ISM Science Corner - Opinion Piece

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Why is February Heart Month?

By now many Canadians know that February is heart month, thanks to annual canvassing of the Heart and Stroke Foundation of Canada. February, it turns out, is the peak month for heart attacks, but did you ever wonder why? If you subscribe to the notion that high cholesterol is the main or major risk factor for heart attacks, then you would be surprised to know that seasonal differences in cholesterol levels amounts to 2 to 3 %, not enough to significantly affect risk. Then what risk factor for heart attacks is seasonal and peaks in February?

A link between heart attacks and flu season

Foster ED *et al*, published a study in 2013 which partially addresses this issue.[1] By analyzing USA hospital discharge data using international disease codes, they found a correlation of peak heart attacks (acute myocardial infarctions) with peak flu season, but only in individuals over the age of 65. Moreover, this correlation strengthened with advancing age consistent with the notion that immunosuppression was the main problem, but also relating to activation of an antiviral (flu) response. To rule out simply a seasonal co-incidental finding such as weather or February blahs, they showed that in 2009 when there were two peak flu seasons, the regular one in February and then the swine H1N1 flu in fall of 2009, there was also a correlation with a second heart attack peak. But what does this mean physiologically that heart attacks relate to a problem with immunosuppression of an antiviral response and how does this relate to atherosclerosis (blockages in arteries)?

A central role of foamy macrophages in atherosclerosis

Well, we do know that foamy macrophages are involved in atherosclerosis and some believe that they actually initiate atherosclerosis. Aside from pathologists seeing these foamy cells in sections of atherosclerosis,[2] no one really knows much about them. They are not seen when white cells isolated from blood are cultured in the test tube. It is commonly believed that the foam represents droplets of lipid and cholesterol taken up by activated monocytes which then become foamy macrophages.[3] While studies in mice or in human leprosy exudates appear to involve these lipid droplets, attempts to induce foamy macrophages in culture by activating

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[1] Foster ED, *et al*. Acute myocardial infarctions, strokes and influenza: seasonal and pandemic effects. *Epidemiology and Infection 2013*, **141**:735-744.
[2] Falk E, *et al*. Update on acute coronary syndromes: the pathologist's view. *European Heart Journal 2013*, **34**:719-728.
[3] Crowe SM, *et al*. The macrophage: the intersection between HIV infection and atherosclerosis. *Journal of Leukocyte Biology 2010*; **87**:589-598.

human monocytes in the presence of different amounts of cholesterol failed to induce foamy macrophages.[4, 5] So, what would be a common cause of foamy macrophages in humans?

Induction of an endogenous foamy virus (HERV-K102) appears to induce foamy macrophages in humans

Luckily and just by chance, we stumbled upon a method to induce foamy macrophages while I was Research Manager of the Blood Zoonotics Unit, in the Blood-borne Pathogens Division at the Public Health Agency of Canada. We had started to use human cord blood (CB) as an indicator cell to study viruses potentially transferred from pig spleen cells, when we immediately noticed that we had induction of foamy macrophages. This occurred when CB was cultured in IMDM media **(Figure 1)**, but *not* when the cells were cultured in traditional RPMI media (data not shown). Others have also reported the induction of $CD14^{++}CD16^{+}$ foamy macrophages from CB in IMDM media following stimulated stem cells.[6] We knew it involved a foamy retrovirus as high numbers of 100 nm immature particles with envelope spikes were budding into vacuoles **(Figure 2)**, but not through the cell surface membrane. We also knew the virus came from inside the cells because foamy macrophages accumulated regardless of the source of serum used. For example, foamy macrophage induction occurred when serum from the same CB donor as the cells (autologous serum) or when an AB serum (screened to be negative for infectious diseases), was employed for the culture **(Figure 1).** Accordingly, we pursued the identity of the foamy virus-like endogenous retrovirus as detailed in **Figure 2**, and identified it as human endogenous retrovirus K102 (HERV-K102)

[see additional data in "Potential Role of Human Endogenous Retrovirus K102 (HERV-K102) Particles in Resistance to HIV-1 Transmission" (PDF download)]

By the time of this discovery, HERV-K102 activity (RNA as well as antibody) was already described in the literature in breast cancer. However, we were first to show in our 2007 paper: HERV-K102 could be induced in culture; it had essential features of non-pathogenic foamy retroviruses (see a complete tabular list on our website); particles were made but were only found to be budding into vacuoles **(Figure 2C)**, and this was associated with the creation of foamy macrophages.[7] As well in the same article, we showed direct evidence that particles were made during active disease in a chronic fatigue syndrome patient, an acute Epstein Barr Virus patient with lymphoma and a patient newly diagnosed patient with multiple sclerosis, but particles were no longer made when these same patients went into remission. Given that particles were also found in 2 of 4 normal CB samples, but not in 30 of 30 normal adults, this led us to suggest HERV-K102 particle production was likely part of the innate immune response (newborns do not have adaptive immunity developed yet). Thus we suggested HERV-K102 activation might defend the host against viruses, tumors and may also be associated with autoimmune diseases.

So, how then does HERV-K102 particle production relate to the flu?

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[4] Hughes DA, Townsend PJ, and Haslam PL. Enhancement of the antigen-presenting function of monocytes by cholesterol: possible relevance to inflammatory mechanisms in extrinsic allergic alveolitis and atherosclerosis. *Clinical and Experimental Immunology* 1992; **87**: 279-286.

