

CANTOS Ushers in a New Calculus of Inflammasome Targeting for Vascular Protection—and Maybe More

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Despite overwhelming basic science linking inflammation to the pathobiology of atherothrombosis, the specific clinical evidence indicating cardiovascular benefits from anti-inflammatory pharmacotherapy has been lacking. The CANTOS trial (Ridker et al., 2017a) now provides the first largescale proof of concept that inflammasome targeting can reduce cardiovascular events—and, surprisingly, lung cancer.

Over three decades of intense basic and translational biology have uncovered a critical role of inflammation in the initiation, propagation, and natural history of atherosclerosis and its key complications, namely myocardial infarction and stroke (Libby and Hansson, 2015). What was initially thought to be simply “rust within the pipes” and an inevitable consequence of aging is now considered to be a highly complex interplay of the innate and adaptive immune system. One of the earliest insights into the role of the cellular inflammatory response in atherosclerosis was introduced by Professor Hansson in 1985 (Jonasson et al., 1985). In this seminal paper, atherosclerotic plaques were found to have abundant expression of the inflammatory marker HLA-DR, suggesting that an immune-inflammatory mechanism was present in advanced vascular disease. Since then, the thesis has moved from being purely observational and associative to elegant experiments in animals and humans linking increased/aberrant inflammation as a causal and potentially primordial risk factor in atherosclerosis (Verma et al., 2002).

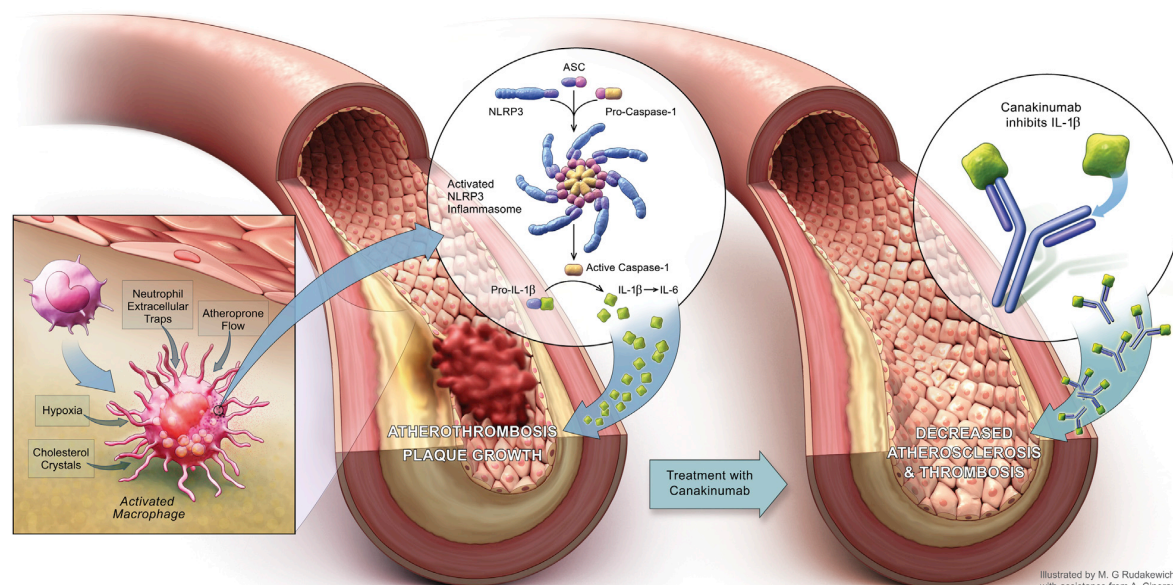
The inflammation hypothesis of atherosclerosis was fueled by several well-designed studies linking levels of high-sensitivity C-reactive protein (hs-CRP) to vascular risk in both primary and secondary prevention cohorts (Ridker, 2016). Largescale studies and meta-analyses subsequently emerged showing that measures of hs-CRP offered prognostic information for future cardiovascular events, with a magnitude that was at least as large as other conventional risk factors such as

dyslipidemia and hypertension (Emerging Risk Factors Collaboration et al., 2010). As the field evolved, it became clearer that inflammation played an independent role and added prognostic information beyond traditional risk factors and risk calculators for cardiovascular events.

