Viewpoint

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A topology for cells in Virchow's *Schleimgewebe?*

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Abstract

Mucus as an anatomical entity has been unjustly overlooked in bioscience, despite being recognised as an influential microenvironment for cells or hosts with disease-causing properties. In addition to his description of cell function, Rudolf Virchow considered the effect of mucus, to which we owe today's thinking on cell biology. He coined the term *'Schleimgewebe'*. These spaces of mucus, formed by 'connective tissue' (wrongly 'fasciae', formerly described as 'tela'), can be revealed without cells by Ott's method. The fact that correct cells redevelop locally through blood perfusion in determined spaces is further evidence of local effectiveness of *Schleimgewebe*. As further evidence for a mucus topology, we can conclude that topological thinking is clinically very successful in cancer treatment.

Keywords: biofactors; biomarkers; cancer; cell host; cell free matrix; cell space; extracellular matrix; fascia; micro environment

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Introduction

An unconventional perspective on anatomy is adopted in this Viewpoint. Building on an earlier anatomical idea that mucus can exert local influences on cells, it is unsurprising that such an approach has received limited acceptance within contemporary biomedical science. In the Western tradition, anatomy is predominantly interpreted through a cell-biological framework. Consequently, the spaces occupied by cells tend to be discussed in cellular or molecular terms rather than as anatomically defined entities with discernible borders. Within this prevailing paradigm, the possibility that mucus may exert beneficial effects on the body has received little consideration. Traditionally associated with pathological processes, mucus is rarely regarded as a functional anatomical substance acting independently of direct cellular activity, which remains the principal focus of modern cell biology. As a result, its potential role as a spatial and regulatory element has largely been overlooked.

In this context, the role of locally organized mucus in shaping both local and global patterns of cell differentiation is emphasized. Such an influence is proposed to be inherently spatial and is interpreted here in terms of a topology that constrains and guides cellular behavior.

A Topology for Cells in Virchow's Mucous Tissue

The fundamental importance of cells in health and disease was articulated nearly 150 years ago by Rudolf Virchow in Germany. At that time, German scientific thought occupied an intermediate position between the rational, empirically oriented Anglo-American tradition and more metaphysical approaches associated with Eastern philosophies. This intellectual environment allowed for conceptual frameworks in which material, spatial, and functional aspects of biology could be considered together.

A return to Virchow's original anatomical perspective is therefore advocated. Alongside his seminal contributions to cellular pathology, Virchow repeatedly emphasized the importance of *Schleimgewebe* (mucous tissue) in both physiological and pathological contexts. This tissue was described as a gelatinous, water-rich, intercellular substance occupying anatomically defined spaces. In the present Viewpoint, evidence is brought together to suggest that such bordered spaces must exist in order to influence cellular behavior and, consequently, health and disease. This notion closely parallels earlier medical conceptions in which mucus—together with blood and bile—was regarded as a fundamental determinant of bodily function.[1]

In order to substantiate this hypothesis, a structured four-step line of argument is outlined in the sections that follow.

1st Evidence: Virchow's View on Mucous Tissue Surrounding Cells

At present, the consideration of mucus as an important anatomical and functional entity may appear outdated. If it is assumed that Rudolf Virchow denied the relevance of mucus, this assumption is incorrect. On the contrary, mucus was explicitly addressed and defined by Virchow in the context of both physiological and pathological tissues. As stated in his own words: *"I have demonstrated for a large number of physiological and pathological tissues that mucus also occurs in the interior of tissues in the same glassy, gelatinous, swollen form as it appears freely on the surface of mucous membranes … essentially as an intercellular substance. I have therefore been compelled to propose a mucous tissue which is neither identical with the mucous tissue of Bichat, nor with that of the mucus glands. It is not an epithelial tissue, but belongs to the group of adhesive substances"*.[2]

A common misconception persists that connective tissues are predominantly solid in nature. In reality, even structures commonly regarded as dense, such as tendons, consist largely of water, with water content reaching approximately 65%. From this perspective, a tendon may be understood as a water-rich structure supported by specific organizational components. Earlier knowledge of *Schleim* (mucus) as a material property of tissues has largely been forgotten.[1] Nevertheless, this characteristic can readily be appreciated through the examination of fresh or Thiel-fixed anatomical specimens (**Figure 1a**).

