International Journal of Science Academic Research
Vol. 07, Issue 10, pp.1629-1632, October 2026
Available online at http://www.scienceijsar.com
ISSN: 2582-6425

Research Article

ENGLISH TRANSLATION OF GAO-DE LI'S 1986 CHINESE-LANGUAGE ARTICLE TITLED AS 'ABNORMALITIES IN CHROMATIN FIBRE CONFIGURATION AND MALIGNANT TUMOUR FORMATION'

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Received 19th August 2026; **Accepted** 16th September 2026; **Published online** 30th October 2026

Abstract

Forty years ago, when I was 30-years old, I published a Chinese-language article named as 'Abnormalities in chromatin fibre configuration and malignant tumour formation'. By literature search, this article might be the first one over the world, which proposed that 3D genome structure might be closely linked to gene expression, cell differentiation, and tumour formation. The assumption of 'cancer reversal', and 'reversal drugs' were also proposed in this article. To help researchers understand this article, I have used Google Translate to translate the original article into English, with a few minor changes. Besides, since this article might occupy a very important position in exploring history of 3D genome structure development, it is a must to translate this Chinese article into English.

Keywords: Hypothesis, 3D genome structure, Chromatin fibre configuration, Cancer formation, Cell differentiation, 'Cancer reversal', 'Reversal drugs'.

INTRODUCTION

In 1986, I published an article titled as 'Abnormalities in chromatin fibre configuration and malignant tumour formation' [1]. The preparation for this paper began from the period when I was pursuing master's degree (1982 to 1985). My master's project was study of piperaquine resistance in rodent malaria parasites, exploring the mechanism of cancer formation was my favourite hobby. The inspiration for this idea occurred in the master's degree course of electron microscopy. I realised that if we imagined that the nucleus in eukaryotic cells could be three-dimensional (3D) ball-like and chromatin fibres inside could be 3D reticular structure. This distribution of 3D chromatin fibres must be strictly ordered and otherwise the protein expression will be affected and might cause cancer formation as well. I felt so exciting that hurried to write a manuscript of the paper in 1984. I submitted this manuscript to 'Medicine and Philosophy' journal at the early stage of 1985, having waited for about one year until the paper was published in February of 1986. The drawback of this paper was no list of references, which was because in Chinese-language books including textbooks at that time didn't contain original references, also, no internet search available. As the paper was published in Chinese, it may have been overlooked or misunderstood by many international researchers. Till now, 40 years passed, no articles worldwide have cited it. To help researchers understand this article, I have used Google Translate to translate the original article into English, with a few minor changes. The following is the English translated version of this article.

ABNORMALITIES IN CHROMATIN FIBRE CONFIGURATION AND MALIGNANT TUMOUR FORMATION

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Malignant tumours (cancer) may well be one of the most intractable challenges facing modern medicine, a problem requiring the concerted efforts of multiple disciplines to resolve. Consequently, when exploring the fundamental nature of the disease, it is essential to uphold the principle of 'letting a hundred schools of thought contend' to broaden our horizons. Offering a personal perspective, this article attempts to investigate the mechanisms underlying the formation of malignant tumours from a novel angle.

- **Conceptualization regarding configuration of chromatin fibres**

In the interphase nucleus, eukaryotic chromosomes exist in a dispersed state known as chromatin. When specimens dually fixed with glutaraldehyde and osmium tetroxide are examined under an electron microscope, small, darkly staining masses, often distributed along the inner nuclear membrane can be seen scattered within the nucleoplasm; these dense regions are termed heterochromatin. The lighter, brighter areas situated between regions of heterochromatin correspond to euchromatin. The heterochromatin and euchromatin located both within and surrounding the nucleolus are collectively referred to as nucleolus-associated chromatin. High-resolution electron microscopy reveals that this chromatin is composed of tightly coiled fibrils of varying thicknesses that are continuous with one another. These fibrils are known as chromatin fibres and are composed of DNA, histones, and non-histone proteins.

If the cell nucleus envisioned as a large, spherical spaces, then chromatin fibres can be viewed as intricate, three-dimensional network structures residing within these spaces. Chromatin fibres undergo a series of dynamic changes prior to cell division, ultimately condensing into chromosomes; following division, within the daughter cells, the chromosomes decondense, and the fibres revert to the state characteristic of the non-dividing cell. It can thus be inferred that the arrangement of chromatin fibres within the nucleus is not haphazard but rather highly ordered. Such a regular arrangement is likely essential to ensure the equal distribution of genetic material during each cell division. We collectively refer to the three-dimensional form of chromatin fibres as their

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'configuration,' designating the configuration observed during interphase as the 'stable-state configuration' and those in other phases as 'unstable-state configurations.'

