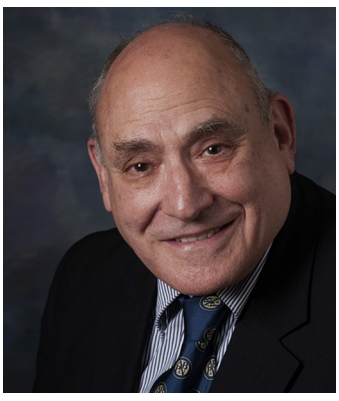
Editor-in-Chief's Note

"Inflamma" and Other "Somes"



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For this month's Update, Professor Peter L. Thompson, our Topic Editor for Cardiology and Cardiovascular Diseases, has assembled articles that focus on the use of colchicine in various cardiovascular diseases.[1–5] To understand why colchicine has value in these disorders, it is essential to appreciate that the NLRP3 inflammasome contributes to the inflammatory processes underlying atherosclerosis, and it is essential to understand the many effects of colchicine, including its effects on the NLRP3 inflammasome.

For this month's Note, my focus is on various cellular elements, which I have nicknamed "somes." The following paragraphs briefly summarize, compare, and contrast selected properties of certain "somes," including the inflammasome. I do so because I assume that, like me, not all of our readers are well versed in cell biology. I also assume that the persons who originally named these "somes" were anglicizing the Greek word *soma* (σῶμα), which means body. Most, but not all, "somes" are vesicular structures; as discussed later, some are multimeric protein complexes.

EXOSOMES AND ECTOSOMES

In 2014, I penned a Note about cell-to-cell communication and suggested an analogy between bacterial plasmids and human exosomes.[6] Plasmids carry resistance information from one bacterium to another; exosomes carry information between human (eukaryotic) cells. Exosomes are small (50–100 nm in diameter), vesicular structures that are bounded by a lipid bilayer and released from the plasma membrane. Some carry mRNAs and microRNAs; others are involved in cellular immunity.[7] Exosomes play a role in the immune system's response to cancers and pathogens. They were identified and characterized in the mid-1980s.[8] I now realize that my analogy was at best limited. Plasmids are not vesicles; they are small, circular DNA molecules transmitted by conjugation through the pili of bacteria.

I initially thought that exosomes were the same as ectosomes, vesicles that result from the outward budding of the plasma membrane which then move into extracellular space. Although they do share some similarities, they really are not the same. A thoughtful article by Cocucci and Meldolesi[9] spells out the relevant distinctions. Exosomes start from inward budding of the endosomal membrane before they are released by exocytosis; ectosomes result from outward budding and fission of the plasma membrane.[10] Ectosomes are also larger (100–500 nm in diameter) and more rapidly released than exosomes. These 2 extracellular vesicles are an important component of cell-to-cell communication. Recent studies have explored the potential clinical applications of exosomes, particularly as biomarkers, immunomodulators, and drug delivery vehicles.[11]

MICROSOMES

My colleague, Dr. David Greenblatt, introduced me to hepatic microsomes when we began our studies of drug metabolism ~25 years ago.[12–14] In contrast to extracellular vesicles, microsomes are totally artificial. They are reformed, vesicle-like structures created by homogenization and differential centrifugation of eukaryotic hepatic cells. Derived from the endoplasmic reticulum, they contain cytochrome P450 isoforms as well as flavin-containing

monooxygenases, epoxide hydrolases, and other metabolic enzymes. Microsomes vary in size from 20 to 200 nm in diameter.[15]

LIPOSOMES

Another artificial "some" is the liposome. These manufactured vesicles have at least one lipid bilayer and can be created from cholesterol and nontoxic phospholipids after sonication in an aqueous medium. Other liposomes are made from fatty compounds such as hydrogenated soy phosphatidylcholine and distearoyl phosphatidylglycerol plus cholesterol. Liposomes are hydrophobic and can range from relatively small to larger vesicles (20−400 nm to >1 μm in diameter). They are a useful transport system for certain drugs (eg, the positively charged antifungal, amphotericin B).[16]

PEROXISOMES

The peroxisome is another vesicular "some" that is important for cellular health. Peroxisomes are intracellular compartments that are believed to arise from the endoplasmic reticulum. They contain catalase and other enzymes that are important in fatty acid metabolism and for the conversion of reactive oxygen species into less harmful molecules. Peroxisomes are also involved in the detoxification of alcohol and play a role in the synthesis of other critical substances such as cholesterol and myelin. These vesicles vary in size from 100 nm to 1.5 μm.[17] A peroxisomal defect is responsible for the very rare disease adrenoleukodystrophy, which was the subject of the 1992 movie *Lorenzo's Oil*.[18]

LYSOSOMES

Lysosomes are similar in certain respects to peroxisomes. Lysosomes are intracellular vesicles of ~500 nm in diameter that contain acid hydrolases. Malfunctioning intracellular components or unwanted material such as complex carbohydrates, amino acids, and phospholipids are then degraded within the lysosome; some of the latter may have penetrated the cell through endocytosis. Although their degrative functions have long been recognized, a critical role of lysosomes in cellular metabolism and signaling has emerged over the last decade.[19] Lysosomes are synthesized by the Golgi apparatus. The Golgi apparatus itself is a system of folded membrane vesicles that is adjacent to the plasma membrane, which is the source of the degrading enzymes in Golgi-generated lysosomes.[20] Lysosomes are involved in both programmed cell death and autophagy.

