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COMMENTARIES

How relevant are genes for understanding biological processes?

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Commentary on
Martincorena et al., 2018, "Somatic mutant clones colonize the human esophagus with age", *Science*, vol. 362 (6417), p. 911-917

1. Too many mutations

A relevant body of research has been devoted to identify those genes that are deemed to play a causative role in several diseases. Unfortunately, despite having identified "hundreds of common variants whose allele frequencies are statistically correlated with various illnesses and traits, the vast majority [of those studies] have no established biological relevance to disease or clinical utility for prognosis or treatment' (McClellan and King, 2010). Inadequacy of such approaches is clearly epitomized by researches carried out on "identical twin pairs, which allow outcomes from two identical genome sequences to be compared, show that, for the majority of common diseases, knowing the causes of death or disease history of one twin gives only marginal guidance as the causes of death or disease suffered by the other" (Annila and, Baverstock, 2014). Broadly, speaking, biology has no substantive answer to the question from where does the 'causative principle' lays in living system.

This especially applies in carcinogenesis studies. It is usually taken for granted that Cancer is a "disease of mutations". Tumor cells are riddled with genetic mutations not found in healthy cells. Yet, often facts deny theories based on wrong premises. Several lines of researches have cast on doubt the relevance of mutation as causative drivers of carcinogenesis, thus questioning the reliability of the so-called Somatic Mutation Theory (Bizzarri et al., 2008). Recently, major surprises came from studies focusing on the 'mutational burden' of non tumoral tissues. Indeed, it turns out that a large portion of the cells in healthy people carry far more mutations than expected, including some mutations thought to be the prime drivers of cancer.

A paper from Iñigo Martincorena (Martincorena et al., 2018) found that, in normal middle-aged and elderly donors, clones with cancer-associated mutations covered much of the esophagus epithelium, with NOTCH1 and TP53 mutations affecting 12 to 80% and 2 to 37% of cells, respectively. Unexpectedly, the prevalence of NOTCH1 mutations in normal esophagus was several times higher than in esophageal cancers. Similar results have been previously reported by the same team when studying normal and cancerous skin samples (Martincorena et al., 2015). As the Authors outline, "The higher frequency of cancer-associated mutations in normal esophagus […] is unexpected, particularly given the lower mutation rate in the esophagus". Moreover, the observed frequencies in mutational rate of healthy tissues

proven not to be associated with known risk factors (alcohol consumption, tobacco, etc.). In other words, the rise of these mutations may just be an intrinsic part of getting older, when relevant changes occur not only in epithelia, but also in the surrounding (aged) microenvironment (Maffini et al., 2005).

2. Are mutations really needed for explaining cancer?

The study from Martincorena et al. (2018) raised a lot of (troubling) questions. Foremost, the identification of mutations usually associated with cancer doesn't mean actually these tissues are cancerous. Therefore, recognition of mutation does not help very much in identifying people at risk of developing cancer. Second, presence of mutations in healthy tissues casts on doubts the role of mutation as causal carcinogenic factors. And finally, given the abundance of cancer mutations in healthy people, why isn't cancer more common?

Overall this finding "emphasizes how little we know about somatic evolution within normal tissues, a fundamental process that is likely to take place to varying degrees in every tissue of every species". The Authors were very cautious in their conclusions. Yet, it is quite unsatisfactory saying so a little. I would like to highlight that such kind of discovery greatly contribute in (further) dismantling the Somatic Mutation Theory. Time is gone for rethinking the carcinogenesis theory, isn't?

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