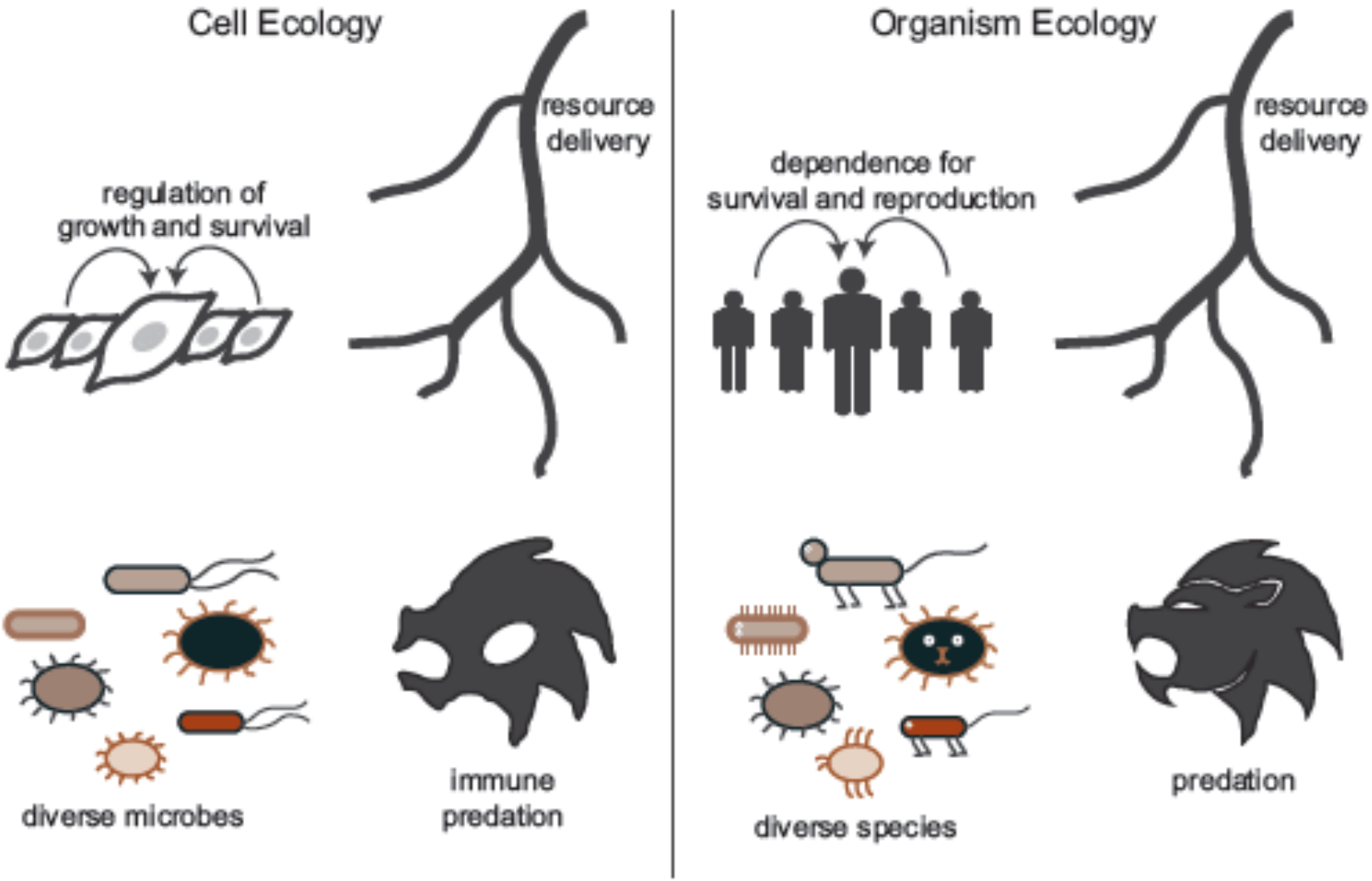
How is this MLS2?