PROTEASOMES

Proteasomes differ from all of these aforementioned "somes," although they work in concert with other naturally occurring "somes" to promote cell survival and maintain health through innate and adaptive immunity. They do not have a vesicular membrane. The proteasome is a large cylindrical protein complex that converts other proteins into peptides and enables the destruction and removal of maladaptive cells such as cancer or infected cells. Because it helps the cell to eliminate harmful fragments or components, it is similar in its function to the lysosome. Damaged or unwanted cellular materials become conjugated with cytosolic ubiquitin and are then picked up by proteasomes and destroyed.[21]

INFLAMMASOMES

Like the proteasome, the inflammasome is a complex or platform of oligomeric proteins; it is also not a vesicle.[22,23] It was discovered in murine monocytes and named by Tschopp and colleagues in 2002.[24] Since then, various inflammasomes have been shown in other cell types, including macrophages, neutrophils, endothelial and epithelial cells, microglial cells, and neurons. Through the actions of caspase 1, the inflammasome causes the maturation of interleukin-1beta, which is a major proinflammatory cytokine along with interleukin-6 and tumor necrosis factor alpha. In addition to promoting inflammation through these cytokines, inflammasomes contribute to cell repair and the removal of damaged cells. Triggers for the inflammasome are varied. Activation occurs after exposure to bacteria and viruses as well as intracellular pathogens. Of interest for this month's Update is that various crystals and fibers are also potent promoters of inflammation via the inflammasome. These include alum, asbestos, cholesterol,

silicates, and urates. It is via the actions of colchicine on the NLRP3 inflammasome subtype that urate-induced gout is ameliorated. The actions of colchicine on the NLRP3 inflammasome are hypothesized to explain some of its potential beneficial role in atherosclerosis; however, its actions on endothelial cell and neutrophil function are also likely to be relevant.

A TWO-PRONGED APPROACH TO ATHEROSCLEROSIS?

A report in a recent issue of the *New England Journal of Medicine* suggests that alirocumab, a humanized monoclonal antibody against PCSK9, reduces the likelihood of further adverse cardiovascular events in patients with preexisting coronary artery disease who did not fully benefit from statins.[25] PCSK9 is a protein that governs the amount of LDL receptors. This finding raises the question of whether combined treatment with a PCSK9 inhibitor and colchicine could have merit.

Happy New Year to all! May we all wish for a reduction in the rhetoric and fighting that continue to inflame tensions around the world. With that our world could become a "non-inflammazone."

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This month's Cardiology and Cardiovascular Diseases Update is a special feature which is available as FREE ACCESS content on the journal's website. One of the previous Cardiology and Cardiovascular Diseases Updates, entitled "**Hypertension**," was published in Volume 38, Issue 10 of Clinical Therapeutics. To view the previous Update, see the articles below:

Thompson PL. Modern Challenges in Treating Hypertension.

Atkins ER, Rodgers A. More Versus Less Blood Pressure Lowering: An Update.

O'Brien E, Dolan E. Ambulatory Blood Pressure Monitoring for the Effective Management of Antihypertensive Drug Treatment.

Hering D, Schultz C, Schlaich MP. Device Therapies for Resistant Hypertension.

Kim K, Shin M-S, Ihm S-H, Youn H-J, Sung K-C, et al. A Randomized, Double-blind, Multicenter, Phase III Study to Evaluate the Efficacy and Safety of Fimasartan/Amlodipine Combined Therapy Versus Fimasartan Monotherapy in Patients With Essential Hypertension Unresponsive to Fimasartan Monotherapy.

Kim S-H, Jo S-H, Lee S-C, Lee S-Y, Yoon M-H, et al. Blood Pressure and Cholesterol-lowering Efficacy of a Fixed-dose Combination With Irbesartan and Atorvastatin in Patients With Hypertension and Hypercholesterolemia: A Randomized, Double-blind, Factorial, Multicenter Phase III Study.

Park CG, Ahn TH, Cho EJ, Kim W, Kim HS, et al. Comparison of the Efficacy and Safety of Fixed-dose S-Amlodipine/Telmisartan and Telmisartan in Hypertensive Patients Inadequately Controlled with Telmisartan: A Randomized, Double-blind, Multicenter Study.

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