One of the most intriguing twists in this story was the realization that there was a poor correlation between measures of cholesterol and inflammation. Said differently, hs-CRP levels, and hence inflammation-mediated vascular risk, seemed to be unrelated to the level of cholesterol (Ridker, 2016). This was important, since it would be of little value to measure inflammation if it provided information and prognostication that were similar to elevated cholesterol. The fact that many myocardial infarctions occurred in patients with so-called low cholesterol, but high inflammation, led to speculation that this population of patients might be candidates for further anti-inflammatory targeting beyond lowering cholesterol. This question was addressed indirectly in the JUPITER trial—a study in which 17,802 patients with low cholesterol but high hs-CRP received 20 mg rosuvastatin per day (Ridker et al., 2008). These patients had no indication for statin therapy based on their cholesterol levels but were recruited based on higher levels of inflammation. Importantly, there was a profound reduction in major adverse cardiovascular events in the trial. As statins lower both hs-CRP and LDL-C, the central question of whether or not inflammation reduction or cholesterol reduction drove these benefits remained unanswered. The only way to

test the hypothesis would be to use an agent that targets inflammation without affecting cholesterol levels. And that was CANTOS (Ridker et al., 2017a).

The CANTOS trial recruited 10,061 patients who had a previous myocardial infarction and were treated with optimal medical and lipid-lowering therapy, and randomized them to receive canakinumab, a fully human IL-1 β antibody, or placebo (Ridker et al., 2017a). Patients were eligible for the study if they had persistently elevated hs-CRP levels. Forty percent of the patients in the study also had diabetes. Canakinumab is commercially available and is a high-affinity human monoclonal anti-human IL-1 β antibody currently indicated for the treatment of some uncommon IL-1 β -driven inflammatory diseases (cryopyrin-associated periodic syndrome, Muckle-Wells syndrome, etc.). It is designed to bind to human IL-1 β and functionally neutralize the bioactivity of this pro-inflammatory cytokine. It has a long half-life (4–8 weeks) with CRP and IL-6 reduction noted for 3–6 months following a single dose administration. IL-1 β is the main product of the macrophage NLRP3 inflammasome, a key receptor of the innate immune system (Próchnicki and Latz, 2017), which is believed to be one of the key transducers through which risk factors (including cholesterol crystals) are linked to atherogenesis (Figure 1). Strikingly, canakinumab (at the 150 mg dose administered every 3 months) was associated with a significant 15% reduction in major adverse cardiovascular events. Notably, this occurred in the absence of any change in LDL-C levels and was



Illustrated by M. G. Rudakewich
with assistance from A. Cineranti

Figure 1. Canakinumab Acts via the NLRP3 Inflammasome to Reduce Inflammation and Cardiovascular Risk

The macrophage NLRP3 inflammasome can be stimulated by various stressors, including cholesterol crystals, which results in the eventual conversion of pro-IL-1 β into IL-1 β , a quintessential and upstream cytokine involved in vascular inflammation and atherothrombosis. Canakinumab is a human IL-1 β antibody that was used in CANTOS. It binds to IL-1 β , leading to a significant reduction in IL-6 and hs-CRP and attenuated atherothrombotic cardiovascular risk. ASC, apoptosis-associated speck-like protein containing a CARD; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; NLRP3, nucleotide-binding domain (NOD)-like receptor protein 3.

observed in addition to other relatively optimal evidence-based cardiovascular risk reduction therapies. Secondary analyses revealed that the benefits were driven through further reductions in recurrent myocardial infarction and a marked decrease in the need for coronary revascularization procedures (such as angioplasty or bypass surgery).

As with most advances, CANTOS answers a key question, but raises many more. Inflammation targeting in the trial caused a small, but statistically significant, increase in the rate of fatal sepsis. This finding, while not unexpected, will require careful monitoring of any potential patients treated with the medication. Although cardiovascular mortality was not reduced, there was a profound 60% reduction in cancer-related mortality related to lung cancer (Ridker et al., 2017b). Even though this was a hypothesis-generating outcome of the study, it validates the basic biology also linking interleukins to the tumor microenvironment, tumor progression, and metastases (Dinarello, 2010). A large number of patients in the study were either past or current smokers and likely had a higher predispo-

sition to having pre-cancerous lesions, the progression of which into overt cancers was possibly arrested by canakinumab. However, prospective validation of this construct will be required.

The calculus of secondary prevention of atherosclerosis is now complex, and a new era of personalized medicine will be required. Targeting ischemic residual risk will require a fundamental understanding of what processes are the dominant drivers of residual risk. While residual risk and recurrent events are likely multifactorial, a personalized approach to prioritizing therapies based on biology, biomarkers, clinical outcomes, and value/economics will need to be developed. A post-myocardial infarction patient treated with lipid-lowering therapies to lower LDL-C levels, but who has evidence of high hs-CRP, may benefit to a greater extent by inflammation reduction than further cholesterol reduction. Likewise, a patient with low hs-CRP levels with persistently high LDL-C would have a high residual lipid risk that would need to be prioritized. The personalization of therapies will be complex since other therapies (such as SGLT2 inhibitors in patients with diabetes and very low

dose novel oral anticoagulants in patients with stable atherosclerosis) have also been recently demonstrated to reduce mortality in high-risk patients through inflammation- and lipid-independent pathways. Integrating and prioritizing these approaches will therefore require a thoughtful and individualized approach.

