王弘毅 教授 (Hurng-Yi Wang, Professor)

職稱：教授
最高學歷：師範大學生物系博士
專　長：族群遺傳學、分子演化學、基因體學
E-mail: hurngyi@ntu.edu.tw
研究室:
電話：（02）23123456轉66614
傳真: (02) 23709820

近年研究主題

以基因組中與生殖隔離有關的基因座分析基因交流在種化過程中的角色

新種形成的遺傳機制一直是演化學研究的主題。異域種化模型認為物種經過隔離而形成，因此基因組內不同區域的分化程度應該是相當均值的。而根據種化基因交流假說，基因組內與物種形成有關的基因會因為天擇的干預不易在兩物種間交換。在其它基因可以交流的情況下，前述區域會在基因組內形成相對歧異度較大的區段或稱為。然而種化過程中，如果基因組內部突變率或是基因互換率有差異，即便沒有基因交流，也會造成不同區域分化程度的差異。因此問題在於如何區別基因組內的分化不均值性是由基因交流所造成。種化基因交流模型具體的指出基因組內與種間差異有關的基因會有較大程度的分化，而異域種化模型則沒有這樣的推測。本研究預計整合族群分化以及與物種性狀有關的遺傳學研究來探討基因交流在物種形成時所扮演的角色。

我們首先會以模式物種黑腹果蠅進行先期研究。黑腹果蠅的兩個品系□Z and M□有不同的交配行為，而影響這些行為的基因主要在體染色體。因此我們預測Z/M兩品系果蠅的體染色體比性染色體要有較大的分化。此外過去研究發現薜荔與愛玉小蜂小蜂因為不同生活環境，而有不同的溫度適應。我們預測兩者之間與能量產生有關的基因比起其他的基因會有較大的分化。

Testing speciation with gene flow by comparing the loci responsible for reproductive isolation with the genomic patterning of differentiation

The genetic details of how new species arise have been major topics of evolutionary research. Allopatric mode speciation considers that all genes between two species were diverged at the same time, thus genetic differentiation across the genomes between two species should be homogenous. An alternative model of speciation with gene flow presumes that the loci involved in reproductive isolation or ecological specialization would result in strong selection against their introgression between species, leading to heterogeneous pattern or “genomic islands” of differentiation in the genome. Nevertheless, level of divergence between two species can be heterogeneous in the absence of gene flow, if some biological processes, including variation in local mutation and recombination rates and selection, have been involved. The problem is whether the observed heterogeneous landscape of genomic differentiation can be explained solely by a combination of several biological processes, or gene flow has to be invoked. Speciation with gene flow specifically predicts that genomic regions with elevated divergence will contain genes responsible for species isolation, whereas other models make no such prediction. This proposal aims to test the speciation with gene flow model by integrating studies of population differentiation with genetic studies of phenotypes responsible for species distinction.

We first conduct a pilot study on model organism, Drosophila melanogaster. The genes responsible for behavior differences between two races, Z and M, are majorly mapped on autosomes. Thus, we expect autosomal loci exhibit greater divergence than X-linked loci. We next test this hypothesis on fig wasps. Jelly-fig wasp, Wiebesia pumilae, which is the pollinator of endemic fig tree, Ficus pumilae var. awkeotsang or jelly fig, and creeping-fig wasp, pollinator of F. pumilae var. pumila or creeping fig. From previous studies, two fig wasps are separated by different altitudes of their host figs, > 800 m for jelly fig and < 500 m for creeping fig. While two wasps show different temperature adaptations related to their different living environments, gene flow between them is observed. Therefore, we should expect to see the elevated divergence in the genetic regions responsible for energy production and metabolism. The divergence in the rest of genome would be homogenous because of constant gene flow.

Innate myeloid cells (especially Kupffer cells) and their PRRs in establishing tolerance to hepatitis B virus

B型肝炎病毒是世界上最常見的感染疾病之一。據世界衛生組織，超過三分之一的世界人口（二十億人）已感染B型肝炎病毒。其中，有2.5億人在全球是慢性帶原者。慢性B型肝炎病毒感染很少有肝外表現。他們往往不知道疾病已經法展到肝硬化相關的併發症的存在下，以及肝細胞癌（通常在40歲後），或肝硬化及肝細胞癌兩者存在。雖然，有效的疫苗是目前可行的方法，但它無法幫助慢性感染者已經發展為肝硬化和肝癌的風險。因此，開發有效治療慢性B型肝炎病毒感染，仍然被認為是必要的。