Chromatin fibre configurations are objective realities; however, there is currently no technology or equipment capable of revealing the full configuration of chromatin fibres within the nuclei of living cells. We can only infer these configurations by observing the distribution of chromatin within the nucleus. For instance, observations via light or electron microscopy reveal varying chromatin distribution patterns across different nuclei; consequently, we can surmise that different cells may possess distinct chromatin fibre configurations. Furthermore, it can be inferred that cells of the same type at the same stage of the life cycle should exhibit essentially identical or similar chromatin fibre configurations. Any observed differences are likely attributable to factors such as specimen preparation, the functional state of the cells, or the angle of observation.

- **Chromatin fibre conformation and gene activity**

Intracellular genetic material exists in a series of interconnected, hierarchical forms: single nucleotides, DNA molecules, chromatin fibres, and chromosomes. Genes are functional segments within DNA molecules. Given this hierarchical and interconnected nature of genetic material, we hypothesize that there may be an intrinsic link between chromatin fibre conformation and gene activity. Although such a perspective and related experimental study have not yet appeared in the literature, the possibility of this connection can be inferred from existing knowledge. For instance, at the molecular level, a chromatin fibre is not a smooth-surfaced strand but rather an irregular, cord-like structure composed of countless chemical groups, most belonging to DNA molecules and the rest to chromatin protein molecules. Their spatial arrangement shifts with changes in the chromatin fibre's conformation; for example, regions where the fibre twists or folds may bring chemical groups into proximity or cause them to interlock, whereas extended regions may result in chemical groups being sparsely spaced and isolated from one another. Since DNA molecules are embedded within chromatin fibres, processes such as gene activation prior to replication and nucleotide incorporation during replication are inevitably influenced by the surrounding chemical groups. Furthermore, because the spatial arrangement of these groups is determined by the chromatin fibre's conformation, it follows that changes in that conformation can influence gene activity.

Furthermore, the synchrony between changes in cellular function and nuclear chromatin morphology during cell differentiation offers a glimpse into the mutual adaptation between chromatin fibre configuration and patterns of gene activity. For instance, observations of hematopoietic stem cells differentiating into various blood cells reveal that as differentiation progresses, functional differences between the cells widen, accompanied by increasingly distinct differences in nuclear chromatin morphology. Early-stage cells in this lineage, such as prolymphocytes, promonocytes, and promyelocyte exhibit little variation in chromatin morphology or function. As they differentiate into the next stage (lymphoblasts, monoblasts, and myelocytes), differences in chromatin morphology begin to emerge, potentially correlating with slight functional variations. By the time they fully differentiate and mature into functional blood cells, both their functions and nuclear chromatin morphologies have become vastly different; examples include lymphocytes secreting antibodies (following differentiation into plasmablasts and then plasma cells) and monocytes phagocytosing foreign matter or entering tissues to become various types of phagocytes. Differences in cellular function reflect differences in patterns of gene activity. Thus, it appears that the differentiation process confers distinct gene activity patterns (in terms of the types and quantities of genes involved) upon cells by establishing specific chromatin fibre configurations; in other words, distinct gene activity patterns rely on specific chromatin fibre configurations, or specific chromatin fibre configurations are adapted to specific patterns of gene activity.

- **Mechanisms of tumour cell formation**

Existing evidence from tumour research suggests the following: 1. Despite the diverse nature of carcinogenic agents (including physical, chemical, and biological factors), tumours arising from the same cell type in animals or plants show little difference; 2. During the transformation of normal animal cells into tumour cells, whether induced by X-rays, chemical carcinogens, or viruses. one or more rounds of cell division are required for the cells to stably maintain their neoplastic phenotype; 3. Although malignant tumours vary widely in type, their nuclei share common characteristics: enlargement, morphological abnormality, and a marked increase in unevenly distributed intranuclear chromatin. Points 1 and 2 suggest that tumour formation may involve a common mechanism linked to cell division. Point 3 implies that abnormal chromatin fibre configuration is a widespread feature of tumour cell nuclei. Given the facts that many tumour cells possess a complete set of chromosomes and that some are capable of reversion, the abnormal chromatin fibre configuration likely does not stem from mutations caused by DNA deletion, substitution, or permanent recombination; rather, it may result from the failure of daughter cells to restore a stable chromatin fibre configuration following cell division. Based on this, we propose the following hypothesis regarding the mechanism of tumour formation.