[5] However blood CD14++CD16+ monocytes (Mon 2) do upregulate CD11c in response to triglyceride-rich lipoproteins *in vivo*, and levels correlate with parameters involved in myocardial infarction. Foster GA *et al*. On-chip phenotypic analysis of inflammatory monocytes in atherogenesis and myocardial infarction. *PNAS 2013*; **110**: 13944-13949.

[6] Stec M *et al*. Expansion and differentiation of $CD14+CD16^{-}$ and CD14++CD16+ human monocytes subsets from cord blood CD34+ hematopoietic progenitors. *J Leuko Biol 2007*; **82**:594-602.

[7] Laderoute MP, *et al*. The replicative activity of human endogenous retrovirus K102 (HERV-K102) with HIV viremia. *AIDS 2007*; **21**:2417-2424.

HERV-K102 particle production is a common host response to viral infections

Spurred on by the semi-quantitative findings discussed above that HERV-K particles were found in disease states, we went on to develop a real time PCR ddCt method to quantitate the amount of HERV-K102 particles made and tested normals versus patients with viral infections. In our 2007 paper using these new methods, we showed exogenous viruses commonly induce HERV-K102 particle production where plasma levels of about 10^{12} particles per ml of plasma were frequently observed.[7] We actually clocked the induction of HERV-K102 particles from zero particles per ml of plasma to 10^{11} by 84 hours in the chronic fatigue syndrome patient. So HERV-K102 particle production was robust and fast and more than likely would be strongly induced by flu and other respiratory viral infections. It is also expected to be induced by intracellular bacteria such as *Chlamydia pneumoniae* where foamy macrophages appear to contribute to atherosclerosis.[8]

Amino acid requirements for HERV-K102 particle production

Endogenous retroviruses make up about 8% of the human genome. They are commonly named according to the transfer RNA used to initiate reverse transcription. The K in HERV-**K** refers to the use of the transfer RNA involving **lysine** (**K**). Foamy virus particles reverse transcribe upon release of the particles from cells and would contain about 100 lysine (K) molecules per particle. If there are commonly 10^{12} particles per ml of plasma in response to active viral infection,[7] and roughly 3000 mls of plasma in an adult, it is not difficult to imagine how quickly the body can go into lysine (K) deficiency upon initial induction. Perhaps this is why lysine, which is an amino acid and has no direct antiviral activity, is commonly sold as an antiviral to help speed up recovery such as for herpes virus infections. Accordingly, lysine and other amino acid supplementation may be useful to support ongoing HERV-K102 particle production, a point well established and utilized in the 20,000 patient-years of follow-up at Immune System Management Clinic and Lab (ISM).

Levels of HERV-K102 particles in plasma in response to viremia are diminished with immunosuppression

In the test tube, we found the first major round of release of HERV-K102 particles occurred at 7 days when about 30% of the cells lysed (**Figure 2D**). Recall that HERV-K102 does not bud through the cell surface membrane, but into the vacuoles which then requires lysis of the cell for particle release **(Figure 2)**. Immunosuppressive molecules such as alpha-fetoprotein (AFP)[9] may not only immunosuppress the immune system, but because it also induces resistance to cell lysis in cells expressing the 67 kD AFP receptor such as activated macrophages,[9] it can stop the lysis of foamy macrophages and block the release of HERV-K102 particles. Thus, when the individual is immunosuppressed and when there also an active viral infection, foamy macrophages can abnormally accumulate in the circulation. While AFP is not known to undergo an increase with advancing age per se, a molecule dehydroepiandrosterone (DHEA) which has been shown to specifically bind and inactivate AFP,[10] diminishes with age. This loss in DHEA could help explain increased immunosuppression and chronic inflammatory diseases[11] and thus cardiovascular risks,[12] with advancing age. In Canada, and unlike the USA,

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[8] Choroszy-Krol I, *et al*. Infections caused by Chlamydophila pneumonia. *Adv Clin Exp Med 2014*; **23**:123-126.

[9] Laderoute MP. Modernized version of Todaro and De Larco's 1978 hypothesis on the autocrine nature of tumor growth. *J. Natl. Cancer Inst. 1996*; **88**:1239-1240.

[10] Laderoute, MP. DHEA but not DHEA-S may bind and inactivate active alpha-fetoprotein (AFP) and prevent AFP mediated apoptosis resistance conferred upon binding to the 67 kD AFP receptor. *Unpublished data 1990*. Table available at www.aminomics.com.

[11] Heffner KL. Neuroendocrine effects of stress on immunity in the elderly, implications for inflammatory disease. *Immunol Allergy Clin North Am 2011*; **31**:95-108.

[12] Savineau JP *et al*. Role of DHEA in cardiovascular diseases. *Biochem Pharmacol 2013*; **85**:718-726.

DHEA (brand name Prasterone) is not considered a natural health product and it is listed in Schedule IV of the Controlled Drugs and Substances Act.[13] Delisting DHEA (or 7-keto-DHEA which cannot be converted to other sex hormones) from Schedule IV and making it available as a natural health product for the prevention and/or treatment of chronic diseases might be considered a priority for cardiovascular disease prevention in Canada.

