Study shows dying cells impact on surroundings causing changes to tissue shape and structure

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(Phys.org)—A study conducted by researchers affiliated with three major institutions in France has found that dying cells appear to cause more changes to surrounding tissue than has been previously thought. In their paper published in the journal *Nature*, the team describes how their study of a fluorescent version of myosin undergoing cell death led to the discovery that as cells die, they undergo a process that is involved in epithelium folding. Claudia Vasquez and Adam Martin with MIT offer a News & Views perspective in the same journal issue on the work done by the team in France and offer more insight into the role that cell death plays in epithelial tissue structural changes.

For many years, biologists have assumed that when cells, die (apoptosis), they simple shrink, fall apart and disappear. Recent research has found that there is a lot more to the process, and it depends on where in the body it occurs. In epithelium cells for example (which make up epithelia tissue—the stuff that lines body cavities keeping them separate) researchers have found that dying cells maintain physical ties with still living cells, pulling on them, causing deformations. In this new effort the researchers sought to better understand this process by studying the leg joints of fruit flies still in their larval stage, which prior research has shown are impacted by apoptosis.

To better understand what impact apoptosis has on fruit fly development, the researchers caused some to be fluorescent, to make

them more easily seen. They found that protein accumulated on the polarized apical-basal axis part of the dying cells. They also noted that the dying cells pulled on nearby cells which caused levels of myosin in them to increase, which in turn caused them to constrict and then fold. The researchers found that in dying, myosin function in the cells was inhibited causing less buildup of myosin in the surrounding cells, which made them more vulnerable to the pulling that would follow. This all suggests that apoptosis, rather than existing as a mere byproduct of cells birthing and dying, is actually a vital part of fruit fly maturation. And that has implications for us humans—while it is clear that apoptosis is involved in tissue change, what is not, is just how big of a role it plays in tissue formation overall.

More information: Apico-basal forces exerted by apoptotic cells drive epithelium folding, *Nature* (2015) DOI: 10.1038/nature14152

Abstract

Epithelium folding is a basic morphogenetic event that is essential in transforming simple two-dimensional epithelial sheets into three-dimensional structures in both vertebrates and invertebrates1. Folding has been shown to rely on apical constriction. The resulting cell-shape changes depend either on adherens junction basal shift or on a redistribution of myosin II, which could be driven by mechanical signals. Yet the initial cellular mechanisms that trigger and coordinate cell remodelling remain largely unknown. Here we unravel the active role of apoptotic cells in initiating morphogenesis, thus revealing a novel mechanism of epithelium folding. We show that, in a live developing tissue, apoptotic cells exert a transient pulling force upon the apical surface of the epithelium through a highly dynamic apico-basal myosin II cable. The apoptotic cells then induce a non-autonomous increase in tissue tension together with cortical myosin II apical stabilization in the surrounding tissue, eventually resulting in epithelium folding. Together our results, supported by a theoretical biophysical three-dimensional

model, identify an apoptotic myosin-II-dependent signal as the initial signal leading to cell reorganization and tissue folding. This work further reveals that, far from being passively eliminated as generally assumed (for example, during digit individualization9), apoptotic cells actively influence their surroundings and trigger tissue remodelling through regulation of tissue tension.