Understanding cancer progression and its control: the (im)balance between tissue construction, destruction and reconstruction?

*Conceptual analysis of immune activation in the context of the tumour microenvironment*

Elena Rondeau, Thomas Pradeu, Nicolas Larmonier

*CNRS-UMR5164 ImmunoConcept, University of Bordeaux, France*
Cancer: defining characteristics?

Cancer cell - centered characteristics

Contextual and environmental characteristics

Cancer: defining characteristics?

- Cell proliferation and migration
- Angiogenesis
- Epithelial/mesenchymal transitions
- Role of extracellular matrix

- Organ-specific origin of malignant cells
- Differentiation plasticity
- Long-distance communication

- Stroma remodelling
- Inflammation and immune activation
- Vascular alterations
Two biological analogies for cancer

- Cell proliferation and migration
- Angiogenesis
- Epithelial/mesenchymal transitions
- Role of extracellular matrix

- Organ-specific origin of malignant cells
  - Differentiation plasticity
  - Long-distance communication

- Stroma remodelling
  - Inflammation and immune activation
  - Vascular alterations

Organ development?

Tissue repair?
Organ development?

Tumors as \textbf{Organs}: Complex Tissues that Interface with the Entire Organism

Mikala Egeblad, \textsuperscript{1,2} Elizabeth S. Nakasone, \textsuperscript{1,2} and Zena Werb \textsuperscript{1,2}

\textsuperscript{1}Cold Spring Harbor Laboratory, 1 Bungtown Road, Cold Spring Harbor, NY 11724, USA
\textsuperscript{2}Department of Anatomy, University of California, 513 Parnassus Avenue, Box D452, San Francisco, CA 94143, USA

Correspondence: egeblad@cshl.edu, zena.werb@cshl.edu

DOI 10.1016/S0001-8504(08)00002-8

Tumors are \textbf{unique organs} defined by abnormal signaling and context

Derek Radisky, Carmen Hagiou and Mina J. Bissell

PUTTING TUMOURS IN CONTEXT

Mina J. Bissell and Derek Radisky

Return of de-differentiation: why cancer is a developmental disease

Luis Filipe Teixeira da Costa, PhD

Of Extracellular Matrix, Scaffolds, and Signaling: Tissue Architecture Regulates Development, Homeostasis, and Cancer

Celeste M. Nelson and Mina J. Bissell

Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, California 94720, email: cmnelson@llnl.gov, mina@lbl.gov
Cancer as a developmental process?

Cancer as a developmental process?

Cancer as a **dysregulated developmental process**?

Disorganisation, evasion and functional isolation from other tissues?

---

Tissue repair?

Cancer-related inflammation
Alberto Mantovani1, Paola Allavena, Antonio Sica1 & Frances Balkwill1

Activation of Host Wound Responses in Breast Cancer Microenvironment
Melissa A. Troester,1,2 Myung Hae Lee,3 Matthew Carter,4 Cheng Fan,2 David W. Cowan,2 Erick Roman Perez,4 Jason R. Pirone,2 Charles M. Perou,3,4 D. Joseph Jerry,5,6 and Sallie Smith Schneider6

The wound inflammatory response exacerbates growth of pre-neoplastic cells and progression to cancer
Nicole Antonioli1, Marie Louise Bamberg-Klebe,1,2,4 Laura Chien Ward1,4, John Collin1,4, Ib Jørgen Christensen,2 Torben Mønsebaek2, Henrik Schmitz2,4, Yi-Feng2,4 & Paul Martin1,2,4,5,6

Cancer as an overhealing wound: an old hypothesis revisited
Matthias Schöfer and Sabine Werner
Cancer as a repair process?


Fibrin deposition in the stroma
Cancer as a repair process?

Cancer as a dysregulated repair process?

Stages of tissue repair

- Inflammation (0-48 hours)
- New tissue formation (2-10 days)
- Remodeling (weeks-months)

Wound at days 7–14
Cancer as a dysregulated repair process?

Stages of tissue repair

- Inflammation (0-48 hours)
- New tissue formation (2-10 days)
- Remodeling (weeks-months)

Stages of cancer progression

- Growth
- Survival
- Angiogenesis
- Invasion
- Inflammation

Alteration and/or amplification of healing mechanisms?

Nature Reviews | Cancer
“Cancer cells reactivate a latent behavioural programme that is usually confined to embryonic development and tissue repair, although in cancer cells it occurs in an exaggerated and uncontrolled manner” (Schäfer and Werner, 2008)

Understanding cancer progression and its control: the (im)balance between tissue construction, destruction and reconstruction?
Understanding cancer progression and its control

Conceptual link with the notion of robustness?

Robustness as an active and ubiquitous property of functional persistence

Understanding cancer progression and its control

Conceptual link with the notion of robustness?

Robustness as an active and ubiquitous property of functional persistence

- “Complex biological systems must be robust against environmental and genetic perturbations to be evolvable” (Kitano, 2004)
- Physiological robustness as the “ability to resist perturbations that decrease the probability to survive” (Sholl and Lemoine)

Understanding cancer progression and its control

Conceptual link with the notion of robustness?