For basic and translational scientists in the field, CANTOS represents the “aha! moment”—a vindication and affirmation that inflammation not only drives atherosclerosis, but is also now a validated target for clinical benefit. The ongoing NHLBI-sponsored CIRT study will be a very important next step in this field, since, if positive, the anti-inflammatory agent used, low-dose methotrexate, will likely be more economical than monoclonal antibodies and is an agent for which we have long-term safety data.

In conclusion, CANTOS is a seminal clinical trial that provides convincing evidence that innate immunity can be manipulated to attenuate cardiovascular risk, and hence, targeting inflammation, independent of cholesterol lowering, is a potentially new approach to risk reduction in certain patient populations. CANTOS

will also most definitely stimulate the field of inflammation research in both cardiovascular disease and cancer, as we continue to refine therapeutics in this area that are efficacious, safe, and cost-effective.

CONFLICTS OF INTEREST

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of Cardiology (Senior Associate Editor, Clinical Trials and News, <http://www.acc.org/>), Belvoir Publications (Editor-in-Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor-in-Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), and WebMD (CME steering committees); Other, Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), and VA CART Research and Publications Committee (Chair); Research Funding, Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi Aventis, and The Medicines Company; Royalties, Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator, Biotronik, Boston Scientific, and St. Jude Medical (now Abbott); Trustee, American College of Cardiology; Unfunded Research, FlowCo, Merck, PLX Pharma, and Takeda.

REFERENCES

Dinarello, C.A. (2010). *Cancer Metastasis Rev.* 29, 317–329.

Emerging Risk Factors Collaboration, Kaptoge, S., Di Angelantonio, E., Lowe, G., Pepys, M.B., Thompson, S.G., Collins, R., and Danesh, J. (2010). *Lancet* 375, 132–140.

Jonasson, L., Holm, J., Skalli, O., Gabbiani, G., and Hansson, G.K. (1985). *J. Clin. Invest.* 76, 125–131.

Libby, P., and Hansson, G.K. (2015). *Circ. Res.* 116, 307–311.

Próchnicki, T., and Latz, E. (2017). *Cell Metab.* 26, 71–93.

Ridker, P.M. (2016). *Circ. Res.* 118, 145–156.

Ridker, P.M., Danielson, E., Fonseca, F.A., Genest, J., Gotto, A.M., Jr., Kastelein, J.J., Koenig, W., Libby, P., Lorenzatti, A.J., MacFadyen, J.G., et al.; JUPITER Study Group (2008). *N. Engl. J. Med.* 359, 2195–2207.

Ridker, P.M., Everett, B.M., Thuren, T., MacFadyen, J.G., Chang, W.H., Ballantyne, C., Fonseca, F., Nicolau, J., Koenig, W., Anker, S.D., et al.; CANTOS Trial Group (2017a). *N. Engl. J. Med.* 377, 1119–1131.

Ridker, P.M., MacFadyen, J.G., Thuren, T., Everett, B.M., Libby, P., and Glynn, R.J.; CANTOS Trial Group (2017b). *Lancet*. Published online August 27, 2017. [http://dx.doi.org/10.1016/S0140-6736\(17\)32247-X](http://dx.doi.org/10.1016/S0140-6736(17)32247-X).

Verma, S., Wang, C.H., Li, S.H., Dumont, A.S., Fedak, P.W., Badiwala, M.V., Dhillon, B., Weisel, R.D., Li, R.K., Mickle, D.A., and Stewart, D.J. (2002). *Circulation* 106, 913–919.

Resistance Is Futile: Targeting Mitochondrial Energetics and Metabolism to Overcome Drug Resistance in Cancer Treatment

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Metabolism is a key regulator of cancer biology; however, its role in therapeutic resistance has remained largely unresolved. Several new studies disclose that mitochondrial metabolism and oxidative phosphorylation at least in part drive chemoresistance in cancer and thus have important implications for targeted and more effective chemotherapies.

Despite a complete remission following intensive treatment with chemotherapeutic agents, prognosis is very poor for several types of cancer, including acute

myeloid leukemia (AML), due to frequent relapses caused by chemotherapy-resistant cancer clones. Many hypotheses have been proposed to explain therapeutic

resistance: drug efflux, detoxification enzymes, poor accessibility of the drug to the microenvironment and local niche, supportive effects of stromal cells and



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