With the dominance of cell-biological thinking—summarized by the notion that "the human is made of cells"—general attention to mucus gradually receded from anatomical discourse and, consequently, from medicine and broader scientific understanding. Connective tissue came to be regarded primarily as a passive filler, often conceptually reduced to material that could be removed without functional consequence. As a result, experimental approaches that might have supported earlier concepts regarding the form and function of mucus have largely not been pursued for decades. Despite this historical neglect, evidence supporting Virchow's concept of mucous tissue and its functional, spatially organized compartments extends beyond his original descriptions alone. These additional lines of evidence are outlined in the following sections.

2nd Evidence: Recent Cell Biological Observations on Carcinogenic Properties of Cell-Surrounding Spaces

In contemporary cell biology, increasing attention has been directed toward the immediate spatial environment of cells in the context of carcinogenesis. Kufe emphasized that the space surrounding cells and their membranes is closely associated with cancer-related processes, particularly through mucins and the cellular *microenvironment*.[3] Subsequently, Luo and Liu introduced the spatial term host to describe environments somewhat larger than Kufe's microenvironments, suggesting that metabolites within such spaces may contribute to carcinogenic processes.[4]

Despite these developments, considerable terminological and conceptual heterogeneity persists in the description of comparable spatial entities. The tissue organization field theory proposed by Soto and Sonnenschein conceptualizes *whole tissues* as the primary targets of carcinogens, with disease arising from disturbances in the biophysical and biomechanical communication between *parenchyma* and *mesenchyme or stroma*.[5,6] Similarly, Cox and others have emphasized the role of the *extracellular matrix* in relation to cell differentiation and malignant transformation.[7]

Across these approaches, a consistent underlying principle can be identified. Cellular behavior in cancer is widely acknowledged to be influenced by its surrounding spatial environment, including biofactors and matrix-associated components.[8] This influence is implicitly spatial and can be interpreted in topological terms. However, within current cell-biological frameworks, these cell-influencing environments are typically defined without reference to clear anatomical borders, leaving their spatial organization conceptually incomplete from an anatomical perspective.

3rd Evidence: Spatial Properties of Larger Anatomical Spaces in Cancer, as Demonstrated by Clinical Experience

Clinical experience provides substantial evidence that cancer progression follows spatially organized anatomical patterns. In Leipzig, the gynecologist Höckel achieved high oncological success by recognizing that tumor spread is constrained by a topography defined by connective structures.[9–11] These spaces were conceptualized as cancer *fields* derived from practical surgical experience, with their spatial origin explained in terms of ontogenesis.

