Inflammation and infarction: the explored, the unexplored and the individual response to inflammatory stimuli

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In this issue of the Journal the minisymposium series "The search for the causes of myocardial infarction" continues with the hot topic of inflammation. Four years ago Attilio Maseri wrote a remarkable editorial comment entitled "Inflammation, atherosclerosis, and ischemic events - exploring the hidden side of the moon"[1] to the Paul Ridker's article on the prognostic role of C-reactive protein in the Physicians' Health Study[2]. After 4 years part of the hidden side has been discovered, but many issues remain to be explored. Three of the authors who present their news in this issue are among those that most have contributed to the explosion of clinical and experimental data on inflammation, ischemia, and acute coronary syndromes[3-5]. Yet, even after their articles, not all questions are solved.

This minisymposium answers to some questions: 1) we should search for the origin of inflammation; so far no hypothesis on the source of inflammation is proven; 2) we should search more about plaque life; we know a lot about its morphology, but much less about its formation, growth and remodeling; 3) we should search for the reasons of the strong association between inflammatory markers and lipids, well known risk factors for myocardial infarction; 4) finally, although not directly related to the search for the causes of myocardial infarction, we should search for novel, anti-inflammatory therapies. In turn, these therapies, if effective, could prove definitely the pathogenetic role of inflammation in acute coronary syndromes.

These four points already represent a rich task for future explorations, but, will answering to these questions shed light on all problems? Why, for example, some patients have inflammation and others not, why some have a myocardial infarction and some not?

In the last 5 years, in Rome, we have addressed considerable attention to the possibility that an individual response to inflammatory stimuli may play a major role as a precipitating cause of myocardial infarction.

Myocardial infarction is a multifactorial disease. It would not be reasonable to consider inflammation as the precipitating cause in all patients, nor to search for a common cause of inflammation in all patients with infarction. Indeed, inflammation is a component of the atherosclerotic background[6], but the latter is common not only to people suffering a myocardial infarction, but also to almost all otherwise apparently healthy subjects[7-9]. Atherosclerosis is a disease which is not fatal *per se*, but fatal are its complications: myocardial infarction, sudden death, and stroke. How can a low degree of inflammation that remains stable for years lead suddenly to myocardial infarction? Accumulating data suggest that a sudden inflammatory burst may induce a pre-infarction condition: an increase in pro-inflammatory mediators such as C-reactive protein, serum amyloid A, interleukin (IL)-6, IL-1Ra and tumor necrosis factor-α has been consistently shown in many patients with unstable angina and myocardial infarction[10-15]. These cytokines and acute phase reactants may induce plaque rupture or endothelial activation and a pro-coagulant state, mainly via macrophage activation with subsequent release of proteolytic agents, including matrix metalloproteinases[16] and activation of the tissue-factor pathway[17,18]. However, no

apparent cause for this inflammatory reaction has been demonstrated: in particular no signs of acute infections, including *Chlamydia pneumoniae*, have been convincingly found[19]. Although activated T lymphocytes are present in the plaque, these are polyclonal or oligoclonal and so far there is no consistent evidence for a specific antigenic activation of the plaque cells[20] but in very few cases[21,22]. If specific causes of inflammation are not found, it is possible that no-specific causes may, in particular situations and/or in predisposed subjects, lead to an enhanced inflammatory response.

Recent data demonstrate that the amount of the inflammatory response to myocardial damage, necrosis, plaque rupture and to no-specific stimuli, such as *in vitro* lipopolysaccharide challenge, strongly differs among individuals[23-25]. Intriguingly the amount of inflammatory response is much larger in individuals with unstable angina and myocardial infarction having elevated levels of inflammatory markers on admission, than in unstable angina and myocardial infarction patients without such an elevation. These findings suggest that patients with increased baseline levels of inflammatory markers may differ from other patients and may have a higher risk of myocardial infarction because of an exaggerated response to some stimuli. This line of evidence may also help to explain why healthy subjects with borderline increased C-reactive protein are at higher risk of myocardial infarction up to 8 years after the baseline sampling[2]. Thus, patients with enhanced inflammatory response, but not patients with mild or absent inflammatory response to the same stimulus, may be predisposed on an individual basis to infarction. Individual susceptibility to infections and to some autoimmune diseases such as diabetes and rheumatoid arthritis is well known and is based at least in part on a genetic background[26]. The identification of candidate genes through a careful analysis of the clinical data may lead to advancements in this field. An increase in IL-6 production after lipopolysaccharide stimulation has been observed for the allele G of the G174C polymorphism of IL-6 and for the allele T of the CD14[27,28]. However, the search for a candidate gene *per se* is unlikely to be successful because of the multifactorial pathogenesis of myocardial infarction. An enhanced inflammatory response might in fact depend also on the failure of the control mechanisms devoted to turn off inflammation when it is no more useful to the organism. It is possible that subliminal and common stimuli may turn on the inflammatory system only in predisposed subjects, or, alternatively, in subjects primed by previous exposure to ischemic or thrombotic stimuli, or, as another possibility, in subjects with defective control mechanisms of inflammation. Thus, it is possible that the search for the causes of myocardial infarction should be moved from the very first cause to the individual predisposing causes of myocardial infarction.

Careful clinical identification of very homogeneous subgroups of patients according to their history, risk factors and inflammatory markers will be the first step of this search. The amount of inflammatory response produced after a stimulus may represent a further marker of individual susceptibility. Once the profile of the patients will be drawn, the causes, genetic or acquired, of the hyperresponsiveness can be searched for, being aware that this will not shed light on the whole dark side of the moon.

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