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Review article

A possible role for epigenetics in cancer initiation

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Abstract. Cancer is one of the leading causes of mortality worldwide. Known since antiquity, its understanding has evolved over time and has significantly advanced with new technologies over the past four decades. Cancer initiation is currently admitted to be explainable by the somatic mutation theory, which postulates that DNA mutations altering the function of oncogenes and tumor suppressor genes initiate cancer. In addition to these mutations, epigenetic alterations, which heritably change gene expression without altering the DNA sequence, also play a key role. Recent data suggests that epigenetic components regulate all aspects of tumor progression, including cancer initiation. These discoveries prompt a reevaluation of the somatic mutation theory, of cancer prevention and treatment strategies.

Keywords. Epigenetics, Cancer, Development, Chromatin, Polycomb proteins.
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1. Introduction

Cancer remains one of the leading causes of mortality worldwide, encompassing a diverse array of pathologies characterized by dysregulation of key biological processes that regulate cellular and tissue homeostasis, such as cell division, diVerentiation and tissue homeostasis [1]. Although its initiation generally occurs within a specific organ or tissue, malignant cells can subsequently spread to other parts of the body and establish secondary tumors through metastasis. Known since ancient civilizations, Egyptian, Greek, Roman, as well as in traditional Chinese medicine, cancer was observed in a new light with the advent of microscopy in the 19th century, enabling, among other advances, the detection of metastases. During these early phases of research on tumorigenesis, several hypotheses were proposed [2]. Theodor Boveri is credited with the first formulation of the widely accepted theory on the origin of cancers, known as the "somatic mutation theory" [3]. This theory posits that cancer arises from a chromosomal alteration, promoting the transformation of a normal cell into a malignant state, subsequently inherited by its daughter cells.

In addition to DNA mutations, epigenetic alterations also play a crucial role in cancer. Epigenetics refers to the study of mechanisms and molecules involved in the inheritance of diVerent gene expression profiles from the same DNA sequence [4]. These regulatory mechanisms are essential not only during development and adulthood but also in aging and in most human pathologies, including cancer [5]. Although epigenetics is often considered of therapeutic interest due to its role in tumor progression and metastasis [6,7], recent data, which will be discussed in this article, suggest that epigenetic alterations can also serve as drivers of tumorigenesis. These discoveries prompt a reconsideration of the role of the DNA sequence in cancer etiology and call for a rethinking of our cancer prevention and treatment strategies.

2. The somatic mutation theory and its impact on modern oncology

In its first formulation in 1914 [3], Theodor Boveri postulated that cancer could originate from

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chromosomal abnormalities, particularly defects in chromosome segregation during cell division. This hypothesis found early support with the discovery of abnormal chromosomes in leukemias [8,9] and was further substantiated by the identification of the first oncogenes by several laboratoires [10]. These discoveries were integrated into a modern version of the "somatic mutation theory" (SMT) to suggest that cancer arises from genetic mutations. However, it is important to emphasize that Boveri did not focus solely on DNA. Chromosomes also consist of associated proteins and RNAs that play a crucial role in regulating gene expression and maintaining chromosomal integrity. Beginning in the 1980s, extensive research into oncogenes and tumor suppressor genes reinforced a mutation-centric view of cancer. This led to the development of a comprehensive catalog of oncogenes and tumor suppressors, establishing a molecular framework that currently shapes cancer research and therapeutic development.

In a seminal article published in 1976 [11], Peter Nowell hypothesized that cancer development occurs in multiple stages. An initial cell (or a small group of cells) undergoes a primary alteration that makes it neoplastic, granting it a proliferative advantage. Subsequent alterations, primarily driven by mutations, would promote clonal selection, ultimately leading to the formation of malignant tumors. This publication is a cornerstone in oncogenesis as it introduces the concept of tumor-initiating cells and their clonal evolution. Following the discovery of oncogenes and tumor suppressor genes, a merger occurred between the hypothesis of clonal initiation of tumorigenesis and the somatic mutation theory, leading to the proposition that mutations arise in the cancer-initiating cell(s) (Figure 1). Alternative hypotheses suggesting a non-genetic origin of cancer, centered on dysregulation of gene regulation, were largely dismissed. The notion that tumors contain clones of cells that have dominated through "evolutionary competition" further strengthened the scientific community's belief that large-scale sequencing of tumor genomes would uncover all cancer-relevant genes.

