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Review

Apoptotic forces in tissue morphogenesis

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ABSTRACT

It is now well established that apoptosis is induced in response to mechanical strain. Indeed, increasing compressive forces induces apoptosis in confined spheroids of tumour cells, whereas releasing stress reduces apoptosis in spheroids cultivated in free suspension (Cheng et al., 2009). Apoptosis can also be induced by applying a 100 to 250 MPa pressure, as shown in different cultured cells (for review, see (Frey et al., 2008)). During epithelium development, the pressure caused by a fast-growing clone can trigger apoptosis at the vicinity of the clone, mediating mechanical cell competition (Levayer et al., 2016).

While the effect of strain has long been known for its role in apoptosis induction, the reciprocal mechanism has only recently been highlighted. First demonstrated at the cellular level, the effect of an apoptotic cell on its direct neighbours has been analysed in different kinds of monolayer epithelium (Gu et al., 2011; Rosenblatt et al., 2001; Kuipers et al., 2014; Lubkov & Bar-Sagi, 2014). More recently, the concept of a broader impact of apoptotic cell behaviours on tissue mechanical strain has emerged from the characterisation of tissue remodelling during *Drosophila* development (Toyama et al., 2008; Monier et al., 2015). In the present review, we summarize our current knowledge on the mechanical impact of apoptosis during tissue remodelling.

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1. Apoptotic force

1.1. Apoptotic force at a local scale

At the cellular level, it was first described (in MDCK cells, chicken and zebrafish embryonic epithelia) that, on the one hand, an apoptotic cell reorganizes its cytoskeleton at the onset of apoptosis to form an intracellular acto-myosin ring (*i.e.* inner ring), and on the other, it sends a biochemical signal to its neighbours, through the sphingosine-1-phosphate pathway, for them to induce the formation of a supracellular acto-myosin cable around the dying cell (*i.e.* outer ring) (Gu et al., 2011; Rosenblatt et al., 2001). This signalling event has been well documented; conclusions supported the view that neighbouring cells were responsible for dying cell extrusion through the generation of the outer supracellular ring of acto-myosin, whereas the dying cell merely provided a biochemical signal for its neighbours without playing a

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mechanical role in its own extrusion (Gu et al., 2011; Rosenblatt et al., 2001) (Fig. 1A). However, a more recent study has shown that, at least in the MDCK model, the removal of dying cells is a multistep process involving distinct actomyosin pools, where the inner ring created in the apoptotic cell and detected before the outer ring is responsible for the apoptotic cell's apical constriction (Kuipers et al., 2014). In summary, dying cell extrusion includes two steps, i) apical constriction which depends on the inner apoptotic acto-myosin ring, ii) extrusion *per se* which depends on the outer acto-myosin ring created by apoptotic cell neighbours in response to an apoptotic biochemical signal. Interestingly, the reorganisation of apoptotic cell neighbours into a rosette is observed at the end of apical constriction, indicating that the force generated by the apoptotic cell is most probably responsible for this apical reorganisation. Consistently, apoptotic cells keep strong adhesion with their neighbours until the completion of cell extrusion (Lubkov and Bar-Sagi, 2014). A recent report suggests that junctional cortex supports actin architectural reorganisation and contractility around the apoptotic cell; cell-cell adhesion allows the recruitment of Coronin 1B, the subsequent organization of F-actin in bundles and Myosin II in aligned minifilaments. This creates efficient contractility at the interface between apoptotic cells and their neighbours (Michael et al., 2016). This way, E-cadherin adhesion would play an important role at the apoptotic/neighbour interface by transmitting contractile stress from the apoptotic cell, thus inducing a mechano-sensitive response in neighbours. Altogether, these recent results highlight the reciprocal mechanical influence between apoptotic cells and their neighbours.

1.2. Apoptotic forces at the tissue scale

The above results considered the influence of apoptosis at a very local scale, focusing on the apoptotic cell and its direct neighbours. However, the notion of force transmission from the apoptotic cell to the surrounding tissue, affecting living cells at a broader scale, was revealed more recently studying two different morphogenetic processes taking place during Drosophila development: dorsal closure in the embryo and fold formation in the developing leg (Toyama et al., 2008; Monier et al., 2015).

Dorsal closure is a robust morphogenetic process taking place at the end of *Drosophila* embryogenesis, which corresponds to the migration of two lateral epithelial cell sheets that progressively cover an eye-shaped opening transiently occupied by the amnioserosa, an extra-embryonic tissue. The first row of epithelial migrating cells, or leading edge, form an acto-myosin cable also called the purse-string, which generates one of the driving forces of dorsal closure. Another driving force comes from the amnioserosa (Kiehart et al., 2000).

