Evolutionary dynamics and treatment of cancer

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1. Chromosomal instability (CIN)

2. Drivers & passengers

3. Mono therapy (CML, colon)

4. Targeted combination therapy
Is genetic instability an early event, a driving force of cancer progression?
Colon cancer

normal          adenoma            cancer           metastasis

APC       KRAS/      PIK3CA/     p53/    …
BRAF      PTEN        BAX    …

time
All colon cancers have genetic instability (85% CIN, 15% MIN)
normal          adenoma            cancer           metastasis

APC       KRAS/      PIK3CA/     p53/    ...

BRAF      PTEN        BAX    ...

Does CIN occur before APC?
Cancer initiation

$TSP^{+/+} \rightarrow TSP^{+-} \rightarrow TSP^{-/-}$
CIN mutations

... cause fast LOH
The diagram depicts the following transitions:

- $TSP^{++}$ to $TSP^{+-}$
- $TSP^{+-}$ to $TSP^{-/-}$

The highlighted area indicates:

- 2 hits

The diagram also includes two instances of $TSP^{++}$ and $TSP^{-/-}$ with the term 'CIN'.
Knudson’s two hit hypothesis

\[ TSP^{+/+} \xrightarrow{1^{\text{st}} \text{hit}} TSP^{+/-} \xrightarrow{2^{\text{nd}} \text{hit}} TSP^{-/-} \]
Knudson’s two hit hypothesis revisited

\[ TSP^{+/+} \xrightarrow{1^\text{st hit}} TSP^{+/-} \xrightarrow{2^\text{nd hit}} TSP^{-/-} \]

\[ TSP^{+/+} \xrightarrow{1^\text{st hit}} TSP^{+/-} \xrightarrow{2^\text{nd hit}} TSP^{-/-} \]
Original CIN

One or a few neutral CIN genes are enough, if one TSP genes needs to be inactivated.

One or a few costly CIN genes are enough, if two TSP genes need to be inactivated (in rate limiting situations).
Accumulation of drivers

Bozic et al., PNAS 2010
Accumulation of passengers

\[ n(t) = vt \]
• Number of passengers \( n(t) = vt \)

• Time to \( k \) drivers
\[
t_k = \frac{1}{2s} \log \frac{4ks^2}{u^2} \log k
\]

• Passengers vs drivers
\[
n(k) = \frac{v}{2s} \log \frac{4ks^2}{u^2} \log k
\]
Geographic mapping of metastatic clones in pancreatic cancer

Yachida et al., Nature 2010
Timing the evolution of pancreatic cancer

Tumorigenesis begins with an initiating mutation in a normal cell that confers a selective growth advantage. Successive waves of clonal expansion occur in the course of tumour evolution. The schema of the genetic evolution of pancreatic cancer illustrates this process.

- **$T_1$** (average of 11.7 ± 3.1 years) is the time interval from the initiation of the tumour to the birth of the cell that founded the tumour.
- **$T_2$** (average of 6.8 ± 3.4 years) is the time interval from the birth of the parental clone to the emergence of subclones with metastatic capacity.
- **$T_3$** (average of 2.7 ± 1.2 years) is the time interval from the emergence of subclones with metastatic capacity to the dissemination of cells to distant organs.

The timing of these intervals can be estimated from the analysis of index lesions and metastatic subclones. By comparing the proliferation rates of normal duct epithelium and cancer cells, we can estimate the time required for the birth of the cell that gave rise to the index lesion. This time point is given by $t_0 = T_1$, $t_1 = T_2$, and $t_2 = T_3$. The time intervals $T_1$, $T_2$, and $T_3$ can be used to estimate the time required for the birth of the cell that gave rise to the index lesion and the time point when the tumour was initiated. The average time from tumour initiation to the birth of the cell that gave rise to the index lesion is $11.7 ± 3.1$ years.

The analysis of metastatic subclones reveals that the primary tumour is a mixture of numerous subclones, each containing large numbers of cells. These subclones are located in proximity to each other within the primary tumour. By contrast, samples representing subclones were non-randomly distributed throughout the primary tumour. The growth advantage of the subclones is not determined by the number of mutations alone but by the selective pressures in the tumour microenvironment.

The analysis of the progression of pancreatic cancer provides insights into the evolutionary pathways of tumour development. The schema of the clonal evolution of pancreatic cancer illustrates the hierarchical structure of tumour development, with successive waves of clonal expansion leading to the emergence of subclones with metastatic capacity. The timing of these events can be estimated from the analysis of index lesions and metastatic subclones, providing valuable insights into the evolutionary dynamics of pancreatic cancer.

