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Editorial
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Focus on the Tumor Microenvironment

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Editorial

About 15 years ago while investigating the expression of a newly cloned protease-activating receptor in human cancers, I noticed its expression in many of the cell types surrounding the metastatic cells (Figure 1), [1]. At that time, the primary focus of cancer research was on the tumor cells, especially concerning gene mutations or oncogenes. For my part, I was not interested in moving my laboratory resources to discover even more potential oncogenes. However an area worth investigating were the cells surrounding the invading tumor cells that appeared to respond in a coordinated manner to signals secreted from the invading cancerous cells. In fact, I would dare say that the stroma reacted as if to an injury. In order for the once-contiguous normal epithelial cells to lose their junctional proteins to metastasize, the cells abnormally secrete proteases to digest such proteins and become detached. Coupled with unregulated proliferation rates, the once-contained normal or even benign "*in situ*" epithelial cells instantly become a malignant carcinoma. Surely, gene mutations may have initiated this 2-stage process, but ultimately, the fate of these renegade cells lies in the stroma cells. Perhaps the first order of business is adapting to survive with limited oxygen supply, and so when these renegade cells become hypoxic they secrete factors initiating angiogenesis. Independent of the origin of the signal (e.g., injured normal cells or malignant cells), the cells in the local tumor microenvironment (TME), such as fibroblasts, vascular cells (i.e., endothelial, smooth muscle cells, pericytes), inflammatory cells, and mast cells, respond by secreting additional signaling molecules for the reconstruction process.

Thrombin, one of the many secreted factors by the tumor cells, has been correlated with the stage and type of carcinoma, and is associated with cell invasion and extracellular matrix degradation [2,3]. Increased proteolytic activity in the TME can favor capillary sprout elongation and lumen formation during angiogenesis [4]. The numerous cellular actions of thrombin on platelets, vascular cells, mast cells, and leukocytes may contribute to tumor invasion. Additionally, thrombin-mediated connective tissue deposition and development of tissue fibrosis, characteristics of normal wound healing, are processes also associated with cellular metastasis [5,6]. Associating PAR expression in the cells of the TME with cell metastasis had to be further demonstrated *in vitro*. By performing a simple *in vitro* scrape wound to a confluent monolayer of quiescent fibroblasts that are typically without PAR expression, showed the up-regulation of PAR in the proliferating fibroblasts as they migrated into the area of mechanical cell damage.

If indeed more and more research shows that the cells of the TME operate in a controlled and predictable manner in response to the signaling metastatic cells, then therapies aimed to inhibit the

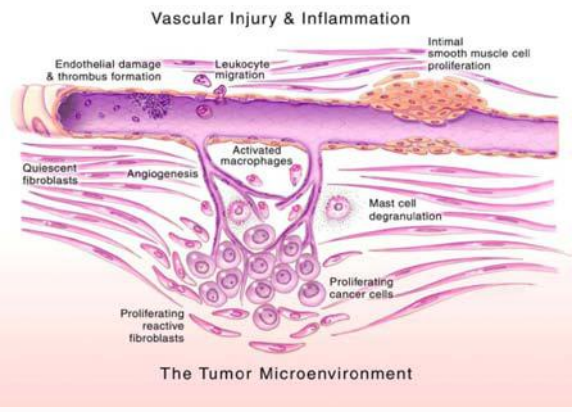

Figure 1: An illustrative representation of PAR-1 and PAR-2 mediated cellular effects during vascular injury, inflammation, and within the tumor microenvironment. (Courtesy of Biochemistry (Moscow) 2002; 67(1): 66-76).

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expression of targets in the cells of the TME should prevent or choke the spread of cancers, independent of their origin.

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