Review of: "Somatic evolution of Cancer: A new synthesis"

Juan Pedro Martinez-Barbera[1]

1 University College London, University of London

Potential competing interests: No potential competing interests to declare.

I find this article very interesting to read. It is very well written and clear. It addresses two contrasting theories of the origin of cancer. I think it is a very stimulating reading and definitely, I would recommend it to students aiming to broaden their views about cancer.

The authors put forward the idea that cancer is not just caused by accumulation of mutations, and reason that in normal, healthy tissues, mutations in some cancer genes may make the cells less competitive rather than becoming super-competitors. However, in the presence of the right (pro-tumorgenic) micro-environment, those cells harbouring oncogenic hits may be able to flourish and give rise to tumours and cancers.

I would like to bring to the authors' attention some papers that may provide further support. For example, as we age, cells in several tissues accumulate gene mutations, including in cancer genes. This is beautifully exemplified in studies using aged human oesophagus (e.g. DOI: 10.1126/science.aau3879, DOI: 10.1126/science.aav5697, PMCID: PMC7116672). I think similar findings have been described in skin and other organs. The authors could discuss these findings further, as they support the concept that although genetic or epigenetics alterations are necessary for cancer development, they may not be sufficient to generate cancers.

A reason for this may be that the tissue micro-environment may be required to provide the selection pressure that allows those mutant cells to progress into tumours/cancers. The authors do not discuss about the mechanisms that could alter the tissue microenvironment. However, compelling evidence supports a role for senescent cells in generating pro-tumourigenic niches through the senescence-associated secretory phenotype (SASP). I urge the authors to read some of the relevant papers and discuss further this aspect.

Senescent cells accumulate during ageing in several tissues. They produce secreted factors, including inflammatory mediators, extracellular matrix modifiers, growth factors, etc that are used during wound healing. Indeed, senescent cells are involved in tissue regeneration and wound healing (e.g. PMID: 36552241, PMID: 32850866, PMID: 25499914). I suggest some general reviews (e.g. PMID: 24954210) or specific on senescence in cancer (e.g. PMID: 29670296). A more specific example linking ageing, senescence and pro-tumourigenic niches has been shown in two recent papers (PMID: 37267953, PMID: 37267954). Here, it was found that pro-tumourigenic macrophages found in KRAS-driven lung adenocarcinoma share a molecular signature (including secreted factors) with normal macrophages in normal, non-tumourigenic aged lungs. This supports the idea that ageing may lead to the accumulation of senescent cells (macrophages in this case) which creates an environment that may lead to tumour development from epithelial cells

harbouring oncogenic hits.