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When Orden Betrays: Remodeling the Matrix, Rewriting the Tumor's Path

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Editorial

The body is a silent republic. Each cell, each fiber, each molecule knows its place, its time, its duty. There is an ancestral choreography between structure and function, where collagen fibers sustain the architecture of stability, and the cells of the microenvironment-immune, endothelial, mesenchymal-patrol, build, and balance. The extracellular matrix is not merely structural support: it is territory, language, and limit. Everything works-until it doesn't. And what was once a mesh of containment becoming a pathway for invasion. ***Order betrays***. And among the first to betray is collagen-which, through remodeling, abandons its role as barrier and assumes that of a guide.

In healthy tissue, collagen fibers are distributed heterogeneously, with varied orientation, preserved length, and a natural waviness-properties that confer mechanical flexibility and biological resilience. This extracellular mesh acts as a physical and biochemical barrier to tumor dissemination. However, as the microenvironment is progressively remodeled, these properties change. In our studies using multiphoton microscopy and Second Harmonic Generation (SHG) analysis, we observed that carcinomas with metastatic potential display shorter, straighter, and more aligned fibers. This seemingly ordered yet pathologically permissive configuration reflects a silent collapse of the stromal barrier. Collagen no longer contains-it guides. And so, the matrix that once limited expansion becomes a route of escape.The breakdown of physical barriers does not occur in isolation. It is often accompanied-or even preceded-by the dysfunction of local immune cells. Among these, tumor-associated macrophages (TAMs) are key players in this role reversal. Rather than promoting phagocytosis and activating protective inflammation, TAMs-reprogrammed by the tumor-begin to secrete factors that promote angiogenesis, matrix remodeling, and local immunosuppression. Our research group, in previous comparative studies of canine and human mammary carcinomas, has explored the role of TAMs in the tumor microenvironment, and the literature consistently associates high macrophage density with unfavorable prognosis and structural disorganization of the stroma. This does not represent a failure of defense by absence, but by subversion. The immune system is present-but no longer resists. It collaborates.Invasion is not a spontaneous act-it is a guided response. As collagen fibers become shorter and more aligned, they not only yield space but offer direction. And as cells in the tumor microenvironment-including macrophages-shift from containment to support, collapse becomes systemic. In our studies, mammary carcinomas with favorable prognosis presented longer collagen fibers, capable of physically limiting tumor expansion. In contrast, tumors with high proliferative indices and unfavorable prognosis exhibited shorter, highly directional collagen fibers. This shortening may reflect a process of stromal remodeling that generates rigid paths allowing cancer cells to escape hypoxic and necrotic zones, guiding them toward better-vascularized regions. In this context, the matrix ceases to resist and begins to serve. Malignancy, then, is not only intrinsic-it is orchestrated by an environment that has betrayed its original function.

For decades, oncology focused its gaze on the tumor cell-the mutating gene, the failing protein, the uncontrolled division. But perhaps the answer lies not only within the tumor, but around it. The microenvironment is not mere scenery: it is a co-author. The architecture of the matrix, the behavior of immune cells, the biochemical composition of the stroma-all of these silently shape the course of progression. To listen, decode, and modulate this dialogue is the challenge of modern oncology. Because destruction does not always begin with a scream. Sometimes, it begins with a beautiful and intact order… that betrays. And recognizing this quiet collapse may be our most honest chance at containment-before the enemy reveals itself.

The story doesn't end here. The matrix still has more to reveal.

The next chapter in this investigation is already being written-and it promises to challenge, once again, what we think we know about the tumor microenvironment.

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