The genome of HERV-K102 which is a type 1 member of the transcriptionally and biologically active HERV-K HML-2 group, contains glucocorticosteroid response elements (GREs)[14] suggesting it is induced by cortisone related to stress. Alpha-fetoprotein also contains GREs, and is induced by hydrocortisone[15] suggesting it too may be induced by stress. Moreover, according to EST profiling for AFP (Hs.518808), AFP mRNA is highly expressed in heart tissue (see ncbi.nim.nih.gov). Therefore high and prolonged stress could lead to a situation whereby HERV-K102 particle production is induced but AFP could block release of the particles. This situation represents a condition which would strongly favor atherosclerosis by promoting the accumulation of foamy macrophages and would be more problematic in adults with lower DHEA levels. Skeptics of the cholesterol hypothesis for induction of atherosclerosis believe stress may be far more important to atherosclerosis and heart attack risk than high cholesterol.[16] Thus, the blocked release of HERV-K102 particles such as by AFP in foamy macrophages is a plausible paradigm to explain heart attack risk related to stress or, high blood pressure as found with corticosteroid use.[17] In this regard, DHEA is considered an anti-stress hormone[11] and in theory should be doubly beneficial to thwart atherosclerosis.

But what is the evidence that induction but blocked release of HERV-K102 particles might be associated with atherosclerosis?

Blocked HERV-K102 particle release is associated with atherosclerosis in HIV-1 patients

We found evidence of a universal induction of HERV-K102 in patients with HIV-1.[7] About 70-80% of HIV-1 patients were found to have antibodies to HERV-K102 envelope peptides (recall the envelope spikes on the particles seen in **Figure 2C**). About 76% of HIV-1 patients had particle associated cDNA detected in plasma by our quantitative PCR method for HERV-K102 *pol* DNA. In total, where patients were tested by both serology (antibody based methods) and PCR methods, 96 % had evidence of HERV-K102 activation whereas in normals this occurred in only 2 to 3% (and where the reactions were only barely positive). While patients with other active viruses in their blood had maximal particle numbers around 10^{12} per ml of plasma, in HIV-1 patients the highest levels seen were 10^{5} per ml of plasma or *about 7 logs lower*. Thus, something was immunosuppressing the production and/or release of HERV-K102 particles, despite clear evidence for universal induction of HERV-K102 in 96% of HIV-1 patients.

Microarray analysis is a method by which the expression of about 50 thousand genes can be analyzed in a test cell type and compared with a control cell type. In a microarray analysis of monocytes from HIV patients, those with untreated high viral loads were found to have strong evidence of typical interferon alpha antiviral responses as expected when compared with normal monocytes from controls who were not infected with HIV. However surprisingly, the LPS response signature was completely absent in these monocytes from patients with high levels of HIV-1 viremia, despite more LPS in their blood.[18] LPS is a molecule found in gut bacteria and increases in the blood when there is “leaky gut syndrome” reflecting

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[13] http://webprod.hc-sc.gc.ca/nhpid-bdipsn/ingredReq.do?id=4639&lang=eng

[14] Ono M. Molecular cloning and long terminal repeat sequences of human endogenous retrovirus genes related to types A and B retrovirus genes. *J. Virol 1986*; **58**:937-944.

[15] Lui VVY, *et al*. Analysis of glucocorticoid receptors in human hepatocellular carcinoma and HepG2 cells. *Hepatology 1993*; 18:1167-1174.

[16] Sinatra ST, *et al.* The saturated fat, cholesterol, and statin controversy, a commentary. *J Am College Nutrition 2014*; **33**:79-88.

[17] 2014 Canadian Hypertension Education Program Recommendations, www.hypertension.ca

[18] Rempel H, *et al*. Interferon-α drives monocyte gene expression in chronic unsuppressed HIV-1 infection. *AIDS 2010*; **24**:1415-1423.

damage to the gut lining which occurs in HIV-1 infection. Since AFP is known to block the LPS response in dendritic cells (a cell type related to monocytes/macrophages),[19] this implies that AFP could be involved in mediating immunosuppression in HIV-1 patients associated with high viral loads and/or progression. Irrespective of whether AFP is incriminated or not, microarray analysis clearly showed a blockage of the LPS response in HIV-1 patients with high viremia suggesting interferon based inflammation occurred but with immunosuppression.

It turns out that patients with HIV-1 are at higher risk of atherosclerosis.[20] Since the antiretroviral drugs they take can cause metabolic health issues, it is preferable to examine atherosclerosis in HIV-1 patients who do not need to take the antiretroviral drugs such as the rare population of elite controllers. Elite controllers are HIV-1 infected patients who have non-detectable HIV-1 viral loads in their blood without antiretroviral therapy. Elite controllers by definition have had their HIV-1 infection for a long time (about a decade) and thus have been through many flu seasons. It was found that in 78 % of elite controllers, 60 % of HIV-1 patients on successful antiretroviral therapy and 42 % of HIV-negative patients in similar age groups (around the age of 47 to 57) had evidence of coronary plaques when measured by a very sensitive method (coronary CT angiography). [21] While elite controllers had significantly higher levels of sCD14 in their blood than the other two groups indicating higher inflammation,[22] interestingly, cholesterol levels did not differ amongst the three groups and remained normal as did triglycerides, HDL and LDL. While we would suspect but have not yet tested if elite controllers may have increased HERV-K102 particle levels in plasma over other HIV-1 patients, the finding of 78 % of elite controllers with atherosclerosis would be consistent with the finding of detectable particles generally in 76% of HIV-1 infected patients.[7] Certainly the cholesterol levels were not elevated in any of the groups ruling out a main or major role of cholesterol in atherosclerosis in humans. Along these lines, about 75 % of the people suffering a heart attack do not have elevated cholesterol, and 50% have optimal levels implying high levels of cholesterol are not a main contributing factor to heart attacks.[23]

Cholesterol reducing drugs do not lower heart attack risks, so what is the story on statins?