**Figure 2:**
- Reproductive sequences of the various stages of pancreatic tumour progression are shown.
- The primary carcinoma is a mixture of numerous subclones, each containing large numbers of cells.
- By contrast, samples representing subclones were non-randomly distributed throughout the primary tumour.
- The growth advantage of the subclones is not determined by the number of mutations alone but by the selective pressures in the tumour microenvironment.

**Figure 3:**
- The evolutionary hierarchy establishing an evolutionary path for tumour progression is illustrated.
- The number of cells in each subclone can be estimated through the analysis of other pieces.
- The timing of the evolutionary events can be estimated from the analysis of index lesions and metastatic subclones.

**Figure 4:**
- The timing of pancreatic cancer progression is shown.
- The average time from tumour initiation to the birth of the cell that gave rise to the index lesion is $11.7 ± 3.1$ years.
- The average time from the birth of the cell that gave rise to the index lesion to the birth of the cell giving rise to the parental clone is $6.8 ± 3.4$ years.
- The average time from the birth of the cell giving rise to the parental clone to the birth of the cell giving rise to the index lesion is $2.7 ± 1.2$ years.

**Figure 5:**
- The timing of pancreatic cancer progression is shown.
- The average time from tumour initiation to the birth of the cell that gave rise to the index lesion is $11.7 ± 3.1$ years.
- The average time from the birth of the cell that gave rise to the index lesion to the birth of the cell giving rise to the parental clone is $6.8 ± 3.4$ years.
- The average time from the birth of the cell giving rise to the parental clone to the birth of the cell giving rise to the index lesion is $2.7 ± 1.2$ years.

**Figure 6:**
- The timing of pancreatic cancer progression is shown.
- The average time from tumour initiation to the birth of the cell that gave rise to the index lesion is $11.7 ± 3.1$ years.
- The average time from the birth of the cell that gave rise to the index lesion to the birth of the cell giving rise to the parental clone is $6.8 ± 3.4$ years.
- The average time from the birth of the cell giving rise to the parental clone to the birth of the cell giving rise to the index lesion is $2.7 ± 1.2$ years.

**Figure 7:**
- The timing of pancreatic cancer progression is shown.
- The average time from tumour initiation to the birth of the cell that gave rise to the index lesion is $11.7 ± 3.1$ years.
- The average time from the birth of the cell that gave rise to the index lesion to the birth of the cell giving rise to the parental clone is $6.8 ± 3.4$ years.
- The average time from the birth of the cell giving rise to the parental clone to the birth of the cell giving rise to the index lesion is $2.7 ± 1.2$ years.
Chronic myeloid leukemia (CML)
Imatinib is an inhibitor of BCR-ABL.
Molecular response to imatinib

first slope: 0.05 … 20 days
second slope: 0.008 … 125 days
5000 fold decline after one year
(169 patients)

Michor et al, Nature 2005
Turnover rate
Life-time

125 days

20 days

stem cells

progenitors

differentiated cells

terminally differentiated cells
Turnover rate
Life-time

125 days

20 days

Decline?

stem cells

progenitors

differentiated cells

terminally differentiated cells
In those 3 patients there was no decline of the cancer (stem) cell population that drives the disease.
Evolution of resistance to targeted EGFR blockade in colorectal cancers

Panitumumab therapy of cancers that are wildtype for KRAS

Diaz et al., Nature 2012
Emergence of mutant KRAS

A

![Graph A]

- Start
- anti-EGFR antibody
- End
- Mutant KRAS allele detected
- G35T
- G34T
- G35C
- G34C

# of Mutant Fragments/ml

Time (weeks)

B

![Graph B]

- Start
- anti-EGFR antibody
- End
- Mutant KRAS allele detected
- G34T
- G35C

# of Mutant Fragments/ml

Time (weeks)
Evolution of resistance

- Probability of no resistant cell at start of treatment: $\approx 10^{-33}$
- Expected number of resistant cells at start of treatment: $\approx 3000$
- About 40 resistant mutations (4 in KRAS)
Time to detection of resistance based on simple exponential growth during treatment

22 weeks, 95% CI 18-25 weeks
Combination treatment (2 drugs)

n1 ... number of point mutations in genome that cause resistance to drug 1

n2 ... number of point mutations in genome that cause resistance to drug 2

n12 ... number of point mutations in genome that cause resistance to drug 1 and 2
If $n_{12}=0$ you have a chance for cure.

If $n_{12}=1$ you have almost no chance.
Simulated response to treatment in one patient

Monotherapy

Dual therapy: $n_{12} = 1$

Dual therapy: $n_{12} = 0$

Bozic et al., eLife 2013
## Probability of treatment failure

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<tr>
<th>Patient</th>
<th>Primary Tumor type</th>
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</table>
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