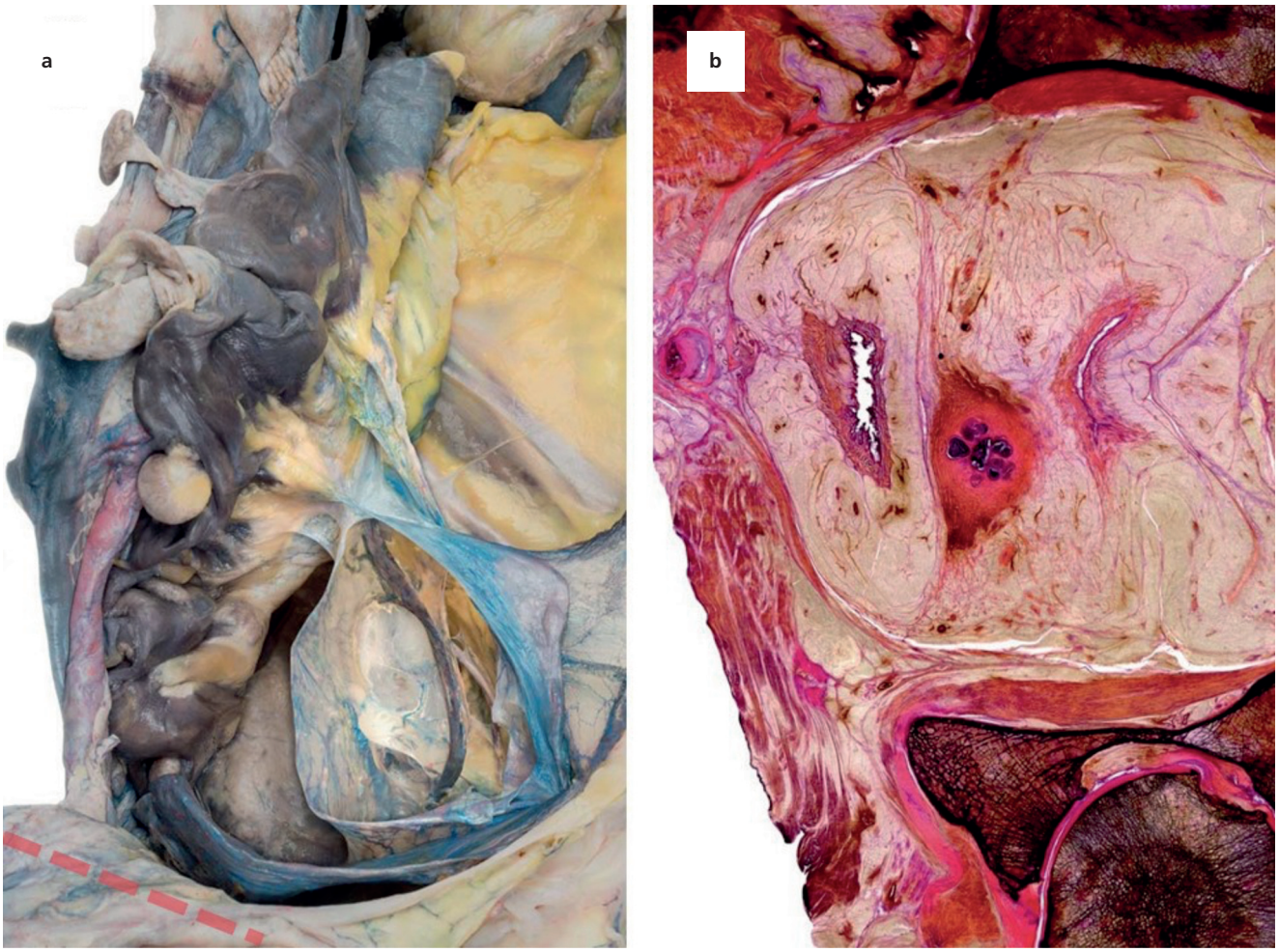


Figure 1. Mucous spaces of the lower abdomen and pelvis. (**a**) Left lower abdomen. Photograph courtesy of K. Rowedder. The anteriorly retracted sigmoid colon (appearing on the left side of the image) remains attached to remnants of the largely removed peritoneum that delineate the abdominal cavity. Its mesocolon persists as a subperitoneal double-layered *tela* extending from the aorta to the sigmoid colon, corresponding to the former dorsal mesogastrium. The ureter, which is embryologically derived from the urogenital crest, is surrounded by a distinct *tela* ("ureter-meso"), forming the flat ureteric space. This ureteric *tela* borders the ovary, which itself is enclosed by additional *telae* ("mesovarium"). These *telae* both connect and simultaneously partition the adjacent spaces, constituting a surgical landmark in "cancer field" surgery (Höckel). Their separability during dissection is demonstrated here. Within the ureter-meso, additional lower-order *telae* associated with supplying vessels (Pirogoff's arterial sheaths, mesodermal in origin) can be observed. A red dashed line indicates the level of section shown in (**b**). (**b**) Horizontal section through the deep pelvic region (plastinated specimen with Schiff's reagent staining for carbohydrates). The section level corresponds to the line indicated in (**a**). Dorsal orientation is to the left. Less intensely stained mucous spaces are enclosed by red-stained pelvic "fasciae" (*telae*). Muscles (red) and bones (brown) are visible inferior to the hip joint. At this level, the sigmoid colon has transitioned into the rectum, seen as the left-sided luminal structure; its lumen appears empty compared to the surrounding, lightly stained mucous compartments. The rectum is enveloped by layered *telae* forming the mesorectum. Centrally, the uterus appears as a red-stained structure. A flattened space is defined by sagittally oriented *telae*, including the mesovarium and the broad ligament (*lig. latum*). On the right, the urinary bladder is identified as a red structure with a lumen, bordered by the *telae* of the urachus. These images demonstrate that organs are embedded within tela-bounded mucous spaces. These compartments are surrounded by multiple fine layers of connective tissue (*telae*), which both separate and interconnect the principal spaces of three embryologically distinct organ systems. Each major space contains further subspaces. For example, concentric compartments around the rectum (relevant in proctology), lamellar extensions associated with the uterus and ureter and the retropubic (Retzius) space surrounding the urinary bladder (urology) can be identified. Notably, these spaces are not empty but contain stained material and exhibit further internal subdivision. *Adapted from Wiersbicki and Steinke (dissertation).*