Much like the distinction between Darwinism and neo-Darwinism in evolutionary biology (Box 1), the modern formulation of the SMT can therefore be considered a "neo-Boverian" perspective, emphasizing DNA mutations as the drivers of cancer while disregarding the potential causal roles of other alterations, such as the composition or structure of chromosomes.

Box 1

Darwinism refers to the theory of evolution of species through natural selection, as developed by Charles Darwin in *On the Origin of Species* [12]. This theory is based on the observation of phenotypic variations among species, particularly within closely related species, suggesting that phenotypic traits evolve over generations. According to Darwinian theory, traits are transmitted through a mechanism called pangenesis, where the entire organism contributes to heredity, notably through the budding of gemmules from its cells, especially in the reproductive organs.

Neo-Darwinism stems from the modern synthesis of the evolutionary theory of natural selection. This updated version of Darwin's theory incorporates later genetic discoveries, particularly Mendelian inheritance and population genetics, as the foundation of evolution [13,14]. In this modern synthesis of evolutionary theory, the source of variations among individuals of the same species lies in the diVerent genetic information transmitted through gametes. Generally, this information is considered to reside in the DNA sequence, and genomic variations are increased by random mechanisms such as mutations and meiotic recombination. The mechanisms of selection depend on the ability of each individual to survive and reproduce within populations of each species. This ability depends on that of other individuals, on the size of populations and on environmental conditions. Epigenetics shows that information other than what is present in the DNA sequence can contribute to phenotypic characteristics. Its contribution to evolution is currently a topic of discussion within the scientific community.

