Complex signaling between blood and stem cells controls regeneration in fly gut

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Drosophila sp fly. Credit: Muhammad Mahdi Karim / Wikipedia. GNU Free Documentation License, Version 1.2

Having a healthy gut may well depend on maintaining a complex signaling dance between immune cells and the stem cells that line the intestine. Scientists at the Buck Institute are now reporting significant new insight into how these complex interactions control intestinal regeneration after a bacterial infection. It's a dance that ensures repair

after a challenge, but that also goes awry in aging fruit flies—the work thus offers important new clues into the potential causes of age-related human maladies, such as irritable bowel syndrome, leaky gut and colorectal cancer.

"We've dissected a very complex signaling interaction," said senior scientist and Buck faculty Heinrich Jasper, PhD. "By doing so temporally we've clearly established a role for the immune system both in initiating the regenerative process and in shutting it down - activities that are essential for maintaining tissue homeostasis."

Publishing in the May 25, advance online edition of *Nature Cell Biology*, researchers in the Jasper lab show that the macrophage-like hemocytes (which comprise the cellular immune system in flies) go to the intestines of *Drosophila* following damage. The hemocytes secrete the growth factor Dpp (a homologue of BMP, which has many functions, including the control of mobility, differentiation and invasiveness of normal cells), setting off the regenerative process by activating specific receptors in stem cells. In a fascinating twist, stem cells switch their response to Dpp in the middle of the regenerative response by turning on other Dpp-related receptors, which in turn instruct the stem cells to go back to a quiescent or quiet state. Jasper says it's a balancing act that both allows for healing and prevents excessive cell proliferation, which could lead to pre-cancerous dysplasia. "The temporal sequence of cell interactions during injury-induced regeneration is only beginning to be understood," said Jasper. "The proper timing of these interactions may be key in maintaining a healthy gut."

Jasper says aging makes it harder for the stem cells to switch gears between proliferation and quiescence and that flies suffer from age-related intestinal dysfunctions similar to those experienced by humans. Jasper says when the flies are young they are able to fend off infection and repair tissues, but that the cumulative effect of damage over a

lifetime takes a toll - signaling goes awry, and stem cells get chronically activated, causing inflammation and dysplasia, which makes the animal more prone to infection and dysfunction. "This is another classic example of 'what is good for us in youth, turns against us with age'," said Jasper. "When we think of interventions, we need to find the sweet spot. We want to promote stem cell repair and regeneration without having those responses become chronically activated."

"In this case we have established a role for macrophage - like cells in influencing tissue homeostasis both during infection and during the aging process," said Jasper. "Macrophages are clearly a target for a number of age-related disease - we need to understand their function better. This is an essential step in that process."

More information: Hemocytes control stem cell activity in the Drosophila intestine, *Nature Cell Biology*, DOI: 10.1038/ncb3174

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