We have learned from Thomas Kuhn that during periods of "ordinary" science, observations and facts accumulate, conferring upon a given problem an increasing degree of complexity, up to the moment that a scientific revolution opens a new horizon and brings back more simplicity.1 Before these revolutions take place, scientists strongly experience the need for placing some order in a field that becomes more and more complicated. A certain proportion of the "ordinary" scientists feel irritated by their colleagues who contribute to the accumulation of new facts thus increasing complexity, which in some instances they call "confusion."

During the last several years, biological and medical researchers as well as the general public have lived with the paradigm, still very popular today, that understanding the genetic basis of a given disease represents the key to understanding its biological mechanisms and to developing efficient therapeutic strategies. While this assumption remains basically true, more and more observations have accumulated in favor of the possibility that epigenetic events play an additional and crucial role in the development and evolution of many pathological situations. This applies particularly to a disease such as atheromatosis that has for a long time been considered to be pluricausal.

In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Braun-Dullaeus et al.2 based on previous work of their laboratory and of other laboratories,3 4 have investigated a particular aspect of arterial smooth muscle cell (SMC) activation, i.e., the hypothesis that the susceptibility of SMC to cytokine stimulation depends on the phase of the cell cycle they are undergoing. The results reported by these authors represent an excellent example illustrating, on the one hand, how epigenetic mechanisms are essential in the development of vascular pathological changes and, on the other hand, how new findings can bring complexity to the interpretation of a given phenomenon.

It is well accepted that SMCs become capable of migrating from the media to the intima on several types of stimulation; here they replicate and produce substances, e.g., extracellular matrix components and/or proteolytic enzymes, that contribute to the formation and evolution of the atheromatous plaque. This process has been defined as SMC activation. The activation state of intimal SMC has been documented in several ways, including the expression of adhesion molecules, such as vascular adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1).5 6 These molecules are induced in vitro by treatment with tumor necrosis factor-α (TNF-α).7 Using this model, Braun-Dullaeus and coworkers have demonstrated that TNF-α stimulates the expression of both VCAM-1 and ICAM-1 in quiescent (G0) cells, but has only a minor effect on SMCs passing through G1 or S phase after serum stimulation; VCAM-1 and ICAM-1 expression were, however, inducible again in later cell cycle phases (G2/M).2 As the authors underline, connections between cell cycle regulation and control of other cellular processes start to be understood.8 9 On the basis of their findings, Braun-Dullaeus and coworkers introduce the concept that the phase of the cell cycle is important to determine the response of SMC to cytokine stimulation; moreover, they suggest that the cell cycle represents a new target for therapeutic strategies aimed at inhibiting SMC activation.2

There is no doubt that the results of this work render more complex the interpretation of the mechanisms controlling SMC activation and, consequently, atheroma formation. If we consider that, as our laboratory likes to think, SMCs may express several phenotypes corresponding to different functions or to different propensities to participate in atheroma development,10 such complexity may tend to become discouraging.

Far from blaming Braun-Dullaeus and coworkers for their contribution, we are sure that this work represents an important and unavoidable step in the comprehension of SMC behavior during pathological situations. We are also grateful to the authors because their results add to the necessity of a new "revolutionary" paradigm that will simplify the understanding of SMC activation and, consequently, of atheroma development.

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