The world of inhibitory κB

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A LIFE IS A MINEFIELD of inflammatory opportunities. The evolutionary conservation of these cellular pathways supports the counterintuitive conclusion that post-stress/injury inflammation must be good. Of the multiple similarities between rodents and humans, the autocrine and paracrine control systems are perhaps the most striking.

In a recent article in American Journal of Physiology-Heart and Circulatory Physiology, Moss et al. (9) address the pathogenesis of cardiovascular disease. Atherosclerosis has become the most frequent cause of both morbidity and mortality of both men and women in the United States. The authors target a cardiomyocyte-signaling pathway that generates myocardial tumor necrosis factor (TNF). TNF is produced by both resident macrophages and cardiomyocytes themselves in response to ischemia-reperfusion, sepsis, chronic heart failure, viral myocarditis, and transplant allograft rejection (7). There is direct correlation between myocardial TNF and myocardial mechanical dysfunction in humans (14). And, an equally direct relationship exists between left ventricular function and survival in all of us (10). Thousands of animal (9) and human (1) studies have identified the transcriptional regulator, nuclear factor-κB (NF-κB), at the nexus of this proinflammatory cellular program. NF-κB resides in the cytosol as a heterodimeric construct of p65 and p50 subunits. In the unstimulated cardiomyocyte, inhibitory κB (IκB) binds the NF-κB heterodimer, preventing its translocation into the nucleus. As delineated by Moss et al. (9), the IκB kinase (IKK) complex is made up of IKKγ, IKKα, and IKKβ subunits. Multiple common injuries, including vascular shear stress (11) and ischemia-reperfusion (13), tip over the most proximal IKKβ-kinase-activating domino. IKKβ phosphorylates IKKα, targeting it for polyubiquitination and degradation. A dismembered IκB can no longer prevent the nuclear translocation of NF-κB with consequent proinflammatory results. Whether you subscribe to the chlamydia (15) initiated infectious disease hypothesis of atherogenesis or the shear stress/vascular injury explanation (12), NF-κB is common to both.

Prevention of atherosclerosis is a logical and appealing public health goal. Nonspecific NF-κB inhibitors like adenosine (6) or N-acetylcysteine (9) prevent downstream effects of this multifaceted regulator of transcription. The consequences of chronic NF-κB depression, however, are unresolved, and NF-κB does protect against ischemia-reperfusion-induced cardiomyocyte apoptosis (8). So, consistent with its evolutionary conservation, is NF-κB a friend or a foe (5)?

NF-κB plays a pivotal role in constructive cardiac preconditioning in both rabbits (16) and humans (3). NF-κB also promotes TNF production (7), which induces apoptosis (2). So, if chronic inhibition of NF-κB is not assuredly safe, must we restrain our therapeutic enthusiasm and just target acute coronary syndromes (ACSs)? That is still a big problem. More than one million Americans die each year of ACS. The problem, of course, is, When do you treat? Patients do not schedule or plan their heart attacks. The beauty of the current contribution by Moss et al. (9) is that specific pharmacological antagonism of the NF-κB inflammatory pathway reduced left ventricular infarct size when the IKKβ inhibitor was provided before the experimental coronary artery ligation. But, clinically, you would need to treat a lot of angry, high-strung executives to time and catch their heart attacks just right.

Consequently, Moss et al. (9) introduced the IKKβ inhibitor at a clinically relevant 2 h following the coronary occlusion and still accomplished a reduction in infarct size. Now, we can do that. The thrombolytic agent, alteplase, has been successfully administered, in large clinical series, to stroke victims in less than 3 h from onset of symptoms (4).

Moss et al. (9) have produced a hypothesis-driven, mechanically based, clinically relevant study. We can derive relevant conclusions based upon our data. Do we have an opportunity, or responsibility, to take the next step from cells to humans to groups of people? In November 1947, the United Nations passed a resolution that formally partitioned the Middle East and established the birthday of Israel as a nation. National, like cellular, partition obligates destructive inflammatory and apoptotic programs. This pattern is characterized during myocardial infarction and was certainly replicated in Israel. The trajectory has proven unavoidable in India in 1948 and in Bosnia in 1995. Now we are watching it evolve in Iraq. Can scientists identify, promote, and target the administration of a geopolitical IKKβ?

REFERENCES

9. Moss NC, Stansfield WE, Willis MS, Tang R, Selzman CH. IKKβ inhibition attenuates myocardial injury and dysfunction following acute...