GENETICS

ONE MUTATION EVERY DAY

20.01.2010

At least some people believe that once it's published in Nature, it must be superior science – even when it's rather trivial (or even wrong). There is a category "Brief Communications Arising" but when you are trying to get your comments there you will get this message by email:

> In the present case, while we appreciate the interest of your comments to the community, we do not feel that they challenge key data or conclusions of the papers by Pleasance et al., and therefore we cannot offer to consider your paper for publication in our Brief Communications Arising section.

Pleasance et al. is a recent paper accompanied by a press release that tells you

> On average, lung cancer develops after 50 pack-years of smoking (where a pack-year is 7,300 cigarettes, representing the number smoked in a pack a day for a year). Candidate gene re-sequencing studies suggest that the mutation prevalence in NCI-H209 is similar to that of primary lung cancers. If the majority of mutations derive from the mélange of mutagens present in tobacco smoke, the clone of cells that ultimately becomes cancerous would acquire, over its lifetime, an average of one mutation for every 15 cigarettes smoked. If this is the case in a localized cluster of cells, then the number of mutations acquired across the whole bronchial tree from even one cigarette must be substantial.

while my comments should make clear that

…, the extrapolation of 365,000 cigarettes smoked in 50 years and induction of 22,910 mutations (“15 cigarettes leading to one mutation”) is an odd biological scenario that gives also a distorted public health message. The sequenced tumour clone may have acquired decisive mutations long before being exposed to smoke during normal lung development and it is far from being clear to what extent the direct tumour progenitor cells have been exposed to carcinogenic substances. In line with that comes the epidemiological observation that the smoking risk of young lung cancer patients is nearly identical to old lung cancer patients when calculated for the exposure period prior to the diagnosis of cancer. In other words, some may get lung cancer from being exposed to a few hundred cigarettes, while others will never get lung cancer despite a million of cigarettes – clearly a situation where averaging risks does not make any sense.
The absolute number of mutations in a fully dedifferentiated cell line may even be unimportant while the “minimal cancer genome” of driver mutations will be interesting. Highly parallel sequencing will allow to examine repeated samples from the same biopsy sites ultimately allowing a reverse engineering of cancer cells.