There appears to be a 'fork in the road' during the normal cell life cycle, a critical juncture where carcinogenic factors can divert a cell onto a path of malignant proliferation. This juncture likely occurs during the mitotic phase (M phase), with the chromatin fibres serving as the specific site of action for these carcinogenic factors. Toward the end of the M phase, the configuration of chromatin fibres in daughter cells begins to transition toward a stable state, a process likely mediated by a series of enzymatic reactions. If carcinogenic factors intervene at this stage, they may interact directly with specific chemical groups on the chromatin fibres or induce structural alterations in certain regions of the fibres. These changes prevent the chromatin fibres from reverting to their stable configuration, locking them instead into an aberrant state. To survive, the cell must adapt through compensatory changes in gene activity patterns to this altered chromatin configuration; conversely, the aberrant chromatin configuration may accommodate the abnormal gene activity (specifically, the activity of tumour-associated genes). Consequently, the cell acquires new biological characteristics, such as autonomous proliferation independent of organismal control, the secretion of proteins unique to tumour cells (e.g., tumour-specific antigens), and varying degrees of morphological and structural alteration. Following prolonged exposure to carcinogenic factors, the cell becomes "accustomed" to this new mode of

existence; even if the carcinogenic factors are subsequently removed, the cell fails to revert to its normal state, thereby completing the transformation from a normal cell into a tumour cell.

During the transition of chromatin fibre configurations to a stable state following cell division, cells of the same type may share a common 'weak link' or a site with an affinity for carcinogenic agents. whereas this affinity site may differ across different cell types. This could explain why various carcinogens induce tumours with similar characteristics in each cell type yet produce tumours with distinct properties in different cell types.

According to this hypothesis, there is no fundamental difference between malignant tumour cells and normal cells; although they exhibit many characteristics distinct from normal cells, these traits do not stem from genetic mutations but rather from abnormal configurations of chromatin fibres within the nucleus and the associated irregularities in gene activity. We propose that if the chromatin fibre configuration of tumour cells can be restored to the state characteristic of normal cells, all their tumour properties will vanish and normal cellular characteristics will re-emerge, thereby achieving the reversal of the tumour cells.

The normal dynamic changes in the configuration of chromatin fibres in normal cells likely proceed through a series of enzymatic reactions or under the influence of specific factors unique to normal cells. Therefore, in-depth research into the underlying mechanism as well as the components and functions of normal cells, particularly those in the M phase may aid in the search for 'reversal agents.' Certain instances of malignant tumour reversal may be linked to the action of these factors found in normal cells. For example, when a nucleus from a Lecat's adenocarcinoma cell of a leopard frog is transplanted into an enucleated normal frog egg, the egg containing the cancerous nucleus can develop into a normal, healthy frog; similarly, when normal cells are fused with cancer cells and cultured in vitro, the cancerous traits of the hybrid cells are suppressed, resulting in the expression of normal cellular characteristics.

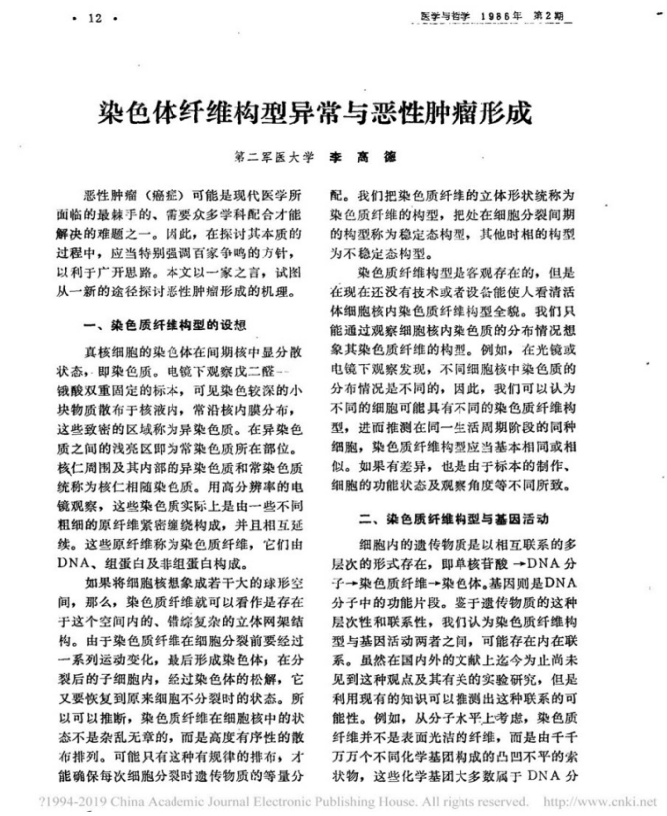
In summary, the concept of tumour reversal appears based on current evidence, which is grounded in objective facts rather than merely stemming from wishful thinking; we hope this article offers a theoretical framework to support the vigorous pursuit of research into tumour reversal.