Although apoptosis has long been known as taking place during dorsal closure (Abrams et al., 1993), it is only recently that its role in this phenomenon has been described. The apoptotic pattern during dorsal closure was initially described by Reed and colleagues (Reed et al., 2004). During dorsal closure, close apposition of yolk sac and amnioserosa is thought to prevent premature anoikis, a particular form of apoptosis induced by loss of adhesion. Then, at the end of dorsal closure, this contact is lost and the whole amnioserosa degenerates through developmentally programmed anoikis (Reed et al., 2004). More recently, it was shown that a subset of amnioserosa cells undergo apoptosis earlier than initially thought (Toyama, 2008). Indeed, they contract their apical surface, extrude, bleb and fragment during the migration of the lateral epithelium (Toyama et al., 2008; Sokolow et al., 2012). In parallel to the extrusion of apoptotic cells, the direct neighbours are distorted and adopt a “rosette” geometry. Rosettes are the consequence of the elongation of neighbouring cells towards the delaminating apoptotic cell, as is the case in monolayer epithelia in culture (Rosenblatt, 2001; Lubkov and Bar-Sagi, 2014). Although the respective contribution of apoptotic cells and neighbouring cells in these morphological changes has yet to be determined, it was proposed that both contribute to this cellular remodelling (Fig. 1B). It was further

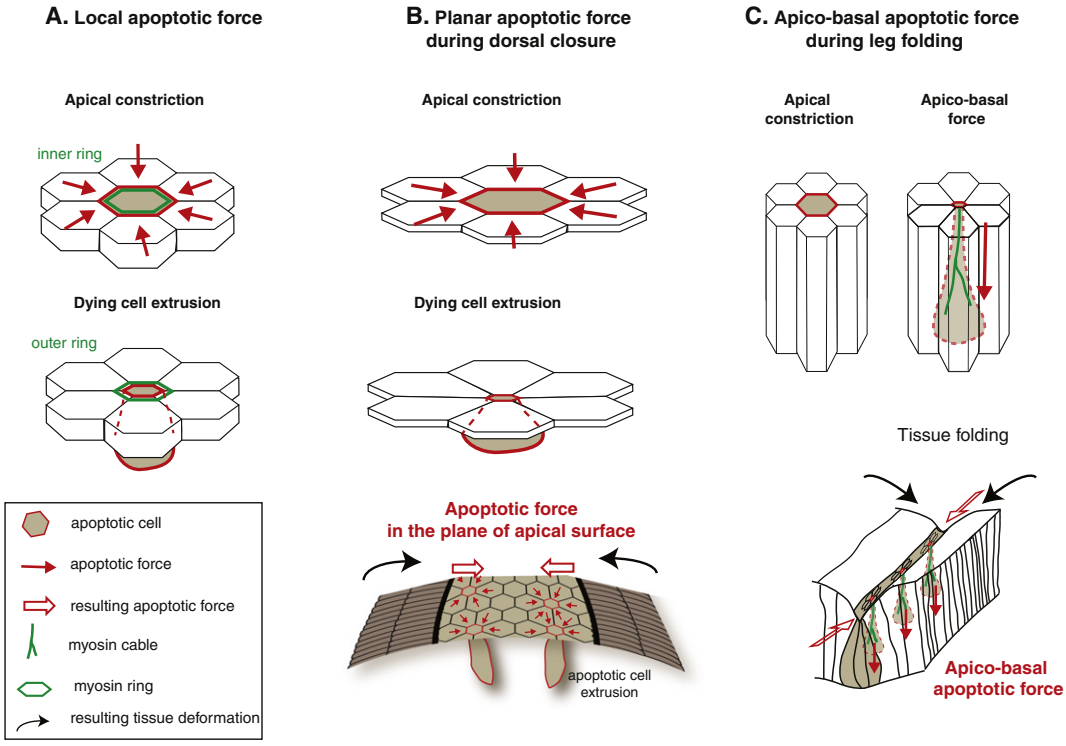

Fig. 1. Apoptotic force at cellular and tissue scale. (A) Apoptotic forces exerted at the cellular level, inner ring responsible for apical constriction and outer ring for cell extrusion. (B) Planar apoptotic force exerted during dorsal closure (force in the plane of apical surface). (C) Apico-basal force exerted by apoptotic cells during leg folding. (B, —C) Upper panels shows the cellular reorganisation during apical constriction and cell extrusion, lower panel shows the resulting apoptotic force (open red arrows) and tissue movement (black arrows).