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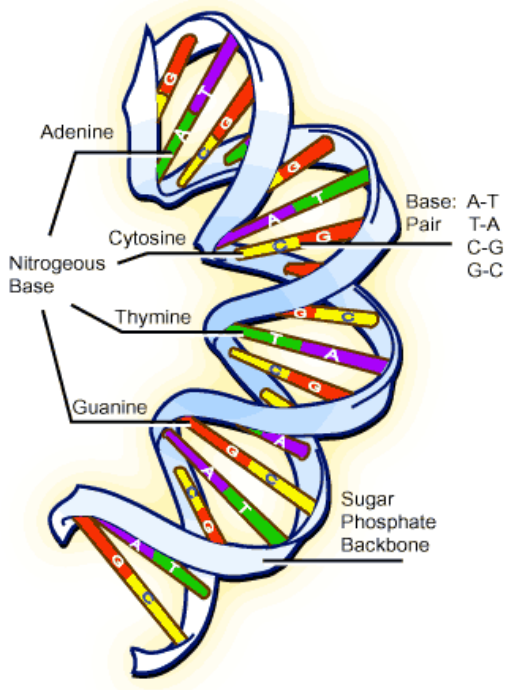
Dr. Cheney comments on the XMRV workshop

"I attended and was a poster presenter at the recently completed XMRV conference at the NIH. It was fascinating and I took perhaps 30 pages of notes.

The bio-political undertones were also intense but I have to say that the presentations of XMRV association with CFS (4 presentations) were much stronger than the presentations of negative XMRV associations with CFS (4 presentations). They were stronger specifically because of the multiple methods they employed and not just PCR.



Very interesting in this regard were comments by the head of the blood working group at the NIH who is trying to determine the cause of the discrepancy. He hinted strongly that it is the way blood is collected and processed for nucleic acids and not the detection methods for XMRV itself that divides the two groups.

In an NIH blood group sponsored study, a group comparison study with both camps represented detect successfully, in a blinded fashion, XMRV spiked buffer in varying concentrations but they nevertheless divide into two camps when clinical blood samples are taken and processed for XMRV nucleic acids.

Using only PCR, one camp sees ~80% positive in CFS and one camp sees 0% positive in CFS. There is no one in between and no middle ground between the two groups which was striking and noted by Joe B. who was also in attendance. There is no evidence by mouse mitochondrial DNA probes, that any of the positive associations were contaminated. However, one of the negative association speakers found non-human mouse virus MLV contamination perhaps localized to heparin tubes used for blood collection. Heparin is often produced in China where mice are common as pets. When the contamination was cleared, she found no association of XMRV with CFS.

"I also wanted to share some other highlights of the conference. Among them, a very interesting presentation was made by a group connected to Abbott Labs that infected male and female Macaques (monkeys closely related to man) with human XMRV to see what happens and where the virus ends up or concentrates itself.

"Within a few weeks, the virus was largely cleared from blood where it was initially injected in high concentration. Even antibody response was lost over time (months) as the infection was largely removed from the blood and virus did not appear to persist in the blood. Apparently, there was not enough viral antigen to keep antibody levels high or persistent.

However, the virus was found more or less in every organ, at least initially, and thought to be carried around the body in T-cells and B-cells during the active phase of infection. This is consistent with the ubiquitous nature of the Xpr1 receptor used by the virus to gain access to almost all cells of the body. Organs where the virus was initially most concentrated appeared to be lymphoid organs such as the spleen, liver and mesenteric nodes of the GI track and in sex organs and in particular the epithelium of the prostate gland where it was highly concentrated at first and then the infected cells later apoptosed and infection disappeared from the epithelium and then the virus was more likely to be seen in the interstitial cells in the stroma or matrix of the prostate, especially the fibroblasts which may be one reservoir in all the various organs that are initially infected. The virus was also found in the epithelium of the cervix in the female macaque.

Over time, the infections of various organs tended to be cleared by either immune mechanisms but especially by restriction enzyme systems present in almost all human cells that hypermutate the virus so it cannot persist as a competent infectious agent. Indeed, mutated viral strains are almost always found in CFS cases by both Judy Mikovits at WPI and Frank Ruscetti at NCI. Sometimes this makes the virus incompetent as an infectious agent and sometimes has no effect on infectiousness.

"Very interesting is that another cell that appears to be a reservoir of XMRV other then fibroblasts within tissue stroma are tissue macrophages. The pulmonary alveolar macrophages were absolutely loaded with XMRV virus and other tissue macrophages could also be a potential reservoir in other tissues as well, especially in the GI tract, sex organs and sinuses. Tissue macrophage reservoirs would be analogous with HIV as well. It would seem that bronchial secretions, nasal secretions and sex organ secretions as well as feces and urine are well positioned to help the virus to spread itself to other macaques, especially if activated.

"As for activation of more or less low level or quiescent but persistent infectious virus, there seem to be several mechanisms. The virus has both a glucocorticoid response element (GRE) and an androgen response element (ARE) in its promotor region. It also has binding regions for NK Kappa B proteins in its response elements. In any organ with high levels of local androgenic stimulation such as the prostate and perhaps during puberty, the virus could activate. No mention was made of the effect of the predominant female sex hormones but estrogen is the equivalent androgen-like hormone in females. As for the GRE in the promotor region, severe stress will activate the virus or the use of glucocortocoid hormones and perhaps any precursor steroid hormone such as pregnenolone. As for the NF Kappa B sites, any strong immune response with an associated cytokine storm would also be a strong stimulant and such stimulation certainly occurs in the bronchial tree which is frequently stimulated with antigen, especially during allergy season.

"Perhaps most interesting of all was what happened with the injection of a bolus of foreign peptides into macaques that had apparently completely cleared the virus from blood. There was a huge reactivation of infectious virus in the blood proving that latent but persistent virus is just below the surface and that XMRV infection cannot be completely cleared from all reservoir sites. The peptide injection mimics an acute infection (? Borrelia or the flu), an immunization or even acute mold exposure.

"The effect of XMRV infection over time was not studied in the macaque but a similar gammaretrovirus called Feline Leukemia virus (FeLV) has been well studied in cats for decades. I will in another post describe a most interesting talk at this conference by a veterinarian on the life history of infection by a gammaretrovirus in cats."

Paul Cheney, M.D.

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