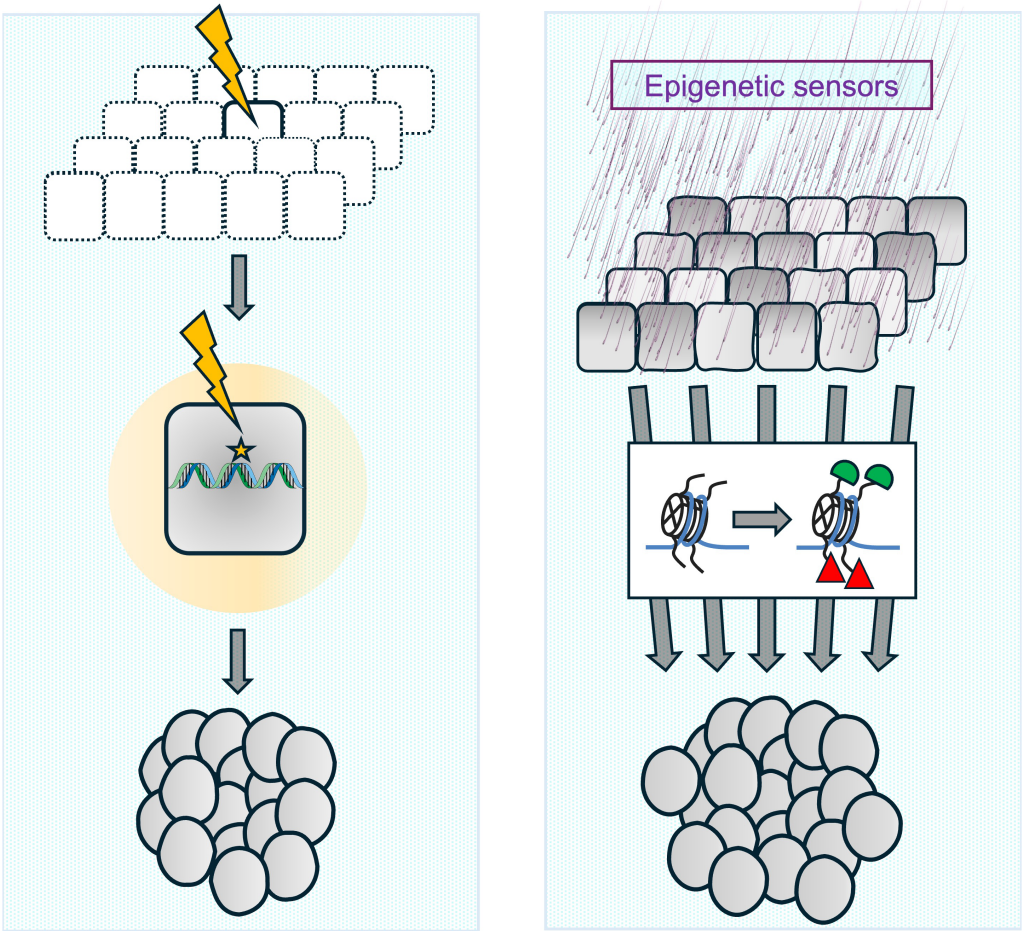

Figure 1. Mutational versus epigenetic origin of cancer. On the left, the dominant hypothesis on the origin of cancers, based on the somatic mutation theory, is depicted. According to this theory, stochastic mutations, potentially caused by exposure to mutagenic agents (illustrated by a yellow arrow at the top), can sometimes activate oncogenes or inactivate tumor suppressor genes, thereby generating the tumor-initiating cell or "cancer stem cell" (center). Subsequent mutagenic events and the selection of specific cell clones ultimately lead to the development of aggressive cancer (bottom). On the right, the hypothesis of the epigenetic origin of cancers is shown. Exposure to non-mutagenic carcinogens, nutritional and metabolic changes, or other sources of stress (top) could aVect a group of cells, altering the chromatin state of some of their genes (center, with altered epigenetic modifications represented in green and red). This induces changes in gene expression, which, if self-sustaining, could initiate a tumorigenesis process that persists even after the stimulus that caused the initial epigenetic alteration has ceased.

With the advent of high-throughput sequencing technologies, large-scale sequencing projects involving cohorts of various cancer types were initiated. These projects rapidly identified genes frequently subject to mutations, amplifications, or deletions in cancer samples [15,16]. Concurrently, functional studies demonstrated that these same genetic alterations can induce tumor formation in mice [17]. This body of experimental evidence, supported by epidemiological data, confirmed DNA sequence mutations as key oncogenic events. As a result, they are regularly used as biomarkers for diagnosis, prognosis, and therapeutic decision-making in clinical practice.

3. Alternative hypotheses concerning the origin of cancers

The SMT, associated with the hypothesis of cancer initiation by Tumor Initiating Cells (TICs), has become the dominant theory in oncology. However, it is important to recognize that Peter Nowell's original formulation did not attribute the first neoplastic event to genetic mutations. In the original article, Nowell pointed out that

> "The biological consequences of the primary alteration may be illustrated with various examples…The specific gene products that produce these biological consequences remain uncertain. Equally obscure is the specific genetic event which produces them. Absence of new gene products in tumor cells and the reversibility of transformation in certain culture systems has led some investigators to suggest that initiation usually involves altered gene expression rather than structural mutation. It is certainly clear that visible alterations in chromosome structure are not essential to the initial change. Transformation can take place in tissue culture and certain tumors can develop in vivo without detectable cytogenetic abnormalities". [11]

The phenomenon of tumor reversion observed in several circumstances presents a compelling argument suggesting that mutations (whose probability of reversion is extremely low) are not causal, at least in these specific cases [18]. Furthermore, large-scale sequencing studies have revealed the limitations of sequencing. First, many mutations identified in such studies are not necessarily su Y cient to explain cell transformation. These same mutations found in cancers are frequently found in normal tissues. Notably, cells harboring so-called "driver" mutations, which are thought to trigger tumorigenesis, are also sometimes present and abundant in healthy tissues [19]. Moreover, the mutation rate in normal cells is comparable to that measured in several cancer types [19]. Finally, even in cases involving oncogenes strongly associated with the emergence of cancers, such as the Ras oncogene, mutation alone rarely triggers tumor formation. Instead, it is tissue lesions that strongly stimulate tumorigenesis by modifying chromatin states and the regulation of gene expression [17].