Comparable observations have been reported in other organ systems. In pancreatic surgery, Alvanos described distinct "fascial spaces" corresponding to the different embryological development of the pancreatic head and tail.[12,13] Similarly, in urology, Stolzenburg observed that prostate carcinoma exhibits a strictly spatial behavior related to disease severity. This spatial predictability enabled the preservation of anatomical structures located in close proximity to the tumor while maintaining high clinical success rates.[14,15]

The boundaries of these clinically relevant spaces are formed by connective structures that are commonly referred to as fascia. Historically, however, these "fascial" structures were described as *telae*, a term that more accurately reflects their anatomical nature[1,16,17] (**Figure 1b**). Regardless of terminology, these boundaries function as effective anatomical delimitations.

On the basis of such clinical observations, it is reasonable to relate cancer behavior to anatomically tela- bounded spaces or *fields*. These may represent diseased compartments of *Schleimgewebe*. The spatial properties described by Höckel, Alvanos, and Stolzenburg are consistent with current clinicopathological experience and support the notion that a topology for cancer may exist.[10–15]

4th Evidence: Cells Differentiate Related to Anatomical Spaces

To regenerate heart cells, Harald Ott had the idea of using embryonic cells.[18] Later he produced cell-free hearts and lungs,[19,20] intestines,[21] kidneys[22] and rat legs[23] (even human arms[24]).

At first glance, Ott's approach appears to be a gimmick with no further epistemological background.

To come to our 4th piece of evidence, we need to think for a moment: Anatomical forms without cells exist, due to these experiments. These preparations encompass all the anatomical spaces and borders surrounding the cells, thus covering all the terms we know to describe them. Ott's preparations are jellyfish-like, sometimes solid, sometimes fluid, depending on the amount of removed cells (Peto's paradoxon: humans have relatively fewer cells but more cancers than other species). We see in such artefacts parts of Virchow's *Schleimgewebe* (**Figure 2**).[2] Ott's experiments are surprising when he (and many other authors then) let foreign blood flow through these cell-free forms.[19–25] The objective that Ott had been striving to attain was ultimately accomplished by this blood: new cells underwent differentiation in these forms. Ott successfully realized his objective of regenerating heart cells.[19] Blood, this special liquid, recognizes a "correct" (cell-free) space and changes accordingly. In other words, a "correct" space recognizes blood from which "correct" cells occur locally. Ott understands this process as 'guided differentiation'.[21] The question thus arises as to what may be the driving force behind the differentiation of cells at the local and global levels if not the remaining elements that persist following the destruction of all cells?

In an effort to regenerate cardiac tissue, Harald Ott initially employed embryonic cells.[18] This work was subsequently extended through the production of cell-free organs, including hearts and lungs,[19,20] intestines,[21] kidneys,[22] and composite tissues such as rat limbs,[23] and even human upper extremities.[24]

At first glance, this experimental approach may appear to lack a broader epistemological foundation. However, closer consideration reveals a fundamental anatomical insight. These experiments demonstrate that anatomical forms can persist in the complete absence of cells. The resulting preparations preserve all spatial compartments and boundaries that normally surround cells, encompassing the full range of anatomical structures used to describe tissue organization. Depending on the extent of cellular removal, these cell-free constructs exhibit a gelatinous or semi-solid consistency, reminiscent of jellyfish-like forms. This variability further emphasizes the predominance of non-cellular material within tissues, a phenomenon that may be viewed in light of observations such as Peto's paradox, whereby humans possess relatively fewer cells yet exhibit higher cancer incidence than many other species.