Robustness as an active and ubiquitous property of functional persistence

- “Complex biological systems must be robust against environmental and genetic perturbations to be evolvable” (Kitano, 2004)

- Physiological robustness as the “ability to resist perturbations that decrease the probability to survive” (Sholl and Lemoine)

→ Disease as a failure/rupture of robustness?

Cancer as a robust system?

Cancer robustness as the maintenance of tumour cell proliferation potential despite genetic and environmental perturbations (Kitano, 2004)

Cancer as a robust system?

Cancer robustness as the maintenance of tumour cell proliferation potential despite genetic and environmental perturbations (Kitano, 2004)

- Functional redundancy through cellular heterogeneity
- Feedback control through complex interaction loops
- Sensing signals and constraints
- Response to stress and adaptability

Cancer as a robust system?

Cancer robustness as the maintenance of tumour cell proliferation potential despite genetic and environmental perturbations (Kitano, 2004)

- Functional redundancy through cellular heterogeneity
- Feedback control through complex interaction loops
- Sensing signals and constraints
- Response to stress and adaptability

→ Definitional requirements:
- Precise nature of actors: “system”, “functions”, “perturbations”?
- Questioning the “gradual degradation of function in response to damage”?  

Cancer as a robust system?

Fragility trade-offs and implications for cancer therapy

“there are trade-offs between robustness, fragility, performance and resource demands, which explain system behaviour, including the patterns of failure” (Kitano, 2004)
Fragility trade-offs and implications for cancer therapy

“there are trade-offs between robustness, fragility, performance and resource demands, which explain system behaviour, including the patterns of failure” (Kitano, 2004)

- Lessons from the “highly optimized tolerance” (HOT) theory (Carlson and Doyle)
- Focus on the cell cycle, growth and apoptosis
- Reducing heterogeneity and minimizing selective pressure
Cancer as a robust system?

Fragility trade-offs and implications for cancer therapy

“there are trade-offs between robustness, fragility, performance and resource demands, which explain system behaviour, including the patterns of failure” (Kitano, 2004)

- Lessons from the “highly optimized tolerance” (HOT) theory (Carlson and Doyle)
- Focus on the cell cycle, growth and apoptosis
- Reducing heterogeneity and minimizing selective pressure

→ Therapeutic strategies based on the control of cellular dynamics

“robustness can be controlled by carefully selecting modulation targets and the systematic use of multiple drugs”

+ question of applicability in vivo and management of tumour resistance?
Open questions inspired by the tissue (re)construction analogies:

- Exploring the spatial and temporal levels of cancer robustness
Cancer as a robust system?

Open questions inspired by the tissue (re)construction analogies:

- Exploring the spatial and temporal levels of cancer robustness
- Who is robust? (malignant cells / tumour microenvironment / cancer vs organism)
- Where and when? (tumour site(s) and dissemination, stages of cancer progression)
- How much change is allowed/tolerated?
- Cancer typology and degrees of robustness?
Cancer as a robust system?

Open questions inspired by the tissue (re)construction analogies:

- Exploring the spatial and temporal levels of cancer robustness
  -> Who is robust? (malignant cells / tumour microenvironment / cancer vs organism)
  -> Where and when? (tumour site(s) and dissemination, stages of cancer progression)
  -> How much change is allowed/tolerated?
  -> Cancer typology and degrees of robustness?

- Is cancer progression and control a matter of conflicting robustness between tumour and host?
- How can tumour cell migration and metastasis causality be better understood in terms of cancer adaptability to change?
- Investigating the notions of (in)stability, homeostasis, fitness, evolvability
Cancer robustness in dysregulated development?

- Robustness in normal development and morphogenesis


Attractors as “distinct, self-stabilizing gene expression patterns that encode a particular relatively stable phenotype” (Huang, 2011)
Cancer robustness in dysregulated development?

- Robustness in normal development and morphogenesis
- Cancer: enabling role of mutations
- Status of “cancer stem cells”?

Attractors as "distinct, self-stabilizing gene expression patterns that encode a particular relatively stable phenotype" (Huang, 2011)

Cancer as a robust system?

Cancer robustness in dysregulated development?
- Robustness in normal development and morphogenesis
- Cancer: enabling role of mutations
- Status of “cancer stem cells”?

Broader questions:
- Embryonic vs post-natal development (and robustness of other communication systems?)
- Clonal evolution and “populational” robustness

Attractors as "distinct, self-stabilizing gene expression patterns that encode a particular relatively stable phenotype" (Huang, 2011)

Cancer robustness in dysregulated repair?

“Robustness allows changes in the structure and components of the system owing to perturbations, but the key idea is that robustness leads to the maintenance of specific functions” (Truchetet and Pradeu, 2018)

Cancer as a robust system?

Cancer robustness in dysregulated repair?

