In this issue of the NUHS Research Bulletin, we describe research evaluating the effectiveness of new cervical cancer screening methods in Singapore, the role of microRNA in regulating CNS inflammation, and the hijacking of a lipid metabolic mechanism in the host cell by influenza virus.

**Effectiveness of HPV DNA and Pap co-testing in a subgroup of women in Singapore**

Traditionally, women are screened for cervical cancer using a cytology (Pap) test, which involves evaluating cervical cells by microscopy to detect abnormalities. However, cytology testing is not very sensitive and can miss some cases of cervical cancer. To circumvent this problem, the American College of Obstetrics and Gynecology recommends co-testing every 5 years with a combination of two tests, the cytology test and a human papillomavirus (HPV) DNA test, to screen women from age 30 to 65 for cervical cancer. The HPV DNA test usually detects one or more types of HPV that are associated with an increased risk for cervical cancer.

The recommendations were based on American and European studies showing that co-testing was more sensitive at detecting cervical cancer than was cytology testing alone. However, the effectiveness of co-testing for cervical cancer screening has not been studied in women in Singapore.

A recent study performed by Drs Sarah Li, Ida Ismail-Pratt, Evelyn Koay, and Jeffrey Low (unpublished data) looked at the effectiveness of cytology and HPV DNA co-testing in 300 women aged 30 and above who were patients at NUH. The HPV DNA test detected high-risk HPV in 27 of 272 women (9%) who had a negative cytology result and would not have been flagged for further testing with Pap screening alone. One of these women was subsequently found to have high-grade cervical cancer (CIN3).

Results of this study suggest that co-testing in Singaporean women aged 30 and above improves the sensitivity of detecting women at elevated risk for cervical cancer compared to the Pap test alone. Women who receive a negative co-testing result can be more assured of not having cervical cancer than women with negative cytology alone.

**MicroRNA downregulates CNS inflammatory response mediated by microglia**
Microglia are the immune cells of the CNS. They are temporarily activated in response to injury or infection in the CNS to release pro-inflammatory cytokines that destroy pathogens and infected cells. However, persistent activation of microglia leads to a build-up of such cytokines and other toxic substances. In this environment, neurons start dying in greater numbers. The pattern of persistently activated microglia, excessive inflammation, and neuronal death can be seen in Alzheimer's disease, Parkinson's disease, multiple sclerosis, and traumatic brain injury.

MicroRNAs (miRNAs) are small, non-coding genes that are found in most animals and plants. miRNAs bind to their target genes and prevent them from being expressed. A new study from the laboratory of Associate Professor S. Thameem Dheen, published in the Journal of Neurochemistry, shows that an miRNA (miRNA-200b) downregulates the inflammatory processes that are mediated by activated microglia.

miRNA-200b acts by inhibiting c-Jun, a substrate of the JNK/MAPK pathway, thus reducing production of pro-inflammatory cytokines and the toxic substances nitric oxide (NO) and inducible nitric oxide synthase (iNOS). By this mechanism, miRNA-200b should increase neuronal survival. True enough, the authors showed that overexpressing miRNA-200b in mouse microglial cells caused these effects. miRNA-200b overexpression also reduced the migration of activated microglia, a step in the inflammatory response. As expected, knockdown of miRNA-200b in the cells had the opposite effect—increased JNK activity and increased production of pro-inflammatory cytokines, NO, and iNOS. When the culture medium of the knocked down microglia cells was added to neurons, the neurons died in greater numbers.

Given that miRNA-200b downregulates the CNS inflammatory response, it could be useful in treating chronic neuroinflammatory diseases.

Reference

For more information about miRNA, you can check out the 2008 Nature supplement issue devoted to miRNA (http://www.nature.com/nature/supplements/collections/micrornas/) and this review article on miRNA therapies (http://embomolmed.embopress.org/content/early/2014/06/16/emmm.201100899.long).

Influenza virus hijacks host cell lipid metabolism to increase viral replication, changing lipid composition of the host cell
A recent article in the Journal of Lipid Research introduces a novel mechanism by which influenza virus hijacks a lipid metabolic pathway in order to better replicate itself. Using liquid chromatography-mass spectrometry (LC-MS), Dr Lukas Tanner, Associate Professor Markus Wenk, and colleagues discovered this mechanism by analysing the change in levels of 175 lipids in host cell membranes during influenza virus replication.
What the authors found was that replicating influenza virus inhibits β-oxidation of lipids in host cell peroxisomes (special organelles where lipids are metabolised). One effect of inhibiting β-oxidation is an increase in sphingolipid levels, which may be needed for formation of new viral particles. Another effect is the increased production of the ether-linked form of phosphatidylcholine (PC) and a shift away from ester-linked PC. This remodeling appears to be specific to the influenza virus. The higher the proportion of ether-linked PC relative to the ester-linked form, the more pathogenic the virus (i.e., causes more severe disease).

The discovery of this new mechanism by which influenza virus manipulates the host cell for its own benefit opens the door to new therapies for influenza virus infection. For example, PPARα agonists, which promote β-oxidation in the peroxisome, could reduce virus production in cultured cells in this study. Further research in animals should determine whether PPARα agonists are effective in vivo.

Reference

News from RO:
The Personal Data Protection Act, 2012 (“PDPA”) came into effect on 2 July 2014. This provides a legislative framework for protection of personal data against misuse by regulating the proper management of personal data.

The overarching requirements of PDPA extend into the use of personal data for research purposes. NUHS Research Office held two briefing sessions on 3rd July and 8th July 2014 on the implications of PDPA on research. All materials used for the briefing can be downloaded from the NUHS intranet portal, under “Resource Library” (http://nuhs-portal/communications/personal-data-protection-act-pdpa/resource-library.html). NUHS RO has also compiled a PDPA Guidance on Research and FAQs, which is available from the “Resource Library”.

With effect from 1 Aug 2014, the PDPA Review form (for Research exemption) should be filled up and attached to the online DSRB submission under these conditions -- (i) no consent will be taken AND (ii) identifiable data will be used for the study which will be eventually de-identified prior to publication. The PDPA review form will be reviewed and endorsed by the Department Representatives (DRs) and Institution Representative (IR) in the ROAM system.

If you have further queries on the PDPA or feedback/comments on the NUHS Research Bulletin, please email nuhs_research_office@nuhs.edu.sg

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The National University Health System (NUHS) groups the National University Hospital (NUH), the NUS Yong Loo Lin School of Medicine, the NUS Faculty of Dentistry and the NUS Saw Swee Hock School of Public Health under a common governance structure to create synergies for the advancement of health by integrating clinical care, research and education.