Within these cell-free anatomical artefacts, elements corresponding to Virchow's *Schleimgewebe* can be recognized[2] (**Figure 2**). The relevance of these structures becomes particularly apparent in perfusion experiments. When foreign blood was circulated through such decellularized forms, a striking outcome was observed: new cells underwent differentiation within these predefined spaces.[19–25] In this manner, the original objective of regenerating functional cardiac tissue was successfully achieved.[19]

Blood, as a biologically active fluid, appears to respond selectively to appropriate anatomical spaces. Conversely, anatomically "correct" spaces appear capable of eliciting locally appropriate cellular differentiation from circulating blood-derived elements. This reciprocal interaction was described by Ott as "guided differentiation".[21]

These observations raise a fundamental anatomical question. If cellular content has been entirely removed, what factor remains capable of directing both local and global patterns of cell differentiation? The most plausible candidate is the persistent, water-rich extracellular framework—namely, the anatomically organized mucous tissue that survives cellular destruction and retains positional information.

As hypnotized, Virchow's concept of mucous tissue may be understood as encompassing all anatomically definable spaces capable of carrying positional and func-

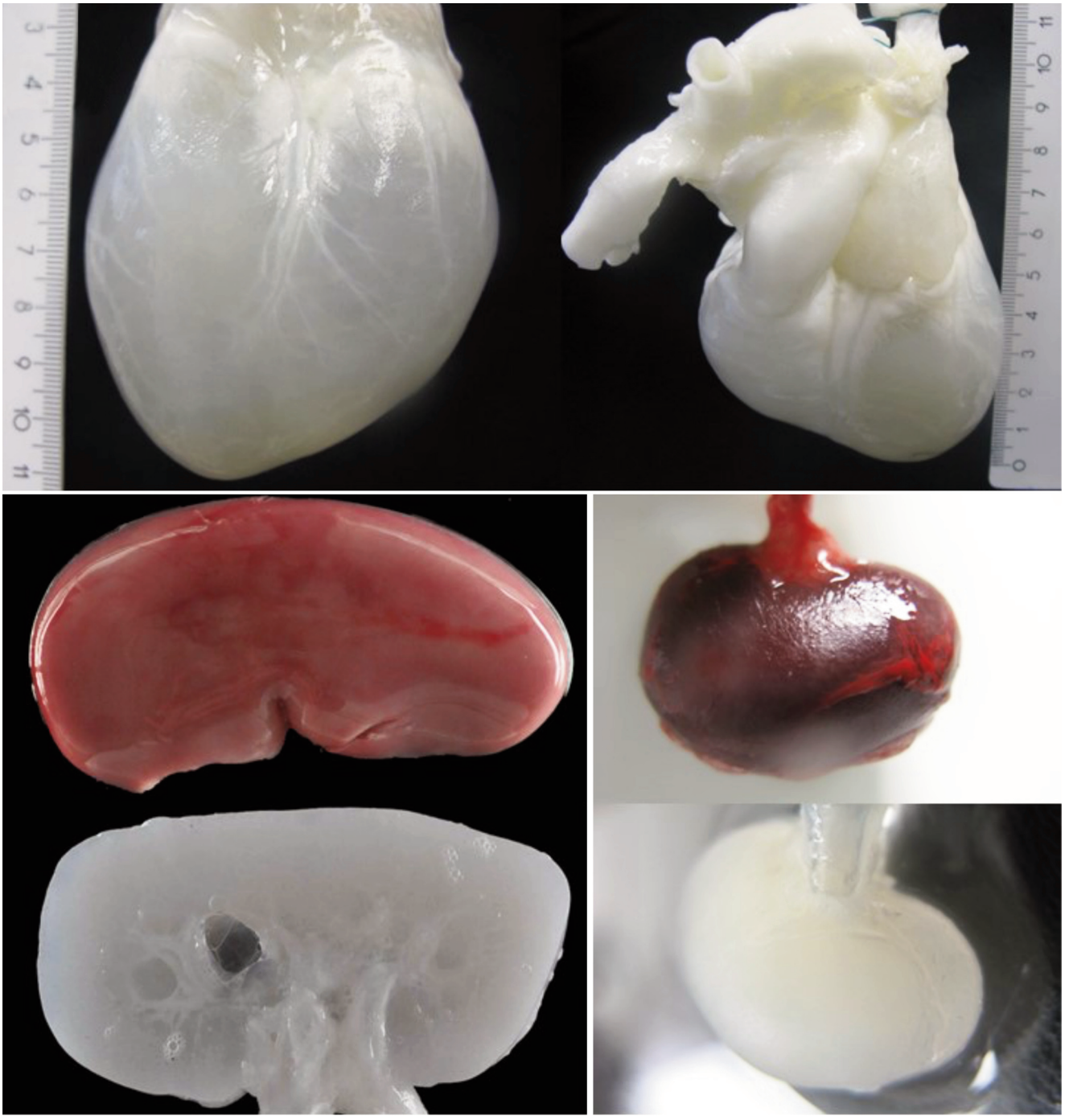


Figure 2. Cell-free organ scaffolds of the heart and kidney (porcine). Cell-free hearts (top row) and kidneys (bottom rows). The bottom series illustrates the kidney following organ retrieval (upper image) and after complete decellularization (lower image). A frontal section demonstrates the persistence of cell-free structural components, including the ureter, renal pelvis, and renal cortex. Produced by the Translational Centre for Regenerative Medicine Leipzig, Institute for Clinical Immunology (courtesy of Dr. A. Boldt).

tional information. An interpretation of this topographical phenomenon solely in terms of Kufe's concept of the cellular "microenvironment" appears overly restrictive. Across a wide range of cell-free anatomical constructs—including kidney, lung, heart, and extremities—regeneration has consistently been observed to begin with the emergence and specialization of locally appropriate cells that subsequently acquire organ-specific functions.[19–25]

The phenomenon of such pronounced "guided cell differentiation"[21] could only be dismissed as coincidental if instances of inappropriate or ectopic cell differentiation had been observed. To date, such deviations have not been reported.