其中一個B型肝炎病毒感染最顯著特點是在感染時的年齡差別。對於在一歲以下感染成為慢性帶原者的風險為90％。一至五歲之間的兒童風險降至30％。對於5歲以上和成人，從匯集的數據顯示風險降低到2％左右。推測“肝臟耐受性”和“免疫不成熟”對B型肝炎病毒的結果，在嬰幼童時期具有高病毒的持續性，但在晚期年齡肝臟免疫環境成熟時具有病毒清除能力，然而，這種成熟的過程尚未闡明。

為了方便我們瞭解B型肝炎病毒感染時年齡相關的免疫活化，我們研究團隊已經建立了一個年齡和腸道菌相關的B型肝炎病毒持續性小鼠模式。在成年（12週齡）的C3H /HeN小鼠約在注射B肝病毒後6週內快速清除B型肝炎病毒，而年輕（6週齡）的C3H /HeN小鼠在注射B型肝炎病毒後26週仍保持B肝病毒呈現陽性。使用抗生素5至12週齡的小鼠，清除腸道菌群可以防止成年小鼠快速清除B型肝炎病毒。我們還證明肝臟的巨噬細胞在年輕小鼠表現出耐受性的表現型以及在成年小鼠打破耐受性的表現型。

利用這小鼠模式，我們的目標是進一步瞭解年齡和腸道菌在調節肝臟的免疫反應，尤其是肝臟的巨噬細胞，對抗B型肝炎病毒和人類慢性B型肝炎病毒感染的影響。為此目的，我們的目標是（1）在不同年齡組的小鼠中表現型和不同的肝臟巨噬細胞群的功能，（2）識別肝臟的巨噬細胞群的病原體相關分子模式（PAMP）和模式識別接受器（PRRs）（3）檢查的年齡和腸道菌群的作用在調節Kupffer細胞及循環血液外來巨噬細胞的功能來對抗B型肝炎病毒，（4）研究肝臟的巨噬細胞和其他免疫細胞之間的相互作用，和（5）探討在慢性帶原者和其他動物中的肝臟巨噬細胞的表現型和功能。

Hepatitis B virus (HBV) is one of the most common infectious agents in the world. According to world health organization (WHO), more than a third of the world’s population (2 billion people) has been infected with HBV. Of these, 250 million people worldwide are chronic carriers. Patients with chronic HBV infection seldom have extrahepatic manifestations. They are often unaware of the disease until the presence of cirrhosis-related complications, hepatocellular carcinoma (HCC)(usually after the age of 40), or both. Although, the highly effective vaccine is currently available, it does not help those who have already been chronically infected and are at risk of developing cirrhosis and HCC. Thus, efforts of developing the effective treatment of chronic HBV infection are still considered a necessity.

One of the distinctive features of HBV infection is that the risk of chronicity varies greatly with the age at which the infection is acquired. For those who acquire the infection under the age of one the risk of becoming chronic carrier is 90%. The risk drops to 30% for children between one to five years old. For children older than 5 years and for adults, the risk from pooled data decreases to around 2%. It is postulated that “liver tolerance” and “immune immaturity” to HBV result in the high viral persistence

in early stage of life, but that the maturation of liver immune environment in late age empowers HBV clearance. However, this maturation process has not been clarified.

In order to facilitate our understanding of age-dependent immune activation during HBV infection, our group has established an age and gut-bacteria related HBV persistent mouse model. While adult (12-week-old) C3H/HeN cleared HBV within 6 week postinjection (wpi), their young (6-week-old) counterparts remained HBV-positive at 26 wpi. Sterilization of gut microbiota from 5 to 12 weeks of age using antibiotics prevented adult mice from rapidly clearing HBV. We also demonstrated liver macrophages showed tolerant phenotypes in young mice, and the tolerant phenotypes were dismissed in adult mice.

Using this model, we aim to understand the influence of age and gut bacteria in regulating liver immune response, especially liver macrophages, against HBV and the possible connection with human chronic HBV infection. To that end, we aim to (1) characterize the phenotypes and functions of different liver macrophage subsets in different age groups of mice, (2) identify pathogen associated molecular patterns (PAMPs) and pattern recognition receptors (PRRs) within a subset of liver macrophages, (3) examine the role of age and gut bacteria in regulating the function of KC and MoMs against HBV, (4) study the interaction between liver macrophages and other immune cells, and (5) investigate phenotypes and function of liver macrophages in chronic carriers and other animals.

