Role of Adenosine in Response to Vascular Inflammation
Joel Linden

The first known function of adenosine was as a central factor in the biochemistry of energy production. Perhaps as a result of that role, it also evolved as a signaling molecule that links metabolic stress and tissue damage to the activation of 4 G protein coupled adenosine receptors. An early appreciation of the physiology of adenosine preceded by many decades the discovery of the cell biology of adenosine signaling. The first recognized physiological activity of adenosine was “disturbance of the heart beat” initially described in a remarkably elegant study for the year 1929, conducted at the University of Cambridge by Drury and Szent-Györgyi. This preceded by 34 years the realization, articulated by Robert Berne, that adenosine is responsible for the “metabolic regulation of coronary blood flow.”

Once adenosine receptors were identified in the 1980’s and 1990’s and selective agonists and antagonists became available, rapid progress was made in pinpointing the identity and function of adenosine receptor subtypes on cardiac and vascular tissues. During that time it was also realized that 1 or more adenosine receptors are found on all cell types and their functions are numerous. In recent years the field of adenosine signaling has moved beyond questions of direct cardiovascular effects of adenosine and focused on more complex questions: What are the roles of adenosine in embryonic development and in responses to chronic inflammatory diseases that are often associated with the accumulation of very high tissue levels? The series of reviews in this volume focus on newly appreciated roles of adenosine in embryonic development and vascular pathophysiology. It is notable also that the expression of adenosine receptors on various tissues, and the expression of enzymes that are involved in adenosine production, such as CD73, are not constant, as once thought, but are now known to be highly transcriptionally regulated by certain cytokines, pathogens, and hypoxia. Thus, it is now appreciated that in chronic diseases, both the production of adenosine and the expression of adenosine receptors undergo major changes.

In their article about the control of erectile function, Wen and Xia compare and contrast the roles of the major vasodilators, nitric oxide and adenosine, in health and disease. The article serves to illustrate that either overproduction or underproduction of adenosine can produce pathology. The review also serves as a reminder that adenosine remains a key physiological regulator of blood flow, irrespective of the attention focused on nitric oxide as another vasodilator signaling molecule. Adenosine production normally serves to protect stressed tissues from injury, but adenosine overproduction can contribute to pathology as occurs in priapism. Another newly appreciated important effect of adenosine is on embryonic development. Rivkees and Wendler summarize recent findings demonstrating that disruption of adenosine signaling in embryos, particularly during hypoxia, produce changes in cardiac function that persist into adulthood. Interestingly, they also identify caffeine, a widely consumed adenosine receptor antagonist, as possibly dangerous to the fetus. This emphasizes the point that adenosine produced during tissue stress plays a critically important role in engaging processes to protect cells from injury.

Activation of the immune system, eg, in response to infection, results in a complex interaction between leukocytes and the vasculature involving leukocyte rolling, adhesion, and extravasation. This process is often accompanied by high local concentrations of adenosine produced as a result of tissue inflammation and injury, or in some cases vasocclusion. The reviews by Barletta et al and Haskó and Pacher summarize recent discoveries about how adenosine influences the trafficking and function of neutrophils and monocytes/macrophages, respectively. Adenosine regulates leukocyte adhesion to the endothelium by direct effects on
leukocytes to inhibit adhesion, by influencing the expression of adhesion molecules on endothelial cells, and by regulating the release from many cell types of cytokines that indirectly influence adhesive processes. Not only the function but also the development of macrophage subtypes (M1, M2, etc.) is strongly influenced by adenosine. In addition, adenosine is also a major mediator of angiogenesis. The adenosine that accumulates in hypoxic tissues directly stimulates endothelial cells. Furthermore, adenosine-receptor mediated effects enhance the release of angiogenic factors from macrophages. The macrophage has also come under increased scrutiny as a source of foam cells and cytokines that participate in atherosclerosis. The article by Reiss and Cronstein discusses the recently discovered consequences of adenosine signaling to regulate macrophage cholesterol transport.

In sum, this group of reviews reflects the evolution of our thinking. Early on, adenosine was viewed as a “metabolic regulator” of cardiovascular functions, as articulated by Berne. We now appreciate that adenosine and other purinergic signaling molecules are constantly released and metabolized in the extracellular space and serve to continually relate local tissue metabolism and inflammation to signaling via an array of receptors that control not only blood flow, but tissue excitability, angiogenesis, metabolism, and immune cell functions.

References

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