別紙４－１（課程博士（英文））

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Abstract (Doctor)

Title of Thesis	A study on assessing systemic inflammation due to malignant cells and pesticide exposure

Approx. 800 words

Inflammation plays an important role in body defense mechanism as it fights off the invasion of foreign substances such as pathogens are trying to compromise our defense system. Our body usually response with the release of proinflammatory cytokines in order to recruit cells such as macrophage and resident microglia to eliminate the pathogens. There are two common types inflammation which are acute inflammation and chronic inflammation. Acute inflammation is a rapid response from initial insult to initiate healing process, while chronic inflammation usually occurs across a longer period of time when the body is under continuous and prolonged perturbation. Both are equally dangerous as the progression of inflammation may lead to systemic inflammation. Systemic inflammation is a result of circulating proinflammatory cytokines which can cause multiple reactions before disease manifestation. Therefore, it is hard to pinpoint the exact assault that causes systemic inflammation, making it a prominent target in multiple fields involving medicine, biology, chemistry and physiology. This study proposes an assessment involving cellular biology, signal processing, rat study and genetic engineering in order to evaluate the alterations coming from systemic inflammation.

Chapter 1 consists of the general introduction of this thesis, explaining the background, motivations and objectives and the structure of this thesis.

Chapter 2 discusses on the evaluation of the cellular dynamics through malignant cells using scanning acoustic microscope. Development of non-invasive observational tool to assess the changes in cellular level is necessary as conventional approaches focus more on tissue and organ. This study focus on the dynamic cellular changes during mitotic phase as cell nucleus facilitates most of the cell activities, making it a prime target in disease study and drug design. Malignant cells were arrested in mitotic phase by cell cycle synchronization using demecolcine, a typical anticancer drug mostly used in chemo-radiotherapy. The dynamic changes of the cell nucleus during mitotic phase were successfully captured using scanning acoustic microscope and confirmed using confocal microscopy. This result provided valuable insight in understanding the alteration of cell nucleus in real time and allowed us to explore the possibility to improve drug design and elucidate the disease mechanism. This is an important advancement to bring scanning acoustic microscope closer to application in

biomedical field.

Furthermore, this study explored the potential causes and effects of systemic inflammation through pesticide exposure in rat study. Glyphosate, an active ingredient of Roundup®, with gathering controversies around its usage was chosen. Daily exposure to such xenobiotics is proven to be unsafe to human as the continuous exposure might cause systemic inflammation which is easy to be overlooked. Emerging evidences suggest that glyphosate is a potential health risk and jeopardize the environment, thus making it a suitable target to trigger systemic inflammation in rat study. Chapter 3 explored whether the transient inflammation observed in previous chapter is systemic or not by looking at the gut-brain axis. Gut-brain axis is a bidirectional relationship that affect each other. One of the feasible factors is through the metabolites produced by the gut bacteria. The changes of the gut microbiota and metabolites are indicative of inflammation-mediated alteration. The result showed that there is a strong association in between the cerebellar developmental anomalies and disrupted gut microbiota and metabolites production. These changes pointed towards systemic inflammation as the major propagator that might further irritate the symptoms.

Chapter 4 focus on the effects of prenatal exposure on the cerebellar development in offspring. Prenatal exposure was chosen because multiple biological and physiological events happened during pregnancy, making pregnant dam more susceptible to alterations. The result showed that alteration occurred in the offspring cerebellum inferring that glyphosate might be developmental neurotoxic. Chapter 5 described the alteration of pro-inflammatory cytokine found in offspring cerebellum. Since the alteration observed in previous chapter might be mediated by systemic inflammation, hence, finding out the production of proinflammatory cytokines during early development is essential to understand the mechanism behind the alteration. The result showed that transient inflammation occurred in the cerebellum of juvenile male rat although the production timing differed.

Chapter 6 expand the research scope into adulthood by examining the social behavioral changes in matured animal. Animal behavior study is essential in understanding the brain alteration and disease phenotype. The result demonstrated that adult male rats born from prenatal glyphosate exposed dam animals were less explorative, not grooming as much and more anxious in social interaction. This implied cognitive impairment, and hence, the result inferred that the effects of prenatal GP exposure carried on into adulthood.

Taken together, scanning acoustic microscope has the potential to bridge current approaches in cellular study to translational research. Tracing the living cellular dynamics change might reveal more on the alteration caused by systemic inflammation. Prenatal glyphosate exposure successfully triggered systemic inflammation in the F1 male rat even when they entered adulthood. The effects were significant and assessable through methodology proposed in this study. This implied that the proposed methodology is translatable in human study in order to elucidate disease mechanism.