The local presence of biofactors, including VEGF, TGFβ, and other signaling molecules, as well as structural proteins such as laminin, emilin, and fibronectin, free DNA, and additional components commonly subsumed under the term "microenvironment," can readily be inferred from the existing literature.[3,25–29] It is widely accepted within cell biology that these factors exert significant influence on cellular behavior, including in oncological contexts. Furthermore, it is generally acknowledged that each factor acts in accordance with its local availability and concentration.

Synopsis

It is at this point that the evidence for the topological properties of Virchow's mucous tissue becomes particularly compelling. Each known biological factor is effective only in accordance with its local presence and abundance; in the absence of a factor, no corresponding function can be expressed.

While cell biology has convincingly demonstrated such principles in the immediate vicinity of cells,[3–5] clinical and experimental observations indicate the existence of larger, anatomically defined "fields" or tela-borderd "fascial" spaces associated with cancer development and progression.[9–12,14,15] These spaces represent structured components of a fundamental anatomical entity composed of bound water—mucous tissue as described by Virchow under the term *Schleimgewebe*[2]—which can persist and be observed even in a cell-free state.[19–25]

What was previously regarded by earlier physicians and anatomists as *Schleim* (mucus; Hoffbauer[1]) or *Schleimgewebe* (mucous tissue; Virchow[2]) may thus be reconsidered as a carrier of local and topographical information relevant to both health and disease. This information appears to be conveyed at both local and systemic levels.

On this basis, the existence of a topology for cells within Virchow's mucous tissue must be considered. A return to this mode of anatomical conceptualization would facilitate a more precise understanding of why cellular alterations occur—or fail to occur—in specific locations. Without a comprehensive anatomical framework for *Schleimgewebe*, cell biological research risks becoming an increasingly complex and resource-intensive endeavor, comparable to searching for a needle in an undefined haystack.

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Conflict of Interest

The author declares that there is no conflict of interest.

Author Contributions

All concepts, analysis, and writing of the manuscript were developed and carried out by the main author (HS).

Ethics Approval

This manuscript is an overview article reflecting the author's professional experience and scholarly perspective; therefore, it did not involve human participants, animals, or identifiable personal data and did not require formal approval from an institutional ethics committee. All figures used in this manuscript were produced by the Translational Centre for Regenerative Medicine Leipzig AöR, Institute for Clinical Immunology, and were reproduced with special permission.

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