Taking Fly for Understanding the Molecular Role of HLAB27/hB2m in Spondyloarthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: After more than 40 years of researches, the mechanisms underlying the association of HLA-B27 with spondyloarthritis (SpA) remain poorly understood. The *Drosophila* has been demonstrated to be an extremely useful genetic model in numerous systems. We hypothesized that *Drosophila* might be a relevant model to study HLA-B27 and particularly for deciphering the cellular cascade and the genetic pathways affected by HLA-B27 mutation. To do so we developed HLA-B2705, HLA-B0702 (control) and human Beta-2-microglobulin (hB2m) transgenic *Drosophila*.

Methods: Gateway Technology and UAS-Gal4 system was used for developing transgenic HLA-B/human hB2m *Drosophila*. *UAS-hB2m* transgene was inserted in long arm of chromosome 3 and *UAS-HLA-B2705* and *UAS-HLA-B0702* were alternatively inserted at another position in the short arm of the same chromosome. For each construct, various transgenic lines were obtained and crossed with several tissue specific driver strains, to induce the expression of the coding sequence for *HLA-B0702* and *hB2m* or *HLA-B2705* and *hB2m* placed under the control of UAS sequences.

Results: HLA-B2705/hB2m transgenes were first expressed in *Drosophila* by mean of vestigial-Ga4 driver line allowing to produce targeted protein in *Vestigial* domain (dorso-ventral frontier of the wing epithelia). We observed positive staining with HC10 antibodies (class I heavy chain) and W6/32 antibody (HLA-A, HLA-B and HLA-C conformation) for both tested HLA-B/hB2m but only HLA-B27/hB2m was labelled with ME1 (anti-HLA B/C) antibodies, suggesting a different conformation of HLA-

B27 and HLA-B7 with hB2m in the wing epithelia. Furthermore, by mean of the nubbin or engrailed drivers which drive the expression in a larger part of the wing, we observed specific loss of posterior cross-vein following HLA-B27/hB2m expression but not HLA-B7/hB2m.

Conclusion: We have established *Drosophila* lines allowing tissue specific expression of different HLA-B alleles. Our data suggest that the expression of HLA-B/hB2m transgenes in epithelial cells leads to a plasma membrane localization for HLA-B2705/hB2m but not for HLA-B0702/hB2m. Furthermore, we observed that tissue specific expression of HLA-B27/hB2m but not HLA-B7/hB2m induced specific loss of cross-vein suggesting it interferes with developmental pathways involved in differentiation. This is the first time that difference in localization between HLA-B2705, subtype associated with SpA, and HLA-B0702, which is not associated with the disease are reported. These results show that transgenic *Drosophila* might be a pertinent model to decipher molecular mechanisms involved in HLA-B27 trafficking and to better understand potential different behavior of HLA-B subtypes.

Disclosure: N. Jah, None; **B. Grandon**, None; **A. Rincheval-Arnold**, None; **I. Guénal**, None; **S. Gaumer**, None; **C. André**, None; **M. A. Breban**, None; **G. Chiocchia**, None.

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