As discussed above, various lines of evidence point to a lack of biological plausibility that high cholesterol causes atherosclerosis. One, epidemiological evidence does not show significant seasonal increases resulting in higher cholesterol and thus, there is no correlation with peak, seasonal cardiovascular risks. Two, incubation of activated monocytes with cholesterol does not lead to foamy macrophages. Third, the majority of heart attacks occur in people without high cholesterol. Fourth, a common cause of foamy macrophages appears not to be high cholesterol but to be the induction of an endogenous foamy virus, HERV-K102 by viruses and other intracellular pathogens or tumors. HERV-K102 particle production and release is postulated to help clear the pathogen/tumor and is a protective response uniquely found in humans.

Foamy macrophages would have increased cholesterol and lipids due to the presence of extremely high numbers of particles and the high number of vacuoles which are composed of cholesterol and lipids. Accordingly, the cholesterol and lipid which makes up the central lipid or necrotic core of older plaques, then could result from lysis of foamy macrophages, as summarized by Lo and Plutzky.[24] However, what appears to be inaccurate in the biological

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[19] Yamamoto M, *et al*. α-fetoprotein impairs activation of natural killer cells by inhibiting the function of dendritic cells. *Clin Exp Immunol 2011*; **165**:211-219.
[20] Schrestha S *et al*. HIV, inflammation and calcium in atherosclerosis. *Arterioscler Thromb Vasc Biol 2014*; **34**:244-250.
[21] Pereyra F, *et al.* Increased coronary atherosclerosis and immune activation in HIV-1 elite controllers. *AIDS 2012*; **26**:2409-2412.
[22] Scherberich JE, NockherWA. CD14++ monocytes, CD14+/CD16+ subset and soluble CD14 as biological markers of inflammatory systemic diseases and monitoring immunosuppressive therapy. *Clin Chem Lab Med 1999*; **37**:209-213.
[23] http://dietheartpublishing.com/Cholesterol/10/09
[24] Lo J & Plutzky J. The biology of atherosclerosis: general mechanisms among HIV-infected patients. *J Infect Dis 2012*; **205 (Suppl 3)**: S368-S374.

mechanism proposed by Lo and Plutzky and others is that they state the conversion of activated monocyte to foamy macrophage occurs only once the activated monocyte transverses the endothelial cell layer lining the lumen of the vessel and into the intima. In this location in the intima layer (at least at the beginning), there is no direct access to cholesterol, i.e., the cholesterol is in the blood and is not in the intima layer. So a fifth reason for rejecting the biological plausibility of high cholesterol initiating atherosclerosis is that there is likely no access to cholesterol in the intima layer where the foamy macrophages are said to develop and initiate atherosclerosis.

Accordingly, it is not at all surprising that while high blood pressure medications do lower cardiovascular risks, cholesterol reducing drugs have been shown not to decrease heart attack risks, except paradoxically, statins.[25] This led authors of this review to suggest statins must have some other mechanism by which they block progression of plaques; an opinion shared by others.[16] Indeed accumulating evidence now strongly suggests statins are immunosuppressive. Statins are immunosuppressive both on adaptive immunity (the T and B cell responses),[26] as well as blocking the alpha-interferon antiviral response in monocytes.[27] It is strongly suspected that the induction of the endogenous, foamy virus HERV-K102 which generates foamy macrophages is part of the alpha-interferon, antiviral response in human monocytes, macrophages, and/or dendritic cells. So if statins block foamy macrophage induction, then this would be expected to block progression of plaques.

However, the problem with the use of statins is that the fast acting innate component of antiviral immunity in the host is blocked, along with other adaptive mechanisms. This early innate antiviral mechanism would include HERV-K102 particle production, but also other antiviral mechanisms induced through the alpha-interferon pathway. This could be problematic particularly for encounters with new viruses never seen before. For a short while, blocking plaque enlargement potentially could be beneficial especially right after a heart attack, but the problem is that the effects of continued immunosuppression are cumulative. That is to say the longer one is immunosuppressed, the more likely the person is going to get into trouble including latent viruses and other pathogens. When I was a reviewer of adverse events of marketed immunosuppressive drugs, it became very evident to me that by the second and third years on immunosuppressive drugs, rare conditions appeared like Bell's palsy, Guillain-Barre Syndrome and Progressive Multifocal Leukoencephalopathy (PML). PML involves reactivation of a common polyomavirus known as John Cunningham Virus (JCV) in the brain and is often fatal. What I thought was more striking was the finding that some immunosuppressive drugs appeared to double the myocardial infarction risks every 3 months (personal observations). While statins may not contribute to myocardial infarction risks because they block the alpha-interferon response, they would be expected to lower host immunological defense mechanisms against tumors, viruses and other pathogens. Therefore, at least in theory, statin use could potentially create more morbidity and mortality in the longer run. For example, there is emerging evidence that statins might increase the risk of new onset diabetes, in addition to increased risk of myotoxicity, increased liver enzymes, cataracts, mood disorders, dementias, hemorrhagic stroke and peripheral neuropathy.[16,28] Clearly these additional risks are not acceptable, especially in the adult who does not have high blood pressure to begin with, irrespective of whether or not they have high cholesterol. Furthermore, at ISM, we have found it difficult to achieve full immunological and biochemical rebalance in clients who take statins. It could be a co-incidence, but one client experienced cancer recurrence by 3 months on statin therapy after being a decade in remission.

