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ENDOGENOUS RETROVIRUSES AS CONFOUNDING FACTORS IN THE PATHOGENESIS OF AIDS

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Introduction Little was known about human endogenous retroviruses (HERVs) at the beginning of the AIDS era; recognition of the existence and characteristics of HERVs offers the possibility of resolving differing views as to whether HIV exists or whether it exists but is harmless. In fact, about 8 percent of the human genome consists of sequences incorporated from retroviruses and, consistent with these observations, the role of HIV in causing AIDS is increasingly questioned. The XVIII Intl Conf on AIDS in Vienna (July 2010) confirmed a shift of focus in AIDS research: the immune system is now the focus of AIDS research. This shift followed the words of Prof. Montagnier: "… *Our immune system will get rid of the virus within a few weeks, if you have a good immune system*" a statement reversing the long-assumed cause-effect relationship between HIV and AIDS: it is the immunodeficiency that causes chronic HIV infection and not vice versa (J Biosci 28: 383–412, 2003. J Am Phys Surg 12: 116–20, 2007). If the association between signs attributed to HIV infection and AIDS is simply indicative of pre-existing immunodeficiency, *i.e.* signs of HIV infection are merely "symptoms" and not cause of immunodeficiency, then stimulation of the immune system would eradicate those signs of HIV infection. Such a demonstration would confirm the hypothesis that HERVs act as confounding factors in the pathogenesis of AIDS and HIV cannot be the sole cause of AIDS. The experimental work described in this thesis is based on a seminal paper published in 2009 (J Med Virol 81: 16–26, 2009) demonstrating that Gc Protein-Derived Macrophage Activating Factor (GcMAF) eradicated HIV infection in HIV-positive patients.

Results We demonstrated that GcMAF stimulated human monocyte proliferation and survival and that this response was associated with VDR gene polymorphisms. Since these results were obtained in peripheral blood mononuclear cells, an interplay between lymphocytes expressing VDR and GcMAF-stimulated monocytes producing vitamin D has to be assumed. The effect was dose-dependent and maximal stimulation was achieved using 100 pg/ml. GcMAF sustained cell viability for about 98 h whereas un-stimulated cells were no longer viable after 48 h, as if GcMAF had rescued monocytes from apoptosis. Heparin inhibited the stimulatory effect of GcMAF by binding the N-acetylgalactosamine moiety of GcMAF. GcMAF stimulated cAMP formation in a dose-dependent manner. GcMAF inihibited PGE_2- and MCF-7 (human breast cancer cell)-stimulated angiogenesis in chick embryo chorionallantoic membrane (CAM) assay.

Discussion GcAMF-induced increase of cAMP formation could account for its anti-angiogenetic effect since it was demonstrated that elevated cAMP level inhibited angiogenesis in CAM assay (J Vasc Res 31:195-204, 1994). GcMAF-induced inhibition of angiogenesis could then be crucial in determining its therapeutic effects in conditions where angiogenesis plays a key role in the progression of the disease, from cancer (Exp Cell Res 316:1304-8, 2010) to HIV infection (Angiogenesis 5: 141–151, 2002). In addition, the CAM assay proved to be a rapid, simple and inexpensive method to determine the relative potencies of different GcMAF preparations and their stability; for example, we observed that storage at room temperature for 15 days decreased GcMAF potency by about 50%. These data could prove useful for upcoming clinical trials on GcMAF. In fact, GcMAF is being sold over the internet and it appears that several people are already assuming GcMAF to treat diseases as diverse as cancer and HIV infection.