Journal of
Tissue Science & Engineering

Xiao and Tsutsui, J Tissue Sci Eng 2013, 4:1
DOI: 10.4172/2157-7552.1000e122

Editorial Open Access

# Cell Death and Cavitation: The Beginning of Organogenesis

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During embryonic development, cell death and the control of cell survival play major roles for the formation of various organs. In the solid embryonic structures, such as morula and primordiums, starvation and hypoxia cause central cell death [1]. Dying cells express the "eat-me" signal and are cleaned up by the neighbor cells through autophagy [2,3]. As a result, a lumen or cavity was created that also named cavitation or lumenation. The lumens or caves not only bring nutrition and oxygen for the surviving cells, but also deliver signals for differentiation. Under appropriate conditions created by the cavitation, the surviving cells differentiated into functional mature cells and then form tissues and organs [4-7] (Figure 1).

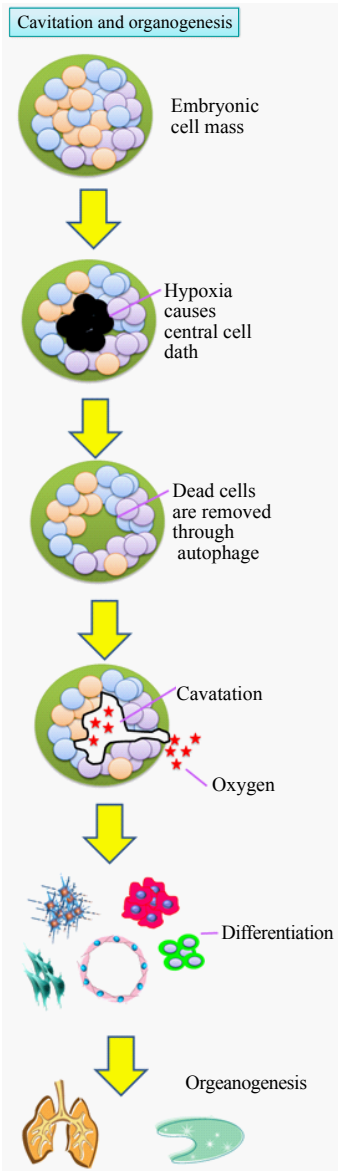


**Figure 1:** Cavitation and hollow organ formation.

For tissue engineering of hollow organs, such as lungs, kidneys and intestines, it is important to represent the above-mentioned process. Embryonic stem (ES) cells and induced pluripotent stem (iPS) cells have been wildly used to study cavitation and embryonic development due to their ability to forming embryoid bodies (EBs). Early in 1977, Martin et al. [4] described how to producing and culturing EBs to study embyogenesis. In 1999, Coucouvanis and Martin [8] reported that EBs *in vitro* could represent the process of cavitation, and signaling for death and survival is the underline mechanism. In 2007, Qu et al. [2] demonstrated that autophagy plays an important role in embryonic cavitation. Embryoid bodies (EBs) derived from cells lacking the autophagy genes fail to cavitation. A recent study showed that after straightly controlled the process of differentiation, human iPS cell-derived EBs were differentiated into intestinal tissue *in vitro* [9]. However, it remains a major challenge to represent the formation of more complicated organs, such as lung and kidney *in vitro*. To achieve the *in vitro* organogenesis of lung and kidney, three factors are considered the main stratagem. 1) Cell source. For the *in vitro* organogenesis, cells must have the ability to form EBs which offers the potential to differentiate into functional mature cells. ES and iPS cells are good cell source for so as we described before. However, because different cell lines of ES and iPS cells show different characters, to find the right one it needs carefully screen. 2) Three-dimensional culture systems which have the hypoxia microenvironment that can cause cell death and induce cavitation. Three-dimensional culture systems, such as spheroid represents a unique opportunity to reflect *in vivo* situations of organogenesis. For example, cancer cell- derived spheroid models not only displayed *in vivo* anti-tumor drug responses but also exhibited numerous pathophysiological features of tumor formation [10-12]. Culture scaffold, such as collagen gel, matrigel, hydrogel and so on also provide 3D environment *in vitro* therefor can be used for the *in vitro* culture. 2) Appropriate molecules stimulation. To drive the surviving cells towards functional mature cells, molecules for cavitation, such as BMPs, Bnip3 and AIF; and molecules for differentiation are necessary. 3) Supply of nutrition and neural stimulation. As the *in vivo* organs all have the network of blood vessel and neuron, the *in vitro* culture system must also offer the similar networks which requires co-culture with endothelial or neural progenitors.

Representing the *in vivo* cavitation and organogenesis is not easy, with the bioengineering technic and the new findings for embyogenesis and development, it would not be far.

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**Received** April 26, 2013; **Accepted** April 27, 2013; **Published** April 30, 2013

**Citation:** Xiao L, Tsutsui T (2013) Cell Death and Cavitation: The Beginning of Organogenesis. J Tissue Sci Eng 4: e122. doi:10.4172/2157-7552.1000e122

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