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[25] Fuchs FD, *et al*. Proof of concept in cardiovascular risk: the paradoxical findings in blood pressure and lipid abnormalities. *Vascular Health and Risk Management 2012*; **8**:437-442.

[26] Jameel A, *et al*. Statin modulation of human T-cell proliferation, IL-1β and IL-17 production, and IFN-γ T cell expression: synergy with conventional immunosuppressive agents. *Int J Inflam 2013*; doi 10.1155/2013/434586.

[27] Wickert LE, *et al*. Simvastatin attenuates rhinovirus-induced interferon and CXCL10 secretion from monocytic cells in vitro. *J Leukoc Biol 2014* [Epub ahead of print].

[28] Bang CN and Okin PM. Statin treatment, new-onset diabetes, and other adverse effects: a systematic review. *Curr Cardiol Rep 2014*; **16**:461.

Cochrane reviews are a series of a meta-analysis (statistical summaries of many similar clinical trials) on a given topic and are highly regarded because of the lack of commercial interests or ties by the authors. An important Cochrane review was published in 2011 summarizing 14 clinical trials which questioned the use of statins to prevent heart attacks in people who did not have evidence of cardiovascular disease (highlights of an interview with the lead author in 2011 are provided in ref. 30).[29,30] A second Cochrane meta-analysis was also published in 2011 by a group of Canadian researchers on 18 randomized clinical trials involving persons hospitalized with acute coronary syndrome which concluded no benefit of early initiation of statins during the first 4 months for risk reduction for all-cause mortality, heart attack or stroke, but did reduce the risk for unstable angina by about 25% at four months.[31] A separate meta-analysis of 17 clinical trials involving mostly men around the age of 61 years (range 55-67) suggested a reduction of LDL-C by about 30% and reduction in plaque volume by 5.32 mm^3 in individuals who took statins for at least 6 months following acute coronary syndrome or stable angina pectoris.[32] It should be noted the latter article differs from the former in that they did not examine risk or benefits on mortality or morbidity.

All in all these meta-analyses seem to be consistent with the notion that there may be few benefits of statin therapy on overall morbidity and mortality and/or heart attack risks, but statins may block progression of plaque size. Consistent with this low benefit/risk of statins, the lowering of systolic blood pressure (SBP) by statins (-2.62 and -3.07 mm Hg for non-hypertensive and hypertensive, respectively)[33] would not be sufficient to move hypertensive individuals (SBP>140) into non-hypertensive range (SBP < 140) whereas low sodium and the DASH diet has been shown to decrease SBP by -7.1 and -11.5 mm Hg in non-hypertensive and hypertensive, respectively in 30 days.[34] Only the latter levels of improvement would be able to reduce SBP by a clinically relevant magnitude. In addition, the lack of significant differences in the decrease of SBP by statins between hypertensive and those who are not (both would be rounded up to -3 mm Hg), might suggest a background placebo effect and no efficacy for statin use in lowering SBP. If a drug is used to lower cardiovascular risks related to atherosclerosis one would naturally expect it to at least lower SBP by a clinically significant amount as has been shown for high blood pressure medications,[17] but paradoxically, this physiological response is not found for statins.

In Canada, there are two schools of thought as to how cardiovascular disease should be prevented and controlled. On one hand, we have the Canadian Hypertension Education Program Evidence–Based Recommendations Task Force supported in part by the Public Health Agency of Canada which makes recommendations to lower cardiovascular risks based on high blood pressure.[17] In contrast, the Canadian Cardiovascular Society issues guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult which makes recommendations for statin use based on LCL-C levels and other risks.[35] Clearly the medical community in Canada is divided on whether statins should be given to individuals with or without high blood pressure.

So while statin usefulness remains hotly contentious, nonetheless the market for statins continues to grow, particularly in adults without evidence of cardiovascular disease. This may be in part due to a more recent update of the 2011 Cochrane Review article published in the

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[29] Taylor F *et al*. Statins for the primary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews* ***2011***. http:summaries.cochrane.org/CD004816/stains-for- the-primary-prevention-of-cardiovascular-disease.

[30] See http://www.medicalnewstoday.com/articles/214079.php for additional comments

[31] Vale N *et al*. Statins for acute coronary syndrome. *Cochrane Database of Systematic Reviews 2011*. http:summaries.cochrane.org

[32] Tian J *et al*. Effect of statin therapy on the progression of coronary atherosclerosis. *BMC Cardiovascular Disorders 2012*; **12**:70.