- Most metastases are not successful.
- Successful metastasis requires multiple "showers" of cells, that travel together with platelets, macrophages, etc.
- This is multi-generational: secondary metastatic showers yield secondary metastases.
- Success depends on:
  - Properties of single cells, inherited from ancestral tumor & cooption of organismic adaptations (signaling pathways)
  - Nice construction (remodeling of the tissue microenvironment)
  - Properties of groups (cooperative interactions)

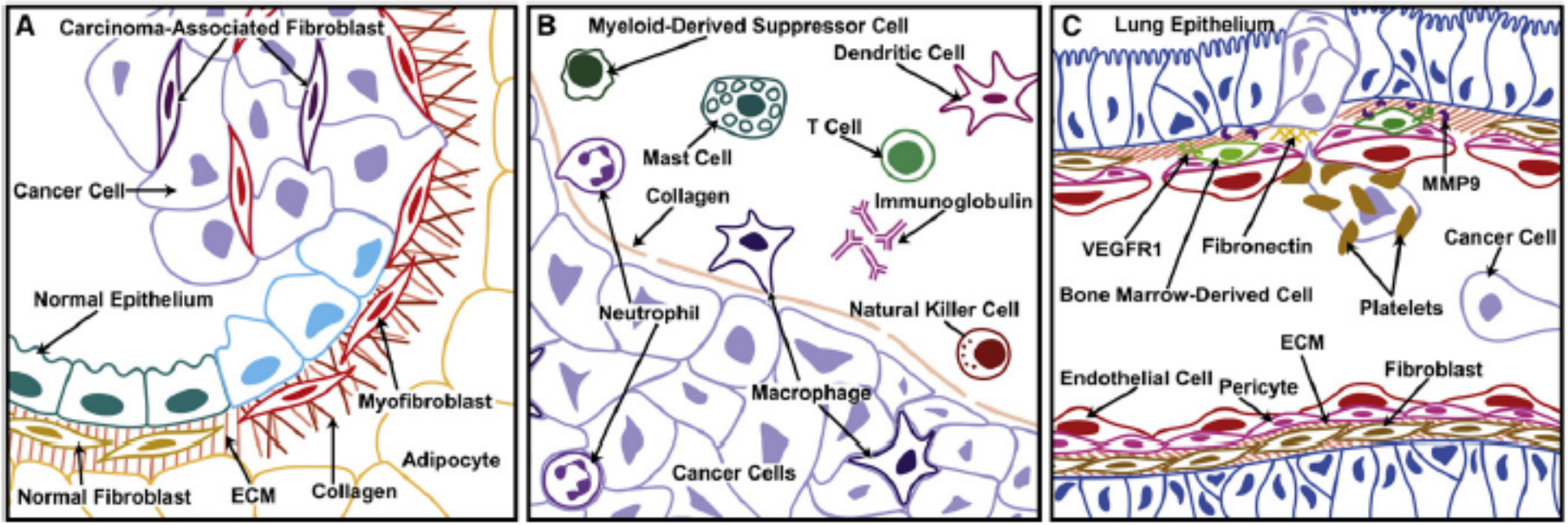
Cooperative interactions in metastasis



Quail and Joyce, 2013. "Microenvironmental regulation of tumor progression and metastasis." Nature Medicine. 19(11):1423-1437.



Aktipis & Nesse, 2013. Evolutionary foundations for cancer biology. *Evolutionary Applications*. 144-159.



Cf. Egeblad, et. al., 2010 "Tumors as organs: Complex tissues that interface with the whole organism," Cell: Developmental Cell Review.

Sterelny on lineages as targets of selection

- **Lineages are interactors** in and of themselves. They have properties in virtue of which they grow well, or fail to grow well…the **characteristics in question depend on the characteristics of the individual organisms** from which the lineages are composed... Yet **though there is dependence, there is no simple reduction**. A lineage may, for example, respond to environmental change because of the **variability of its gene pool, or the range of habitats through which it is dispersed**. These are not mysterious properties, but neither are they the properties of individual organisms. (Sterelny, 1996)

Group level properties that may enhance fitness

- Tumor Heterogeneity
- Complex cooperative organization/spatial organization/potential for stem cell renewal
- Segregation of the germ line (stem cells), metastasis
- Coadaptation (e.g., Paget's Seed and soil)
- Mosaic tissue structure (some tissues more prone to cancer, due to tissue architecture)

Conclusions

- Cancer progression in many ways resembles both a "reversal" and "rehearsal" of the emergence of multicellularity (or, as PGS puts it: "Re-Darwinization.")
- This process involves cooption of organismic adaptations (a byproduct).
- Metastasis is a process that involves both selection at the individual and group level – collective and individual fitness.

MANY Thanks to the Pradeu lab, to the graduate students, faculty and staff for inviting me!