Cancer = evolution

Recall, for example, the disease of familial adenomatous polyposis (FAP; see Section 7.11), in which an individual inheriting a mutant form of the \( \text{APC} \) tumor suppressor gene is prone to develop anywhere from dozens to more than a thousand polyps in the intestine (see Figure 7.22). With a certain low but measurable frequency, one or another of these polyps will progress spontaneously into a carcinoma. (The multiplicity of polyps in these patients and the low conversion rate of polyps to carcinomas—estimated to be \( \approx 2.5 \) events per 1000 polyps per year—effectively preclude association of a carcinoma with a particular precursor polyp.)

The development of carcinomas in other organ sites throughout the body is thought to resemble, at least in outline, the multi-step progression observed in the colon (see, for example, Figure 11.8A). Many of these other tissues, such as the breast, stomach, lungs, prostate, and pancreas, also exhibit growths that can be called hyperplastic, dysplastic, and adenomatous, and these growths would seem to be the benign precursors of the carcinomas that arise in these organs. However, the histopathological Histopathology indicates multi-step tumor progression colon head and neck cervix lung (smokers) breast prostate adenoma dysplastic oral leukoplakia CIN 1 PIN latent cancer 5–20 years 4–10 years 10–15 years 20 years 20–40 pack-years ≥10 years 5–15 years 6–8 years 9–13 years 20 years 3–15 years 10–20 years 6–8 years 20–40 pack-years 10–20 years 6–10 years 3–15 years

CIS, carcinoma in situ; CIN, cervical intraepithelial neoplasia; DCIS, ductal carcinoma in situ; PIN, prostatic intraepithelial neoplasia.

Because more aggressive growths often overgrow their more benign precursors, it is rare to see the multiple states of tumor progression coexisting in close proximity, as is the case in this lung carcinoma. Importantly, while the close juxtaposition of the aberrant growths suggests some relationship among them, an image like this provides no definitive evidence of precursor–product relationships between these various abnormal tissues. (A, courtesy of W.K. Hong. B, courtesy of A. Gonzalez and P.P. Massion.)
Acquired phenotypes of cancer

The Hallmarks of Cancer

Douglas Hanahan* and Robert A. Weinberg†
Acquired phenotypes of cancer acquired *mutations*

Mutation targets

tumor suppressors and oncogenes
Acquired phenotypes of cancer acquired *mutations*

Mutation targets **tumor suppressors** and **oncogenes**
Mutation targets tumor suppressors and oncogenes [drivers]
Oncogenes and tumor suppressors [drivers]

• Oncogenes -- need to be activated
  – by mutations (within a gene or regulatory regions)
  – by chromosomal alterations
  – overexpression/modifications

• Tumor suppressors -- need to be inactivated
  - mutations, chromosomal loss, modifications
Cancer: is hard to stop because it’s an evolutionary process
Finding **driver** events
Rates of somatic mutation vary across cancers: [G.Getz]
Figure 1 | Somatic mutation frequencies observed in exomes from 3,083 tumour-normal pairs. Each dot corresponds to a tumour-normal pair, with vertical position indicating the total frequency of somatic mutations in the exome. Tumour types are ordered by their median somatic mutation frequency, with the lowest frequencies (left) found in haematological and paediatric tumours, and the highest (right) in tumours induced by carcinogens such as tobacco smoke and ultraviolet light. Mutation frequencies vary more than 1,000-fold between lowest and highest across different cancers and also within several tumour types. The bottom panel shows the relative proportions of the six different possible base-pair substitutions, as indicated in the legend on the left. See also Supplementary Table 2.
Somatic Copy Number Alterations (SCNAs)

CONCERNING THE ORIGIN OF MALIGNANT TUMOURS
By Theodor Boveri
Professor at the University of Würzburg

Fig. A.
Can some passengers!
... be deleterious to cancer cells?
... affect progression?

Cancer genomics

100-400 amino acid substitutions
10-40 chromosomal alterations
2-5 drivers
the rest are passengers
Are cancers weighted down by passengers?

Studies of cancer biology and genomics have mainly focused on recurrent driver mutations in key oncogenes and tumour suppressor genes, as these are known to have major roles in tumorigenesis and cancer progression. However, these driver mutations are vastly outnumbered by passenger mutations, which are often assumed to be biologically neutral.

A new computational study suggests that passenger mutations may have detrimental effects on tumour fitness, with therapeutic implications. Random unselected mutations are expected to be, on average, mildly deleterious (that is, they confer a small selective disadvantage). So, Leonid Mirny and colleagues incorporated deleterious passenger mutations into their computer simulations of tumour evolution. In their model, each cancer cell can stochastically die or divide, and the cell divisions can be accompanied by the frequent acquisition of a deleterious passenger mutation or the rare acquisition of a growth-promoting driver mutation.

The simulations resulted in population dynamics in which tumours grew in a sawtooth manner: each acquisition of a driver event resulted in the rapid expansion of the tumour cell population, which was followed by a gradual decline in cell number owing to passenger mutation accumulation until the next driver mutation occurred. Importantly, accounting for deleterious passenger mutations recapitulated some known features of tumour biology, such as dormancy and regression, that are not seen in simpler simulations.

Interestingly, despite the deleterious nature of the simulated passenger mutations, large numbers of passenger mutations accumulated and spread throughout the tumour cell population. This partly occurred by mechanisms that are known from population genetics studies. For example, the positive selection of cells containing driver mutations can increase the frequency of passenger mutations co-occurring in these cells (an effect that is known as genetic hitch-hiking). Overall, this indicates that even mutations that are found throughout a large proportion of cells in a particular tumour might actually exert a negative fitness effect.

So, is there evidence that passenger mutations found in clinical tumours can be genuinely deleterious or might real tumours retain only selectively neutral passenger mutations? The authors assessed the deleteriousness of passenger mutations in the Catalogue of Somatic Mutations in Cancer (COSMIC) database. They used the PolyPhen program, which scores deleteriousness according to the extent to which the mutation has been avoided (selected against) during organismal evolutionary history. On average, these passenger mutations were indeed moderately deleterious, and substantially more so than single-nucleotide polymorphisms underlying normal human population variation. However, it is worth noting that deleteriousness of a mutation during normal organismal evolution might not fully reflect the fitness effects on cancer cells, which typically have altered cell death and checkpoint mechanisms.

Finally, the authors ran simulations and found that enhancing the detrimental effects of passenger mutations — such as by reducing the ability of cancer cells to buffer deleterious mutations — resulted in sustained tumour regression. In practice, such buffering mechanisms include the proteasome and chaperone systems. As pharmacological inhibitors of these systems have been developed that show antitumour activity in some settings, it will be interesting to determine the extent to which sensitivity to these agents is conferred by many accumulated passenger events versus a few key oncogenic mutations.