

Anniversary Issue Contribution

Surfing tissue factor

From the predicted to the discovery and elucidation of unanticipated functions and biology of potential significance

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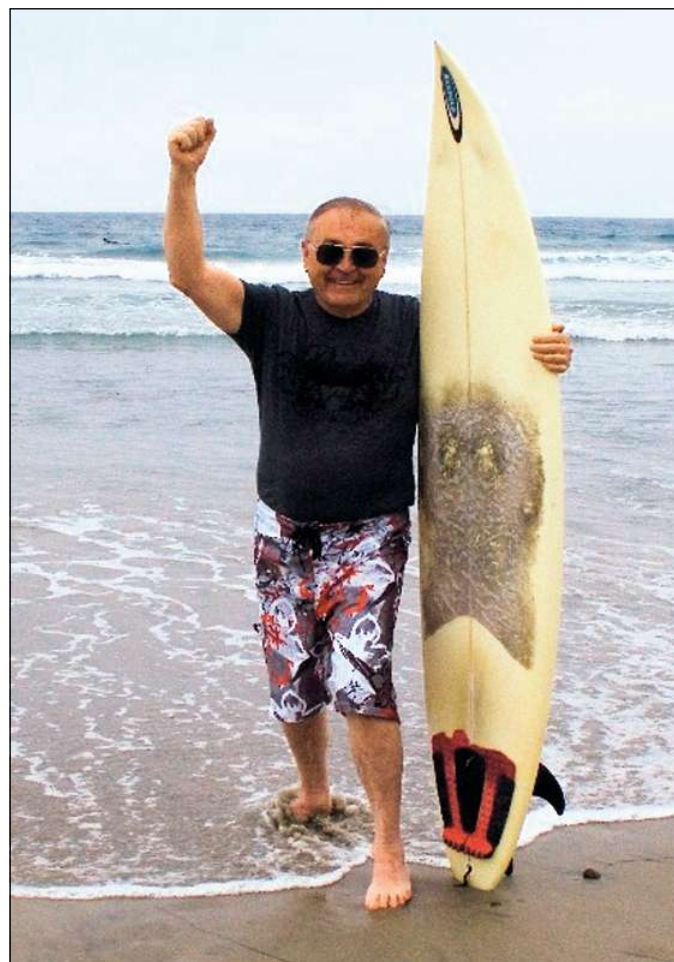
When you catch a wave you can not accurately predict where you will end up. Riding your surf board, you attempt to remain on the wave as long as possible and to follow the end of the wave to a landing on the beach. Riding science and its many waves has led many of us on some wild adventures, sometimes productive if we are lucky. Riding tissue factor (TF) from its early days as an unknown that clotted blood to its current functions in cell signaling and what were unanticipated functions has been an exciting and productive ride, even an adventure.

Quite unanticipated, TF does more than initiate the coagulation protease cascade and play an important role in the pathophysiology of a variety of diseases, functions that now occupy more than 11,000 references in my personal reference library, it has instructed us in the structural basis of function of related molecules.

TF as it is now known was historically chased as thromboplastin, the unknown material in tissues that rapidly clotted blood *ex vivo*. In spite of decades of search for this elusive molecule it was not until 1985 that the protein was isolated and its amino acid sequence established, at least in part. Aided by our collection of more than a thousand kg of fresh human placenta, purification and generation of specific monoclonal antibodies (1), then the engineering of a thousand-fold more sensitive amino acid sequencer, the amino acid sequence of TF and identification of probes for the cloning of the cDNA was accomplished. By 1986 the cDNA for TF was identified and the complete TF protein was successfully expressed in 1987 (2). Subsequently, the complete TF gene was sequenced (3) and then the cellular regulation of transcription of the gene (4, 5).

The scientific trail from 1935 represented a period of remarkable advance in science, biological chemistry, and the emergence of the current highly advanced technology and insight of modern molecular and cellular biology. These advances were necessary for the elucidation of the TF molecule and its multiple functions.

Although assigned to a less favorable position of extrinsic blood coagulation at the onset with belief that the subsequently identified intrinsic coagulation pathway, so elegantly advanced in 1966, was responsible for hemostatic functions *in vivo* as well



Typical high-affinity interaction between tissue factor (shown as a Southern Californian surfboard) and factor VIIa (the author himself in a very recent configuration) that allows high-speed surfing also on unpredictable waves. Only in this tight binding complex both components develop full surfing power, whereas in the absence of surfing tissue factor, factor VIIa would be hardly effective (at least in the Pacific ocean).

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as thrombosis. The map of how the coagulation pathways function has been progressively rewritten with TF at the center and it continues to be advanced with the uncovering of more complex cellular effects mediated by more complex molecular assembly that occurs on the cell surface.

There are investigators riding the wave of how TF influences cell functions through cellular signaling by various means. On one hand, the TF complexes with VIIa interact and signal through PAR-2. The ternary complex of TF with VIIa plus Xa interacts more widely with PAR-1 to drive other signaling pathways (6, 7). The interactions of the cell surface TF complexes with integrins mediate significant cellular responses (8). These cellular responses are of significant importance in the pathophysiology of diseases including infectious disease, severe sepsis syndrome and others.

More recently the small twenty-three amino acid cytoplasmic tail of TF, dismissed early on as too small to be important, is

now being found to be a player, as phosphorylated membrane protein that is indeed involved in cellular responses and cell function (9). Much of the recent published science, and that soon to appear, implicates the TF tail phosphorylation events in concert with other signaling events in biologic functions of interest and potential importance.

The TF wave has not yet dissipated. It still seems to be rolling in. However, on what beach is yet to be determined. There remains more to learn. During the decades that I chased this TF wave stimulated by the delayed hypersensitivity immune response and the identification of TF as important product induced in cells of monocytes lineage by antigen-specific T lymphocytes much has occurred. Much has been learned; and the topic remains of interest and importance to many gifted scientists, both basic and clinical.

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