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Supplement

The photos of Gao-De Li's 1986 Chinese-language article titled as 'Abnormalities in chromatin fibre configuration and malignant tumour formation':



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染色体纤维构型异常与恶性肿瘤形成

第二军医大学 李 高 德

恶性肿瘤（癌症）可能是现代医学所面临的最棘手的、需要众多学科配合才能解决的难题之一。因此，在探讨其本质的过程中，应当特别强调百家争鸣的方针，以利于广开思路。本文以一家之言，试图从一新的途径探讨恶性肿瘤形成的机理。

一、染色质纤维构型的设想

真核细胞的染色体在间期核中显分散状态，即染色质。电镜下观察戊二醛—锇酸双重固定的标本，可见染色较深的小块物质散布于核液内，常沿核内膜分布，这些致密的区域称为异染色质。在异染色质之间的浅亮区即为常染色质所在部位。核仁周围及其内部的异染色质和常染色质统称为核仁相随染色质。用高分辨率的电镜观察，这些染色质实际上是由一些不同粗细的原纤维紧密缠绕构成，并且相互延续。这些原纤维称为染色质纤维，它们由DNA、组蛋白及非组蛋白构成。

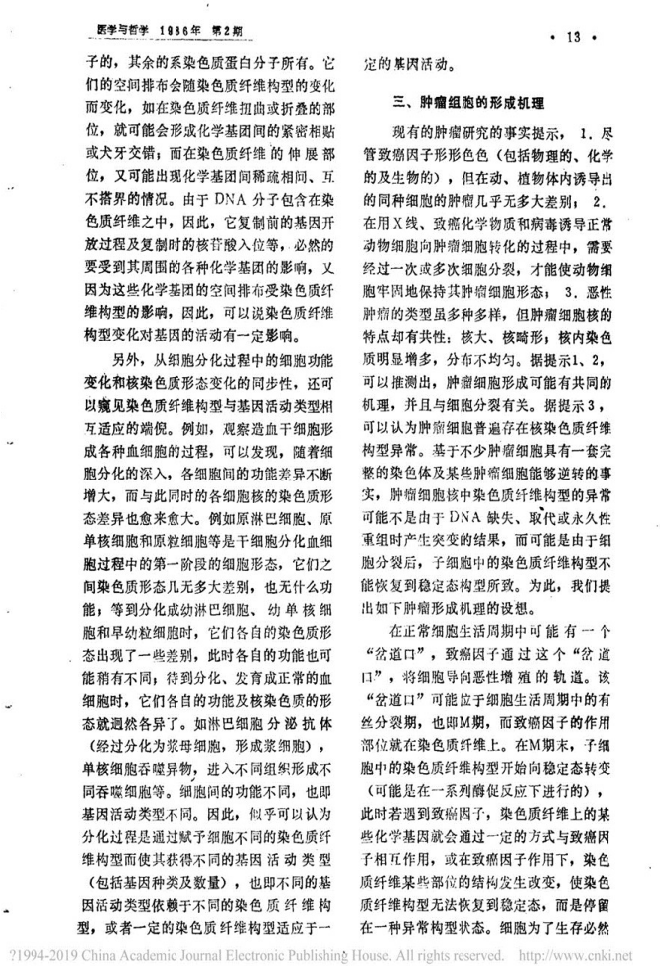
如果将细胞核想象成若干大的球形空间，那么，染色质纤维就可以看作是存在于这个空间内的、错综复杂的立体网架结构。由于染色质纤维在细胞分裂前要经过一系列运动变化，最后形成染色体；在分裂后的子细胞内，经过染色体的松解，它又要恢复到原来细胞不分裂时的状态。所以可以推断，染色质纤维在细胞核中的状态不是杂乱无章的，而是高度有序性的散布排列。可能只有这种有规律的排布，才能确保每次细胞分裂时遗传物质的等量分配。我们把染色质纤维的立体形状统称为染色质纤维的构型，把处在细胞分裂间期的构型称为稳定态构型，其他时相的构型为不稳定态构型。

