

Do stem cell divisions significantly contribute to cancer development?

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Abstract

Cancer is caused by uncontrolled cellular growth, yet some cancer cells may have greater roles in sustaining tumour proliferation and overcoming conventional cancer treatments. The origins of these cancer stem cells, as they are hypothesized, is widely contested. The current opinion points to extrinsic factors such as smoking, diet and sedentary lifestyle to be the primary inducer of cancer stem cells. This dogma was challenged in 2015 when Tomasetti and Vogelstein postulated that two-thirds of the variation in cancer risk could be explained by random mutations arising during DNA replication in healthy stem cells. Their "bad luck" hypothesis sparked fierce debate and controversy in the scientific community. In this point-counterpoint article, we discuss the random mutation cancer stem cell model and its implications for guiding public health through primary and secondary cancer prevention.

Keywords: Cancer; Stem cells; Driver gene mutations; Linear regression

Résumé

Le cancer est causé par une croissance cellulaire incontrôlée, pourtant certaines cellules cancéreuses peuvent jouer un rôle plus important dans le maintien de la prolifération tumorale et peuvent aider à surmonter les traitements conventionnels contre le cancer. Les origines de ces cellules souches cancéreuses, telles quelles, sont largement contestées. Actuellement, on souligne des facteurs extrinsèques tels que le tabagisme, l'alimentation et le mode de vie sédentaire comme principaux inducteurs des cellules souches cancéreuses. Ce dogme a été contesté en 2015 lorsque Tomasetti et Vogelstein ont postulé que les deux tiers de la variation du risque de cancer pouvaient être expliqués par des mutations aléatoires survenant lors de la réplication de l'ADN dans des cellules souches saines. Leur hypothèse de « malchance » a suscité de vifs débats et controverses dans la communauté scientifique. Dans cet article point-contrepoint, nous discutons du modèle de cellules souches cancéreuses à mutation aléatoire et de ses implications pour guider la santé publique à travers la prévention primaire et secondaire du cancer.

Mots Clés: Cancer; Cellules souches; Mutations génétiques directrices; Régression linéaire

Over the past decade, few articles have stimulated such scientific discourse as the origin of cancer in stem cells. While scientists are still working to this day to explain the biological "ground zero" for stem cell cancer, the common belief points to extrinsic factors as the primary cause. This paradigm was challenged in 2015 when Tomasetti and Vogelstein published "Variation in cancer risk among tissues can be explained by the number of stem cell divisions" in *Science* (1). Tomasetti and Vogelstein used mathematical models to demonstrate that cancer risk correlates more significantly with the number

of stem cell divisions than environmental factors or inherited predispositions. According to their research, two-thirds of the variation in cancer risk could be explained by random mutations arising during DNA replication in healthy stem cells (1). Thus, their "bad luck" hypothesis sparked fierce debate and controversy in the scientific community (1-4).

From a deterministic standpoint, cancer discriminates against those who physically harm their bodies. This intuition is best emphasized by the strong correlation between lung cancer and smokers inhaling carcinogens in cigarette smoke (5-7). While a seductive argument, several confounding pieces of circumstantial evidence led Tomasetti and Vogelstein to re-think this conventional wisdom. If cancer is truly the result of grievous bodily

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harm by external factors, how could cancer rates vary dramatically between different tissues in the body? For instance, small intestinal cancers are three times less prevalent than brain tumors, yet the brain is exposed to fewer environmental mutagens than the small intestinal epithelium due to the protective blood-brain barrier (1). Furthermore, toxins ingested by individuals move through the gut having unimpeded interactions with intestinal cells. These anomalies led Tomasetti and Vogelstein to seek an alternative explanation for tissue-specific cancer risk. They postulated that random mutations in stem cell division may be responsible for causing a significant number of cancers. The more cells divide, the more opportunities there are for mutations to occur in these cells, resulting in unchecked growth and ultimately cancer.

To test this hypothesis, Tomasetti and Vogelstein developed a model to predict how the lifetime stem cell divisions (lscd) in a given tissue affects one's lifetime risk of cancer. For each tissue type, empirical estimates of the total number of stem cells and the number of times they divided were used to calculate the lscd. In parallel, the lifetime risks for different cancers were taken from existing literature. Linear regression analysis of lscd versus the lifetime risk for different cancers demonstrated that 65% of the variation in cancer risk could be explained by the number of stem cell divisions in a healthy individual (1). Roughly one-third of the cancers correlated with extrinsic factors (deterministic tumors), while two-thirds correlated with the number of stem cell divisions (replicative tumors) (1). While elegant, Tomasetti and Vogelstein's analysis between cancer risk and cell division is unable to differentiate between the contributions of intrinsic and extrinsic factors (citeWu2016). This shortcoming led to Wu *et al.*'s reply in 2016, which re-interpreted the lscd model, suggesting that extrinsic factors were indeed the dominant cancer-inducing agent (2).

The cornerstone of Wu *et al.*'s Nature publication, "Substantial contribution of extrinsic risk factors to cancer development" was a thought experiment where an extrinsic mutation is introduced into the environment, increasing the cancer risk by a factor of four (2). While the lscd would change little because mutagens do not actively promote cell division, the lifetime risk of cancer would increase by a factor of four (2). Therefore, Tomasetti and Vogelstein's lscd model and subsequent correlation analysis would yield the same relations, whether or not mutagens were present. Using mathematical models on real-world data, Wu *et al.* consistently estimated that extrinsic factors contribute >70-90% in most cancers (2). Because of these new findings, Tomasetti and Vogelstein along with Lu Li published "Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention", a follow-up article that clarified their "bad luck" hypothesis, addressing many concerns in their previous article (3).

It is widely accepted that cancer arises from mutations that may be hereditary, induced by environmental exposure, or the result of DNA replication errors (2, 8, 9). Yet, the scientific debate continues between Tomasetti and Wu. Tomasetti *et al.* have extended their analysis to include driver gene mutations classified into three categories: environmental (E), hereditary (H), and replicative (R). In most cancers, three driver gene mutations are required for tumorigenesis to occur (3). Using a similar thought experiment as Wu *et al.*, where exposure to an environmental mutagen causes a ten-fold increase in cancer, 90% of cancers would be preventable by simply avoiding exposure to the mutagen (3). However, 40% of cancers would still be attributed to R-driver gene mutations (3). On the surface, Tomasetti and Vogelstein's result may be surprising, but the concept of a stochastic and unpreventable cancer is not new. Previous research from Cancer Research UK highlighted that exposure to 14 extrinsic factors was attributed to only 42.7% of cancer in the UK in 2010 (10). This suggests that 57.3% of cancers could not be attributed to extrinsic factors, echoing Tomasetti and Vogelstein's findings.

The scientific community must consider the greater implications of these results on how it guides primary and secondary cancer effort prevention. Tomasetti *et al.*'s classification of deterministic and replicative tumors may better address important public health aspects of cancer prevention. Primary prevention can achieve maximum benefit by focusing on deterministic tumors through preventative measures such as smoking cessation to minimize lung cancer. For replicative tumors, primary prevention efforts are unlikely to be effective; focus should be placed on secondary prevention through early-targeted screening. Replicative tumors should not diminish the importance of primary prevention but highlight that not all cancers can be prevented by avoiding environmental risks. Ultimately, we may never resolve the exact contribution of intrinsic and extrinsic factors to cancer; however, findings from both Tomasetti and Wu should be channeled towards quantifying cancer-causing constituents and guiding public health through primary and secondary cancer prevention.

Competing interests

The authors declare that they have no competing interests.

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