[33] Briasoulis A *et al*. Antihypertensive effects of statins: a meta-analysis of prospective controlled studies. *J Clin Hypertens 2013*; **15**:310-320.

[34] Sacks FM *et al.* Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. *New Engl J Med 2001*; **344**: 3-10.

[35] Anderson TJ *et al*. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult . *Can J Cardiology* 2013; **29**: 151-167.

Cochrane Database in 2013. The results of 4 additional trials to the 14 previously reviewed were added raising the trial participant numbers from 34,272 to 56,934. In the newer review, the same lead author offered a favorable conclusion that statins are likely to be cost-effective in primary prevention of cardiovascular disease such as persons not previously diagnosed with a heart attack.[36] First, it was surprising that there was such a contrast in conclusions from a few years earlier which at that time stated caution in the prescription of statins for primary prevention as there were problems in the reporting of outcomes. This seems to be a persistent problem with statin risk/benefit interpretations as a recent review on cost-effectiveness evaluations showed a statistically relevant increase in likelihood that an industry sponsored clinical trial for use of statins in primary prevention would report favorable cost-effectiveness (100%) versus a trial not sponsored by industry (42 %), implying significant commercial bias in reporting favorable outcomes for statins for primary prevention in people without known heart disease.[37] Second, the updated 2013 meta-analysis stated that statins did not increase the risk of cancer, yet the mean duration of the clinical trials reviewed was not sufficient to address cancer risks (estimated range at 1.5 to 3.3 years). It was also reported in the newer review that statin use would eliminate heart attacks in 1.8% of users over 5 years. It should be noted that up to 10% of participants did have evidence of heart disease, and it cannot be ruled out that it was this population which benefited most and may account for a detected benefit in about 0.36% of the treated population annually. Thus, with rounding, an estimated 100% of the not-at-risk population treated with statins would endure all risk and no benefit, at least on an annual basis. It is therefore, somewhat surprising that these data could lead to a conclusion of cost-effectiveness. When viewed this way, it is no wonder others have alternatively suggested that in Canada about $2 billion or more is wasted on statin prescriptions for individuals without known cardiovascular risks.[38]

Summary

February is heart month because the incidence of heart attacks peaks with flu season. Heart attacks are secondary to atherosclerosis in which foamy macrophages are believed to play a dominant role. The flu virus and other respiratory intracellular pathogens induces an alpha-interferon antiviral response, which in all likelihood, leads to induction of a foamy "protector" virus HERV-K102 in activated monocytes. These particles accumulate in vacuoles converting activated monocytes to foamy macrophages.[7] Foamy macrophages which fail to lyse and release HERV-K102 particles might be a main cause of atherosclerosis rather than high cholesterol levels, as exemplified in HIV-1 patients. This failure to lyse is ascribed to concomitant immunosuppression of the host. No less significantly this failed release of HERV-K102 particles would reduce the ability of the host to clear the pathogen, further contributing to chronic disease.

Consistent with the notion of a causal relationship of infections with risk of heart attacks[39,40] is that we do know that flu vaccination has been shown to diminish the risk of heart attacks and strokes.[41,42] However, since flu season is also associated with other respiratory infections, additional strategies to reduce heart attack risk may be necessary. Better diagnostics and therapeutics for respiratory pathogens associated with foamy macrophages in humans such as *Chlamydia pneumoniae* is one notable area for improvement. The use of DHEA for its anti-stress properties and its non-specific immunoenhancing properties potentially

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[36] Taylor F *et al*. Statins for the primary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews* ***2013.*** http:summaries.cochrane.org/CD004816/stains-for- the-primary-prevention-of-cardiovascular-disease.

[37] Catala-Lopez F *et al*. When are statins cost-effective in cardiovascular prevention? A systematic review of sponsorship bias and conclusions in economic evaluations of statins. *PLoS One 2013*; **8**: e69462.

[38] http://www.healthnewsreview.org/2010/07/columnist-canadians-spend-2byr-on-statins-much-of-it-wasted/

[39] Fong IW. Emerging relations between infectious diseases and coronary artery disease and atherosclerosis. *CMAJ 2000*; **163**: 49-56.

[40] Ravnskov U & McCully KS. Infections may be causal in the pathogenesis of atherosclerosis. *Am J Med Sci 2012;* **344**:391-394.

[41] Loomba RS *et al*. Influenza vaccination and cardiovascular morbidity and mortality: analysis of 292,383 patients. *J Cardiovasc Pharmacol Ther 2012;* **17**:277-283.

[42] Udell JA *et al*. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. *JAMA 2013*; **310**:1711-1720.

related to its ability to inactivate AFP, might also be explored. A range of other lifestyle factors such as the reduction of stress, nutritional supplementation, changes to diet and exercise, and discontinuation of immunosuppressive substances and drugs can be found at the Canadian Hypertension Education Program Recommendations' website for the reduction of cardiovascular disease.[17] The implementation of these lifestyle factors would also be expected to lower risks from other chronic inflammatory diseases. For people needing extra support and help, at Immune System Management Clinic and Lab, our Aminomics program is designed to alleviate immunosuppression, rebalance the immune system, and replenish and rebalance amino acid pathways and metabolism to help the body to stimulate and maintain recovery from chronic diseases. What seems to be underappreciated is the notion that deficiencies in a number of amino acid pathways leads to immunosuppression and activation of T suppressor cell networks, [43] which must be overcome for recovery of health.