染色质纤维构型是客观存在的，但是在现在还没有技术或者设备能使人看清活体细胞核内染色质纤维构型全貌。我们只能通过观察细胞核内染色质的分布情况想象其染色质纤维的构型。例如，在光镜或电镜下观察发现，不同细胞核中染色质的分布情况是不同的，因此，我们可以认为不同的细胞可能具有不同的染色质纤维构型，进而推测在同一生活周期阶段的同种细胞，染色质纤维构型应当基本相同或相似。如果有差异，也是由于标本的制作、细胞的功能状态及观察角度等不同所致。

二、染色质纤维构型与基因活动

细胞内的遗传物质是以相互联系的多层次的形式存在，即单核苷酸→DNA分子→染色质纤维→染色体。基因则是DNA分子中的功能片段。鉴于遗传物质的这种层次性和联系性，我们认为染色质纤维构型与基因活动两者之间，可能存在内在联系。虽然在国内外的文献上迄今为止尚未见到这种观点及其有关的实验研究，但是利用现有的知识可以推测出这种联系的可能性。例如，从分子水平上考虑，染色质纤维并不是表面光洁的纤维，而是由千千万万个不同化学基团构成的凸凹不平的索状物，这些化学基团大多数属于DNA分

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子的，其余的系染色质蛋白分子所有。它们的空间排布会随染色质纤维构型的变化而变化，如在染色质纤维扭曲或折叠的部位，就可能会形成化学基团间的紧密相贴或犬牙交错；而在染色质纤维的伸展部位，又可能出现化学基团间稀疏相间、互不搭界的情况。由于DNA分子包含在染色质纤维之中，因此，它复制前的基因开放过程及复制时的核苷酸入位等，必然的要受到其周围的各种化学基团的影响，又因为这些化学基团的空间排布受染色质纤维构型的影响，因此，可以说染色质纤维构型变化对基因的活动有一定影响。

另外，从细胞分化过程中的细胞功能变化和核染色质形态变化的同步性，还可以窥见染色质纤维构型与基因活动类型相互适应的端倪。例如，观察造血干细胞形成各种血细胞的过程，可以发现，随着细胞分化的深入，各细胞间的功能差异不断增大，而与此同时的各细胞核的染色质形态差异也愈来愈大。例如原淋巴细胞、原单核细胞和原粒细胞等是干细胞分化血细胞过程中的第一阶段的细胞形态，它们之间染色质形态几无多大差别，也无什么功能；等到分化成幼淋巴细胞、幼单核细胞和早幼粒细胞时，它们各自的染色质形态出现了一些差别，此时各自的功能也可能稍有不同；待到分化、发育成正常的血细胞时，它们各自的功能及核染色质的形态就迥然各异了。如淋巴细胞分泌抗体（经过分化为浆母细胞，形成浆细胞），单核细胞吞噬异物，进入不同组织形成不同吞噬细胞等。细胞间的功能不同，也即基因活动类型不同。因此，似乎可以认为分化过程是通过赋予细胞不同的染色质纤维构型而使其获得不同的基因活动类型（包括基因种类及数量），也即不同的基因活动类型依赖于不同的染色质纤维构型，或者一定的染色质纤维构型适应于一定的基因活动。

三、肿瘤细胞的形成机理

现有的肿瘤研究的事实提示，1. 尽管致癌因子形形色色（包括物理的、化学的及生物的），但在动、植物体内诱导出的同种细胞的肿瘤几乎无多大差别；2. 在用X线、致癌化学物质和病毒诱导正常动物细胞向肿瘤细胞转化的过程中，需要经过一次或多次细胞分裂，才能使动物细胞牢固地保持其肿瘤细胞形态；3. 恶性肿瘤的类型虽多种多样，但肿瘤细胞核的特点却有共性：核大、核畸形，核内染色质明显增多，分布不均匀。据提示1、2，可以推测出，肿瘤细胞形成可能有共同的机理，并且与细胞分裂有关。据提示3，可以认为肿瘤细胞普遍存在核染色质纤维构型异常。基于不少肿瘤细胞具有一套完整的染色体及某些肿瘤细胞能够逆转的事实，肿瘤细胞核中染色质纤维构型的异常可能不是由于DNA缺失、取代或永久性重组时产生突变的结果，而可能是由于细胞分裂后，子细胞中的染色质纤维构型不能恢复到稳定态构型所致。为此，我们提出如下肿瘤形成机理的设想。

