May 2012 edition

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Better late than never I hope for the May edition of the MitoAlmanac. We scientists are a nomadic lot. An Englishman who has lived in the US for 40 years, I am still schizophrenic about where my home is. Having spent all of April (2 weddings and a memorial service) in England and Scotland I have been doing “my sums” again. As usual it is a draw: US 5 pluses (the weather, my children and grandchildren are here, the weather, the civility of people, the weather) UK 5 pluses (the different sense of humor, beautiful gardens, good bacon, pork pies and cricket).

For those of you who read my diatribe in the April edition, you may want to read an article in the New York Times published on Apr 17th on page D1, that makes the same points about the state of science, but does it better and with more detail. The following is an excerpt:

University laboratories count on a steady stream of grants from the government and other sources. The National Institutes of Health accepts a much lower percentage of

grant applications today than in earlier decades. At the same time, many universities expect scientists to draw an increasing part of their salaries from grants, and these pressures have influenced how scientists are promoted.

"What people do is they count papers, and they look at the prestige of the journal in which the research is published, and they see how many grant dollars scientists have, and if they don't have funding, they don't get promoted," Dr. Fang said. "It's not about the quality of the research."

MARVELOUS MAVS: MITOCHONDRIA v VIRUS

After a lecture at Cambridge University in the 1970s, a prominent cell biologist with a particularly British sense of humor asked me why anyone would study mitochondria now that Mitchell had been vindicated. I mumbled something stupid, and for the last 30 years have rehearsed my answer should I be asked the question again (James Thurber-style). In addition to listing the role of the organelle in metabolic disease including diabetes, in cancer and in neurodegenerative conditions, my argument will now include the importance of mitochondria in the innate immune response thanks to exciting work of the last few years.

Innate immunity against RNA viral infection involves the activation of multiple signaling steps that culminate in the rapid production of type I interferons, such as IFN-α and -β, and other pro-inflammatory cytokines. Two distinct pathways initiate signal transduction; one involves the endosomal Toll-like receptor 3 which targets RNA viruses entering the cell by endocytosis; the other is prompted by retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), which recognize

cytoplasmic viral- derived double-stranded (ds)RNA. RIG-1 and a second RNA helicase, MDA-5, recognize distinct types of cytosolic RNA species and are recruited to the mitochondrial outer membrane where they interact with the protein, mitochondrial antiviral signaling protein (MAVS): also called IPS-1, VISA and CARDIF. This protein of 56Kd contains an N-terminal caspase activation and recruitment domain (CARD) comprising six helices. The same structure is found in both RIG-1 and MDA-5. MAVS also contains a transmembrane domain that anchors it to the mitochondrial outer membrane. Activation of MAVS leads to downstream translational activation of NF kappaB and/or IRF3/7, inducing rapid production of the interferons and cytokines. It also activates autophagy or apoptosis to rid the cell of viral elements or remove the infected cell from tissue.

Several excellent reviews provide further detail of the RLR pathway and role of MAVS.

WEST AP, SHADEL GS &GOSH S. Mitochondria in innate immune response. Proc. Natl. Acad Sci USA 108. 14590-5 (2011)

TAI MC & IWASAKI A. Mitoxosome: a mitochondrial platform for cross talk between cellular stress and antiviral signaling. Immunol. Rev. 243. 215-34 (2011)

KOSHIBA T. BASHIRUDDIN N. & KAWABATA S. Mitochondria and antiviral innate immunity. Int. J. Biochem. Mol. Biol. 2. 257-62 (2011)

OHTA A & NISHIYAMA Y. Mitochondria and viruses. Mitochondrion 11. 1-12 (2011)

A number of interesting features of the mitochondrial involvement in innate immunity have appeared recently.

Hou et al. have reported that MAVS forms prion-like aggregates to propagate the anti-viral response.

HOU F. et al. MAVS Forms Functional Prion-Like Aggregates To Activate and Propagate Antiviral Innate Immune Response. Cell. 146. 448-61 (2011).

VIRAL CONTROL OF APOPTOSIS

Involvement of other mitochondrial outer membrane proteins in the anti-viral response has also been seen. Takano et al report that TOM70 acts as a viral receptor including for the hepatitis C virus. They showed induction of TOM70 expression by HCV infection, which in turn induced resistance to tumor necrosis factor-alpha (TNF-α)-mediated apoptosis but not to Fas-induced apoptosis in HepG2 cells. TOM70 was found to be induced by the HCV non-structural protein (NS)3/4A protein, and silencing of TOM70 decreased the levels of the NS3 and Mcl-1 proteins.

TAKANO T et al. TOM70 expression is induced by hepatitis C virus and is related to the apoptotic response. J Med Virol; 83.801-9. (2012).

While much is known about the upregulation of MAVS, less is known about its degradation after viral infection. However two proteins have been shown to play such a role recently. These are the poly c-binding proteins (PCBP-1 and PCBP-2. Zhou et al. show that overexpression of PCBP1 impairs MAVS-mediated antiviral response while knockdown of this protein has the opposite effect. PCBP1 is abundantly expressed while PCBP2 shows low basal expression but rapid induction after infection

ZHOU X. YOU F. CHEN H & JIANG Z. Poly(C) binding protein PCBP1 mediates housekeeping degradation of mitochondrial antiviral signaling (MAVS). Cell Res. 22. 717-27 (2012).

THE VIRUS FIGHTS BACK

Several recent studies show how viruses can get the better of a cell. Dong and Feng have recently described how murine gamma herpes virus 68 subverts cytokine production by modifying upstream signaling to MAVS.

DONG X & FENG P. Murine gamma herpes virus 68 hijacks MAVS and IKKb to abrogate NFkappaB activation and antiviral cytokine production. Plos Pathog 7. E1002336 (2011)

Further, Lecouer et al. show that the HIV tat protein reacts with mitochondria to induce permeabilization of the organelle and inactivate cytochrome c oxidase.

LECOUER H. et al. HIV tat protein directly induces mitochondrial membrane permeabilization and inactivates cytochrome c oxidase. Cell Death Dis. 3 e282 (2012).