In closing, the role of exogenous pathogens particularly respiratory pathogens in heart disease seems to have been underestimated and more research is clearly needed in this regard. Now with the knowledge of the induction of HERV-K102 particle production as an antiviral response mediating the formation of foamy macrophages,[7] can we begin to understand why February is heart month.

[43] Wang R & Green DR. Metabolic checkpoints in activated T cells. *Nature Immunology 2012*; **13**:907-915.

TAKE HOME MESSAGES FROM THIS ARTICLE:

1. Lysine (K) which is an amino acid, acts as an antiviral potentially because it supports the particle production of a newly described endogenous "protector" foamy retrovirus of humans [7] which requires high levels of lysine to replicate.

2. Supplementation of lysine and other amino acids might improve the body's ability to combat viruses and tumors in part by supporting HERV-K102 particle production, and in part by blocking immunosuppression in T and B cells[44] and avoiding a default program for induction of Tregs over Th17 cells when certain amino acid levels are diminished.

3. Foamy macrophages which accumulate in atherosclerosis lesions might reflect a blockage in the release of HERV-K102 particles and does not appear to be caused by high cholesterol.

4. Respiratory pathogens might be a common cause of HERV-K102 particle production relevant to heart disease.

5. There seems to be little or no biological plausibility that lowering high cholesterol may protect against cardiovascular disease. However, lowering blood pressure and/or lifestyle changes may protect against cardiovascular disease.

6. Stress might induce HERV-K102 particle production and alpha-fetoprotein secretion leading to the accumulation of foamy macrophages. Many clinicians view stress as a leading cause of atherosclerosis.

7. Dehydroepiandrosterone (DHEA), also known as the youth hormone might help block excessive stress and might also counteract the immunosuppressive effects of alpha-fetoprotein (AFP). This is expected to be beneficial in controlling chronic inflammatory diseases such as heart disease. However its availability in Canada is greatly restricted by its inclusion on Schedule IV of the Food and Drug Act.

8. HERV-K102 particles are found in blood during active disease states, but are absent in remissions and in normal healthy adults. This may be consistent with its protector role as part of the innate inflammatory response.

9. Inhibiting HERV-K102 particle production such as by statin use, may decrease plasma viscosity and inflammation,[16] but may immunocompromise the host.

10. The rationale and safety of longer-term use of immunosuppressive statins is questioned in people with or without heart disease.

11. If immunosuppression does play a key role in chronic diseases, this raises the immediate contentious issue of whether statins might be contraindicated for people diagnosed with cancer, autoimmune disease, and active infections.

12. Flu vaccinations will significantly reduce risks from atherosclerosis and stroke. Since respiratory infections frequently involve other microbes, supplemental strategies to reduce heart attack risks may be better diagnosis and treatment of microbial infections, improvements to diet, and the alleviation of stress and/or immunosuppression.

[44] Wang R & Green DR. Metabolic reprogramming and metabolic dependency in T cells. *Immunological Reviews 2012*; **249**:14-26.

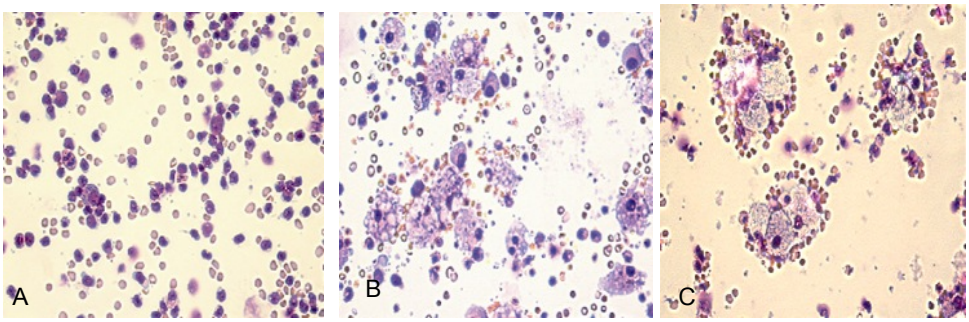

Figure 1. ***Induction of Foamy Macrophages when Human CB is Cultured in IMDM Media.*** *H&E stained Human Cord Blood Mononuclear Cells (CB) were either not cultured (**Panel A**) or cultured for 7 days in autologous serum (**Panel B**) or a very lipid normal AB serum (**Panel C**) in IMDM media. In panels B and C foamy macrophages (CD14) are quite evident along with foamy T cells (CD3) whereas B cells (CD19) did not acquire granulation/vacuolation during the culture (flow cytometry data not shown). It appears there may be more sticking of cells together associated with higher lipid content of the AB serum, which could enhance cell-cell interactions as was reported earlier.*[4,5]