“Robustness allows changes in the structure and components of the system owing to perturbations, but the key idea is that robustness leads to the maintenance of specific functions” (Truchetet and Pradeu, 2018)

→ Nature and kinetics of robustness in cancer?

### Cancer robustness in dysregulated repair?

<table>
<thead>
<tr>
<th>TRS robustness</th>
<th>Cancer (hijacking of TRS robustness)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasticity</strong></td>
<td>- MET/EMT with the tumor-initiating ability required for metastatic colonization [130]</td>
</tr>
<tr>
<td></td>
<td>- Plasticity between the epithelial and the mesenchymal states rather than a fixed phenotype [131]</td>
</tr>
<tr>
<td></td>
<td>- UPR in macrophage polarization and plasticity with shift to M1-like profile [121]</td>
</tr>
<tr>
<td><strong>Functional redundancy</strong></td>
<td>- IL-6 and glycoprotein 130 in the pathophysiology of multiple myeloma [123]</td>
</tr>
<tr>
<td><strong>Constant surveillance</strong></td>
<td>- TRMs in human non-small cell lung tumor tissue [125]</td>
</tr>
<tr>
<td></td>
<td>- Role of amphiregulin in orchestrating responses to tumors [136]</td>
</tr>
<tr>
<td><strong>Restrain</strong></td>
<td>- TAMs recruitment in triple negative breast cancer [124]</td>
</tr>
<tr>
<td></td>
<td>- Tregs in tumor progression [138]</td>
</tr>
<tr>
<td></td>
<td>- Tregs and cancer cell clearance [139]</td>
</tr>
<tr>
<td></td>
<td>- Tregs and cancer immunotherapies with IL-2 [140]</td>
</tr>
<tr>
<td></td>
<td>- To target immune checkpoints such as CTLA4, PD1 or TIGIT to both interfere with Treg function and enhance effector responses at the same time [141]</td>
</tr>
<tr>
<td><strong>Dynamic adjustment</strong></td>
<td>- Cancer cells and use of the dynamic potential of neutrophils [126]</td>
</tr>
<tr>
<td></td>
<td>- CCL26 in colorectal cancer cells invasion by inducing TAM infiltration [142]</td>
</tr>
<tr>
<td></td>
<td>- Inhibitors of the receptor tyrosine kinase c-MET and impairment of the mobilization and recruitment of neutrophils into tumors [143]</td>
</tr>
</tbody>
</table>

Cancer robustness in dysregulated repair?

“the concept of robustness helps better understand TRS-associated pathologies, either as a deficiency in the fundamental processes by which robustness is normally realized (plasticity, etc.), or as an emerging, local form of robustness that is detrimental to the organism” (Truchetet and Pradeu, 2018)

→ Robustness as a *dysfunction* or *dysfunctional robustness*?

Cancer as a robust system?

Cancer robustness in dysregulated repair?

“the concept of robustness helps better understand TRS-associated pathologies, either as a deficiency in the fundamental processes by which robustness is normally realized (plasticity, etc.), or as an emerging, local form of robustness that is detrimental to the organism” (Truchetet and Pradeu, 2018)

→ Robustness as a *dysfunction* or *dysfunctional robustness*?

<table>
<thead>
<tr>
<th>TRS robustness</th>
<th>Cancer (hijacking of TRS robustness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasticity</td>
<td>- MET/EMT with the tumor-initiating ability required for metastatic colonization [130]</td>
</tr>
<tr>
<td></td>
<td>- Plasticity between the epithelial and the mesenchymal states rather than a fixed phenotype [131]</td>
</tr>
<tr>
<td></td>
<td>- UPR in macrophage polarization and plasticity with shift to M1-like profile [121]</td>
</tr>
<tr>
<td>Functional redundancy</td>
<td>- IL-6 and glycoprotein 130 in the pathophysiology of multiple myeloma [125]</td>
</tr>
<tr>
<td>Constant surveillance</td>
<td>- TRMs in human non-small cell lung tumor tissue [125]</td>
</tr>
<tr>
<td></td>
<td>- Role of amphiregulin in orchestrating responses to tumors [136]</td>
</tr>
</tbody>
</table>

Cancer robustness in tumour immunity?
Cancer as a robust system?

Cancer robustness in tumour immunity?

- Elimination phase
  - Cytotoxic activity
  - Dying tumour cell
  - CD8
  - NK

- Equilibrium phase
  - Tumour cell variant
  - Developing tumour cell
  - Antigen-loss variant

- Escape phase
  - Suppressive factors
  - TAM
  - Treg
  - CD8
  - CD4
  - Inhibitory ligands

* Genetic instability and tumour heterogeneity
* Immune selection
Cancer as a robust system?

Cancer robustness in metastasis?

Cancer robustness in metastasis?

“When the environment is not optimal [...] tumour-cell survival can be assured by adaptive changes, responses that change the environment, or migration to a new environment” (Kitano, 2004)

→ Cancer dissemination as an adaptation?
→ Link with causality and tropism of metastasis?
