Selecting for fitness in mammalian development

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Ensuring that mutations are not propagated within stem cell populations is key to proper development and homeostasis. This is especially relevant when it comes to pluripotent cells that can give rise to all lineages, including the germ line. During early mammalian embryo development, cells in the epiblast need to be maintained in a pluripotent state for a considerable period of time. During this period, this stem cell compartment is significantly expanded, providing the potential for the propagation of genetic and epigenetic errors. Interestingly, in the mouse embryo apoptosis peaks during this period of epiblast proliferation, suggesting that embryonic fitness may be actively monitored at this stage of development. We have now shown that cell competition plays such a role during early mammalian development.

Cell competition is a type of cell–cell interaction where the coexistence of 2 cell populations with different metabolic properties or growth rates results in the growth of the stronger population at the expense of the weaker one. Although primarily studied in Drosophila, increasing amounts of evidence suggest it is a process that is conserved in a wide variety of species. By allowing the recognition and elimination of abnormal cells, cell competition provides a mechanism that would control cellular fitness in a wide variety of settings, including stem cell maintenance, organ size control, or tissue homeostasis.

A key trigger of cell competition in Drosophila is the loss of Dpp/BMP signaling. In the early mammalian embryo, BMP signaling is required to sustain epiblast pluripotency. However, cells with impaired activation of the BMP pathway can be maintained in the pluripotent state and contribute to the 3 embryonic germ layers, indicating that the requirements for BMP signaling are likely to be cell non-autonomous. An interesting twist to this observation comes from the analysis of mosaic embryos composed of BMP-deficient and wild-type cells. This revealed that, although a proportion of defective cells are viable, a significant number of these cells are eliminated when surrounded by wild-type cells, suggesting they are out-competed by their neighbors. By using an in vitro co-culture system where BMP-deficient embryonic stem cells (ESCs) are cultured with control cells, we proved that defective ESCs are specifically eliminated at the epiblast stage only when in the presence of wild-type cells. Importantly, this out-competition is not restricted to cells with low BMP signaling, as autophagy-deficient and tetraploid cells are also eliminated in a similar manner. Concurrent with the elimination of defective cells, wild-type cells undergo compensatory proliferation, thereby ensuring homeostasis of the overall cell population. Cell competition thus seems to act as a general cell non-autonomous surveillance mechanism operating in the epiblast at the exit of the pluripotent stage.

But what determines the elimination of defective cells? The MYC family of transcription factors is involved in a variety of biological processes, and in Drosophila, d-Myc has been shown to be a key mediator of cell competition. We observed that when wild-type and defective cells are co-cultured, differential c-Myc protein levels are specifically established between the 2 competing populations, leading to the elimination of the cells with lower c-Myc expression. Furthermore, we and others have shown that in the embryonic epiblast, c-Myc levels are intrinsically heterogeneous, that naturally dying cells preferentially show low levels of c-Myc expression, and that c-Myc overexpression is sufficient to trigger the elimination of wild-type cells. These observations suggest that the elimination of defective epiblast cells follows sequential steps. First, an initial recognition of relative fitness must occur leading to the establishment of differential c-Myc levels. Subsequently, these c-Myc levels must be monitored leading to the apoptotic elimination of those cells with lower c-Myc (Fig. 1).

However, many exciting questions remain to be answered. In the first place, it is essential to understand what does cellular fitness imply. Is it a measure of the growth rate, metabolic rate, or signaling ability of the cells? Then it will be important to tease out how the relative stem cell fitness is sensed and transduced into relative c-Myc levels. A feature that may help to uncover both these questions is to understand why this fitness selection occurs specifically at the epiblast stage and not earlier. Important changes at the level of gene expression, epigenetic signature, and metabolism take place during the first steps of embryonic differentiation, and it will be important to determine how these changes differentially determine cell survival. In the same way, uncovering if similar surveillance mechanisms may become active at other critical steps of embryonic development, namely during the formation of major organs, or even during tissue regeneration in the adult, will be of particular relevance to be able to use what we learn from cell competition in regenerative medicine.

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Figure 1. In the early post-implantation embryo, cell competition involves an initial recognition of relative fitness levels, leading to the establishment of differential c-Myc expression. Subsequent monitoring of these relative c-Myc levels leads to the apoptotic elimination of the cells with lower c-Myc and the compensatory proliferation of those cells with higher c-Myc.

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