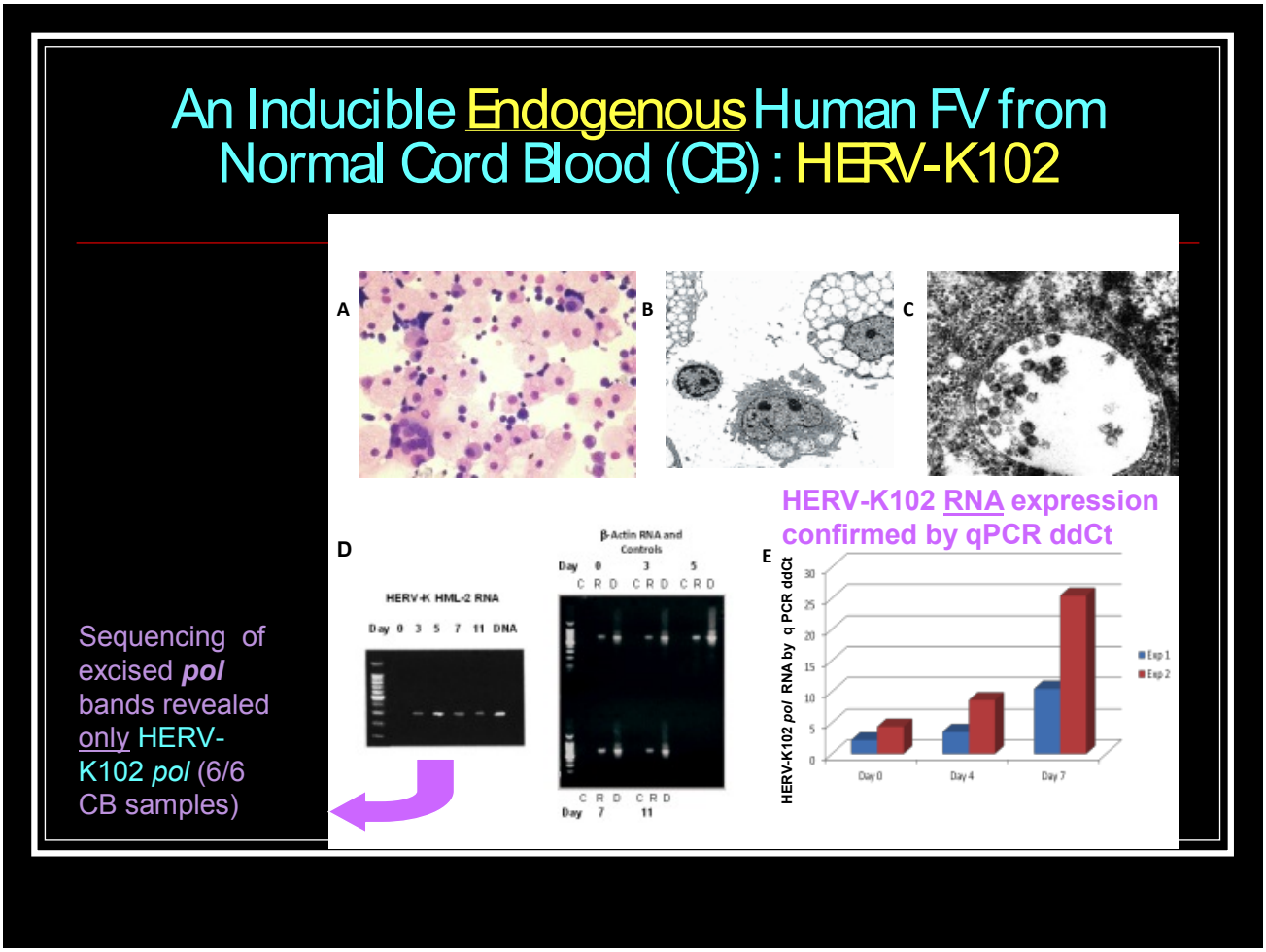

Figure 2. An Inducible, Endogenous Foamy-Like Retrovirus Induced by Culture of Human CB Cells in IMDM Media, was Identified as Human Endogenous Retrovirus-K102 (HERV-K102).

A: Hematoxylin & Eosin stain of CB cytospins from Day 7 of culture in IMDM media showing strong induction of foamy macrophages. No induction was found when CB cells were cultured in RPMI (data not shown). The addition of PHA and IL-2 to the IMDM media (T cell activators of adaptive immunity) significantly blocked the induction of foamy macrophages (data not shown), indicating the response was likely part of the innate immune system.

B: Electron Micrograph of the same cells from A showing a normal lymphocyte, a partially vacuolated cell, and a foamy macrophage with lots of vacuoles.

C: Higher Magnification of the vacuoles in B. All the vacuoles had high levels of 100 nm immature (retrovirus) particles, where envelope spikes are easily seen. Note that all budding took place within the vacuoles and never at the cell surface membrane consistent with the notion of a foamy retrovirus.

D: HERV-K HML-2 retroviruses were known at the time to be the most biologically active and recent immigrants to the human genome. So we designed our own primers for HERV-K HML-2 *pol* to see if HML-2 RNA was being produced by Polymerase Chain Reaction (PCR), which it was, and confirmed the same sequences came from DNA (endogenous or found in the human genome). So we isolated the bands from day 5 and sent this for sequencing. In 6 of 6 independent CB samples, we obtained only sequences corresponding to HERV-K102. Note that RNA levels diminished on day 7 after 30% of the cells underwent cell lysis and release of HERV-K particles.

E: Later on when we developed a quantitative PCR which has a probe built in to confirm the presence of HERV-K102 sequences,[7] we confirmed strong induction of HERV-K102 RNA in the cells.