

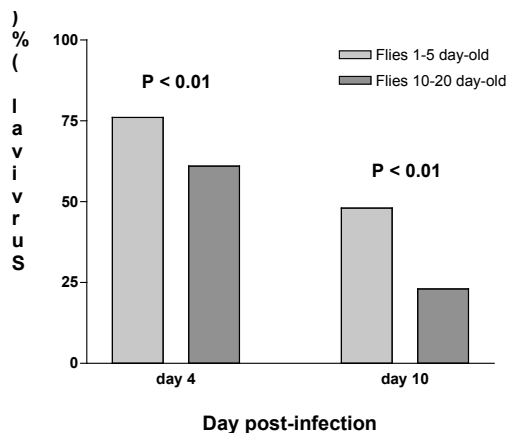
TOLL PATHWAY IN DROSOPHILA MELANOGASTER: A POSSIBLE ROLE TO STUDY THE IMPACT OF IMMUNE SENESCENCE IN POOR RESPONSES AGAINST ASPERGILLUS FUMIGATUS

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Purpose of the study: Invasive aspergillosis (IA) is a common cause of infectious death in heavily immunosuppressed patients. Among other well-known risk factors for poor outcome of IA (i.e. neutropenia, corticosteroid use), advanced patient age has also been associated with unfavorable outcome of this opportunistic mycosis (Peterson *et al*, *Infect Control*, 1983). The worse outcome of IA in older patients is multifactorial. Attenuated immune responses due to immune senescence could potentially play a role. Studies have suggested age-related deterioration in some aspects of innate immunity (Castle SC, *Clin Infect Dis*, 2000). Innate immunity pathways (e.g. *Toll* pathway) are conserved from non-vertebrates to humans and have been extensively studied in the *Drosophila* fruit fly during the past decade (Lemaitre *et al*, *Cell*, 1996; Hoffmann JA, *Nature*, 2003). We hypothesized that *Drosophila melanogaster* could be used as a model to study the potential role of aging on the efficiency of an immune response to *A. fumigatus*.

Summarized description of the project: We infected *Toll^{f-RXA}/Toll^{f632}* mutant *Drosophila* flies (Lionakis *et al*, *ICAAC*, 2003) with the *A. fumigatus* clinical isolate 293. For that, CO₂-anesthetized flies were rolled for 3 min onto YAG plates containing a fresh carpet of AF293 conidia and then transferred to vials containing regular fly food as described previously (Lemaitre *et al*, *PNAS*, 1997). We used flies aged 1-5 days old and 10-20 days old for the infection (the normal lifespan of *Drosophila* flies is 35-40 days). Flies were incubated at 29°C for 10 days and transferred to new vials every 2 days. Survival was assessed at day +4 and +10 post-infection.

Results: *Toll^{f-RXA}/Toll^{f632}* deficient flies aged 10-20 days old had significantly lower survival compared to *Toll^{f-RXA}/Toll^{f632}* mutants aged 1-5 days old [23% (65/277) versus 48% (122/251) at day 10 post-infection, $P < 0.01$]. Survival was also lower in older *Toll*-deficient flies at an earlier timepoint (day +4) of the infection [61% (170/277) versus 76% (192/251), $P < 0.01$] (Figure).



Conclusions: Innate immune response against *A. fumigatus* seems to deteriorate with increased age of flies in a *Toll*-deficient background. This phylogenetically reduced mini-host model could be helpful in increasing our understanding on the interaction between innate immunity and immune senescence. Further studies are needed to verify these preliminary results.