MCBU Projects

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Growth Control

• In normal tissue, homeostasis and growth are tightly regulated via feedback control.

Negative feedback in $p$-values explains homeostatic tissue sizes, rapid regeneration after wounding. SC/CP behavior depends on type/level of feedback present. Lander et al. (2009)

Frequent action of TGF-$\beta$ superfamily

• May also have positive feedback via factors that increase $p$-values rather than $v$-values. Wnt, FGF, EGF, Notch, Shh,...

• Feedback is reason for SC/CP behaviors ($p,v$). e.g., may not be intrinsic differences in cell types but rather a response to the microenvironment
Cell types in the IE crypt. LGR5+ fast-cycling progenitors give rise to LGR5-negative CP, which divide to give rise to TD cells. Paneth cells are niche cells that support LGR5+ cells.
Intestinal organoids
Youssefpour, Edwards, Lander, Calof, Lowengrub, in prep (2012)

Treatment with exogenous BMP

Increasing exogenous Wnt Concentration

Control (EGF, Noggin, R-Spondin)

Wnt3a + IWP1

Wnt3a

Human colon organoid.
Exogenous Wnt
Integral Feedback Contd.

In general, may have positive and negative feedback.

Olfactory epithelium

Branching morphogenesis

Yan, Lander, Calof, Lowengrub, in prep (2012)
Feedback protects against mutations

Hu, Lander, Lowengrub
In prep (2012)

Note recovery in II and III
Self-recovery

- Suggests strategy: Do not fully self-renew, instead allow differentiation.
Lineage strategy

The most deleterious cell differentiates.
Cancer cells hijack “normal” signaling processes for their own gain.
Questions

• How do such organs develop?

• How can they maintain homeostasis while at the same time protecting themselves against deleterious mutations that could lead to cancer?

• We will develop mathematical models of tissue-specific lineages (e.g., stem cells, committed progenitor cells and terminally differentiated cells), together with feedback signaling among the cells and solve these equations numerically using ordinary differential equation solvers and partial differential equation solvers adapted from our research program.

• We will focus on the intestinal epithelium where we have experimental collaborators who will provide data, which we can use to calibrate the models and to test the model predictions.
• Cancer is fundamentally a loss of control of a tightly regulated system

• Control is not always exerted directly.

• Consider an example from engineering:

Altitude results from a balance of lift and gravitational forces.

To control altitude, do not manipulate gravity, or adjust lift directly.

Instead:

  - Change wing shape (flaps)
  - Change thrust

Indirectly these affect lift by modifying airflow over wing.

Failure of control is distinctive.
Lineages and Cancer

• Increasing evidence that lineage progression occurs in tumors

Cells with unlimited potential for self-renewal (CSC/CIC) give rise to large numbers of cells which lack this capability.

PROCR+/ESA+
MDA-MB-231
Cells differentiate
Asymmetrically
In vivo

Hwang-Verslues et al. (unpublished)

Stem cell hypothesis:
cancer diagnostic, prognostic and therapeutic efforts need to be focused on that population of cells—often a small minority—that undergoes long-term self-renewal.

Acknowledges lineage progression, but does not directly address role of lineages.
Lineages and Cancer Contd.

Since lineages exist in tumors, it is reasonable to expect that some forms of growth control (not necessarily normal) still occur in cancer.

If so, this should imply:

- Lineages operate within tumors because feedback processes drive cells to adopt SC and CP behaviors.

- Progressive loss of growth control during tumor progression is connected to progressive loss of feedback regulation.

- Features and behaviors appear during tumorigenesis/progression that reflect the underlying feedback-driven modes of growth control—size, shape, growth rate, stem cell fraction, etc.
Experimental evidence of Control of CSC/CIC % in BRCA1 Mammary Tumors

CSC/CIC populations remarkably consistent after re-implantation

Fig. 1. Control of the percentages of cancer stem cells in the BRCA1 mammary tumor model. B, Approximately 3.8% to 8.0% (mean, 5.9%) of tumor cells express the normal mammary stem cell markers, CD29^{hi}CD24^{med}. C, Sorted CD29^{hi}CD24^{med} cells are tumorigenic (arrows). D, a representative FACS profile of the resulting tumors following CD29^{hi}CD24^{med} cell transplantsations showing the cancer stem cells represent a minority, 5.6%, of the tumor mass. (Shafee et al., 2008).

• CSC/CIC populations remarkably consistent after re-implantation
Low proteasome activity is typical for CSC/CICs

- Cells engineered to express ZsGreen fused to ODC (orthinine decarboxylase), which is degraded by 26S proteasome
Fractionated radiation causes proliferation of cancer stem cells (*accelerated re-population*)

**0 Gy**

**5x3 Gy**

- Ki67
- ZsGreen
- DAPI
Radiation-induced reprogramming of breast cancer cells

Lagadec, Chann; UCLA, Radiation Oncology
Vlashi, Erina; UCLA, Radiation Oncology
Della Donna, Lorenza; UCLA, Radiation Oncology
Dekmezian, Carmen; UCLA, Radiation Oncology
Pajonk, Frank; UCLA, Radiation Oncology
Questions

• But, what induces increasing population of cancer stem cells?

• Do these cells tend to produce more of themselves (self-renewal), do they increase their birth rates?

• Do differentiated cells reprogram to acquire stem cell-like characteristics? We will explore these questions using mathematical modeling and numerical simulation.

• We will develop mathematical models of tissue-specific lineages (e.g., stem cells, committed progenitor cells and terminally differentiated cells), together with feedback signaling among the cells and solve these equations numerically using ordinary differential equation solvers and partial differential equation solvers adapted from our research program.

• We will focus on breast cancer where we have an experimental collaborator who will provide data, which we can use to calibrate the models and to test the model predictions.