開設課程

EEB5045	族群遺傳學	
EEB5035	演化生物學	
EEB5087	分子演化	

代表著作

Google Scholar Research Gate

1. Chaw SM, Tai JH, Chen SL, Hiseh CH, Chang SY, Yeh SH, Yang WS, Chen PJ, **Wang HY***. The origin and underlying driving forces of the SARS-CoV-2 outbreak. Journal of Biomedical Science. *In press* (IF=5.203; Medicine, Research, and Experimental 20/136=14.7%)
2. Hsieh CH, Huang CG*, Wu WJ, and **Wang HY***. A rapid insect species identification system using mini-barcode pyrosequencing. ***Pest management science*** 2019. 76 (4), 1222-1227. (IF: 3.255; Entomology 6/98= 6%)
3. Wu LL, Peng WH, Wu H-L, Miaw SC, Yeh SH, Yang HC, Liao PH, Lin JS, Chen YR, Hong YT, Chen PJ, **Wang HY***, and Chen DS*. Ly6C+ Monocytes and Kupffer Cells Orchestrate Liver Immune Responses Against Hepatitis B Virus in Mice. ***Hepatology***, 2019. 69: 2364-2380. (IF: 14.971; Gastroenterology and hepatology 5/84=6%)
4. Zhang Y, Li Y, Shen X, Zhu T, Tao Y, Li T, Li X, Wang D, Ma Q, Hu Z, Liu J, Zheng C, Ruan J, Cai J, Wu CI, Lu X*, and **Wang HY***. “Genetic load and potential mutational meltdown in cancer cell populations” ***Molecular Biology and Evolution***, 2019. 36: 541-552. (IF: 14.797; Genetics and heredity 4/173=2%)
5. Wen H, **Wang HY**, He H and Wu CI*. “On the low reproducibility of cancer studies.” ***National Science Review***, 2018, in press. (IF: 13.22; Multidisciplinary Sciences 3/69=4%)
6. **Wang HY**, Chen Y, Tong D, Ling S, Hu Z, Tao Y, Lu X and Wu CI*. “Is the evolution in tumors Darwinian or non-Darwinian?” ***National Science Review***. 2018, 5: 15-17. (IF: 13.22;

Multidisciplinary Sciences 3/69=4%)

7. Lin YY, Hsieh CH, Chen JH, Lu X, Kao JH, Chen PJ, Chen DS, **Wang HY***. “De novo assembly of highly polymorphic metagenomic data using in situ generated reference sequences and a novel BLAST-based assembly pipeline.” ***BMC Bioinformatics***. 2017, 18(1):223. (IF: 2.448; Mathematical and computational biology 14/59=23%)
8. Wu CI*, **Wang HY**, Ling S, Lu X. “The Ecology and Evolution of Cancer: The Ultra-Microevolutionary Process.” ***Annual Review Genetics***. 2016, 50:347-369. (IF: 9.589; Genetics and heredity 9/171=5%)
9. Lin YY, Liu C, Chien WH, Wu LL, Tao Y, Wu D, Lu X, Hsieh CH, Chen PJ, **Wang HY***, Kao JH and Chen DS*. “New insights into the evolutionary rate of hepatitis B virus at different biological scales.” ***Journal of Virology***. 2015, 89(7): 3512-22. (IF: 4.368; Virology 8/35=22%)
10. Chou HH, Chien WH, Wu LL, Cheng CH, Chung CH, Horng JH, Ni YH, Tseng HT, Wu D, Lu X, **Wang HY***, Chen PJ and Chen DS*. “Age-related immune clearance of hepatitis B virus infection requires the establishment of gut microbiota.” ***Proc Natl Acad Sci USA***. 2015, 112(7): 2175-80. (IF: 9.504; Multidisciplinary Sciences 5/64=7%)
11. Tseng SP, Li SH, Hsieh CH, **Wang HY*** and Lin SM*. “Influence of gene flow on divergence dating – implications for the speciation history of Takydromus grass lizards.” ***Molecular Ecology***. 2014, 23(19): 4770-84. (IF:6.131; Ecology 10/158=6%)
12. Hsieh CH, Ko CC, Chung CH and **Wang HY***. “Multilocus approach to clarify species status and the divergence history of the Bemisia tabaci (Hemiptera: Aleyrodidae) species complex.” ***Molecular Phylogenetic and Evolution***. 2014, 76: 172-80. (IF: 4.412 Genetics and heredity 34/171=19%)
13. Chiou HY, Hsieh CH, Jeng CR, Chan FT, **Wang HY*** and Pang VF*. “Molecular characterization of cryptically circulating rabies virus from ferret badgers, Taiwan.” ***Emerging Infectious Disease***. 2014, 20(5): 790-8. (IF: 7.422; Infectious disease 4/88=4%)