The inability to fully account for the origin of all tumors by mutations in oncogenes or tumor suppressor genes has spurred the development of alternative hypotheses. A radically diVerent hypothesis from SMT is the "Tissue Organization Field Theory or TOFT" [20,21]. According to this theory, cancers do not necessarily arise from clonal or mutational events. Rather, they result from chronic disruptions in the interactions between diVerent cellular components of a given morphogenic field within a tissue. These perturbations may be caused by exposure to carcinogens or physiological stressors, inducing stable changes in gene expression mediated by epigenetic alterations. This theory echoes the hypothesis that cells, individually or in groups, can undergo stable changes in their destiny, adopting alternative functional states without requiring genetic mutations. This process resembles the dynamic "valleys" of Waddington's epigenetic landscape (Figure 2 and Box 2). However, unlike the stable destinies observed in normal cells, these altered states result from stochastic events or external disturbances such as exposure to carcinogens, which drive tissue-level dysregulation [22,23]. A third hypothesis about the origin of cancers is the "evolutionary reversion" theory, which suggests that cancer cells reach a state of uncontrolled proliferation by reverting to ancestral cellular states resembling those of unicellular organisms, whose default state is proliferation. The mechanisms of proliferative inhibition, typical of tissues subject to size control, are thus lost in cancer cells [24], resulting in a stable proliferative state, at the origin of cancers.

Finally, the developmental constraints model, based on extensive analysis of single-cell transcriptomic data from various types of cancers in comparison to healthy tissues, suggests that the tissues of origin impose diVerentiation constraints on cancer cells. According to this model, cancer cells are limited in the range of cellular states they can adopt, and these constraints are determined by their tissue of origin [25]. This perspective is of considerable interest because it provides an explanation for why each tissue or cell type gives rise to a limited spectrum of cancer subtypes.

Figure 2. The epigenetic landscape in normal development and in cancer. The illustration depicts the famous Waddington landscape, where a marble rolls down a slope with multiple possible trajectories, determined by the hills and valleys encountered along its path. This landscape symbolizes the various cellular fates that can arise from a pluripotent cell, such as the zygote, supporting the hypothesis that epigenetic inheritance contributes to the stable transmission of cellular fates. Epigenetic components or environmental exposures contribute to shaping the landscape and lead to a variety of cellular fates. In the context of normal development (left), cells move down the hill during diVerentiation to acquire normal fates. However, when epigenetic components are disrupted, the landscape itself is altered (right), causing cells to take an aberrant path, which can ultimately lead to cancer.

Box 2: The Waddington epigenetic landscape

The famous Waddington landscape (Figure 2) depicts a marble rolling down a slope, which can follow diVerent trajectories depending on the valleys and hills it encounters along the way. This metaphorical illustration represents the various cellular fates that a cell, initially represented by the zygote, can adopt during its development. This landscape is commonly used to visually explain how epigenetic mechanisms contribute to the stable transmission of cellular fates once they are established by intrinsic and extrinsic signals.

Polycomb complexes can play a major role in shaping this landscape due to their ability to regulate epigenetic inheritance. They enable cells to follow specific trajectories, establishing and stabilizing diVerent diVerentiated states during normal development. However, mutations or disruptions aVecting the activity level of Polycomb complexes can alter this landscape. When these disruptions are strong enough, they can reshape the landscape in such a way that forces cells to follow aberrant, yet intrinsically stable, trajectories, thereby promoting the formation of cancers (Figure 2).

4. Epigenetic components and cancer

Although the precise role of DNA mutations and epigenetic changes at diVerent stages for each cancer type is yet to be clarified, it is important to consider that factors involved in epigenetic inheritance contribute significantly to tumorigenesis [26–28]. These factors can be broadly classified into four major molecular categories.

DNA methylation primarily modifies cytosines in mammals. The maintenance of this mark over time and through cell divisions relies on the DNA methyltransferase DNMT1 and its partner UHRF1, which enhances DNMT1 activity [29,30]. This molecular complex exhibits a unique ability to bind to the epigenetic mark 5-methylcytosine in a CG-rich DNA sequence context (mCpG) when the cytosine is hemimethylated. This occurs notably after the replication of fully methylated sequences, as during repli-