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

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Potential competing interests: No potential competing interests to declare.

Mechanisms of tumorigenesis is a very fascinating topic in a field where the extant doctrine is imperfect and lacks a grand unified theory. The authors explore this topic and present their own views, which have some scientific significance. The central point of the article is that low levels of EGF and other growth factors in modern humans cause cells to overreact to these growth factors and induce tumors. This is one of the more novel ideas and interesting. In addition, some of the points mentioned in the article have some merit, such as the fact that genetic variant dominance does not necessarily lead to tumorigenesis, but also that there has to be a sustained selective advantage. Variants below the branching point are unable to cause a cooperative increase in other cellular functions and cell death occurs, and only those up to the branching point are able to cause cancer (figure 3 in the article).

On the other hand, there is much to question for the theories prompted in this paper:

(1) The doctrine that inflammation leads to tumorigenesis is a classical one, which has been proposed by scholars for a long time and does explain the development of certain tumors, such as malignant tumors caused by chronic ulcers of the skin and mucous membranes. However, ulcer-induced malignant tumorigenesis is a chronic, multifactorial process. Many factors are involved and are not explained by alterations in only a few cytokines. And, in the development of many types of tumors, glioma for example, there is no obvious inflammatory trauma in most cases.

(2) There is no clear evidence that early human lifestyles, such as trauma and stress, can significantly increase growth factor levels in the body.

(3) The relationship between serum growth factor levels and tumorigenesis is unclear. Some studies have shown that growth factor levels are lower in certain tumor patients (Cacina C, et al. Analyses of EGF A61G Gene Variation and Serum EGF Level on Gastric Cancer Susceptibility and Clinicopathological Parameters. Anticancer Res. 2015.), while more studies suggest that growth factor levels are higher in tumor patients (Schölch S, et al. Serum PlGF and EGF are independent prognostic markers in non-metastatic colorectal cancer. Sci Rep. 2019. Masiak W, et al. Evaluation of endostatin and EGF serum levels in patients with gastric cancer. Pol Przegl Chir. 2011. Kozłowski M, et al. Preoperative Serum Levels of PDGF-AB, PDGF-BB, TGF-α, EGF and ANG-2 in the Diagnosis of Endometrial Cancer. Cancers (Basel). 2023. Luo JH, et al. Serum expression level of cytokine and chemokine correlates with progression of human ovarian cancer. Eur J Gynaecol Oncol. 2017).

(4) Lifestyle differences have less of an impact on infants and children, so the theory presented in the article does not explain the occurrence of congenital and childhood malignancies.

(5) Certain environmental factors, such as radiation exposure and chemical agents, can definitively induce the development of malignant tumors. In such cases, inflammatory factors do not predominate.

In order to make the theory presented in the article more convincing, the authors may need to give a clearer explanation

of the above issues. In addition, the article is rather lengthy and some expressions are confusing, so it is recommended that the authors abbreviate the article and concisely express the core ideas and their direct supporting evidence, clear validation methods and prevention recommendations, as well as the shortcomings of the ideas.