在正常细胞生活周期中可能有一个"岔道口"，致癌因子通过这个"岔道口"，将细胞导向恶性增殖的轨道。该"岔道口"可能位于细胞生活周期中的有丝分裂期，也即M期，而致癌因子的作用部位就在染色质纤维上。在M期末，子细胞中的染色质纤维构型开始向稳定态转变（可能是在一系列酶促反应下进行的），此时若遇到致癌因子，染色质纤维上的某些化学基团就会通过一定的方式与致癌因子相互作用，或在致癌因子作用下，染色质纤维某些部位的结构发生改变，使染色质纤维构型无法恢复到稳定态，而是停留在一种异常构型状态。细胞为了生存必然

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要代偿性的以异常的基因活动类型来适应这种染色质纤维构型的异常，或者如前所述，异常的染色质纤维构型适应于异常的基因活动，也即肿瘤相关基因的活动。其结果使细胞获得了新的生物特性，包括不受机体束缚的自主性增殖、分泌肿瘤细胞特有的一些蛋白质（肿瘤细胞特异性抗原等）及不同程度的形态结构改变等。经过致癌因子持续作用一段时间后，细胞就会习惯于新的生活方式，这时即使去除致癌因子，细胞也不会恢复到正常状态，从而完成了正常细胞向肿瘤细胞的转变。

同种细胞的染色质纤维构型在细胞分裂后向稳定态转变的过程中，可能有一个共同的薄弱环节，或称为致癌因子嗜亲部位；而不同种细胞染色质纤维上的这种嗜亲部位可能不同。这可以解释为什么各种不同致癌因子，对同种细胞诱导出肿瘤特点相近，而对不同种细胞诱导出的肿瘤特性各不相同。

按照本假说，恶性肿瘤细胞与正常细胞在本质上没有什么差别，虽然它有许多特性与正常细胞不同，但这不是由于基因突变的结果，而是由于细胞核中的染色质纤维构型异常及其伴随的基因活动异常的结果。我们认为只要设法使肿瘤细胞染色质纤维构型恢复到正常细胞应有的状态，它的所有肿瘤特性就会随之消失，而正常细胞的特性又会重现，从而达到肿瘤细胞的逆转。

正常细胞染色质纤维构型的正常运动变化，可能是在一系列酶促反应下，或正常细胞内才有的某些因子作用下进行的，因此深入研究它们的详细机理及正常细胞、特别是处在M期阶段的细胞的组分及其功能，对于寻找“逆转药物”可能有一定帮助。有些恶性肿瘤逆转的现象可能与正常细胞内的这些因子的作用有关。例如，从豹纹蛙的勒基氏腺癌细胞取出细胞核，把它移植入已去掉核的正常蛙卵细胞里，含有癌细胞的卵可以发育成正常健康的蝌蚪，又如，把正常细胞与癌细胞融合后，在体外培养，会发现杂种细胞中的癌细胞特性受到了抑制，即表现出正常细胞的特性。

总之，从现在看来，肿瘤逆转的提法不仅仅就出于人们良好的愿望，而且是基于一定的客观事实，我们希望本文能为大力开展肿瘤逆转的研究提供一点理论构思。

《酸、碱及电解质紊乱临床生理学》征订启事

河北科技出版社出版的由有关专家、教授翻译的美国马萨诸塞州立大学医院内科及生理学教授、著名的肾脏临床生理学家 Burten Dovid Rose 著的《酸、碱及电解质紊乱临床生理学》一书于1986年出版。本书将基础医学与临床疾病有机地结合在一起。因此，对内、外、妇、儿科临床医生，教学、科研人员及医学生都是有参考价值的实用读物。

全书共分30章，第1～8章：体液生理学、肾功能及激素调节；第9～13章：体液、酸、碱、钠、钾平衡的正常调节；第14～28章：主要的酸、碱及电解质紊乱，包括病因、症状、诊断和治疗。大多数章节末均附思考题，其答案在第29章；第30章：临床实用的一些重要公式和方程式。

该书约40万字，插图约200幅，大32开本。预计1986年第一季度出版，每本平装收工本费5元，精装6元（含包装邮挂寄费）。

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