Seminars in Cell & Developmental Biology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Reflections on cell competition
Growth, proliferation, morphogens and apoptosis

Ludovic Baillon, Konrad Basler*

Institute of Molecular Life Sciences, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland

ARTICLE INFO

Article history:
Available online xxx

Keywords:
Cancer
Growth
Proliferation
Decapentaplegic
P35
DIAP1

ABSTRACT

Cell competition is a process by which otherwise viable cells are actively eliminated due to the presence of more competitive cells. It is a conserved phenomenon and occurs in various developmental and experimental contexts. Competitive elimination represents a safeguard mechanism that potentiates animal development. However, the process can also be hijacked, for example, by cancer cells to promote and sustain malignancy. One of the challenges facing the field is that the term 'cell competition' is used to describe a variety of phenomena whose relatedness is under debate. The goals of this review are to provide an overview of the literature on cell competition-like phenomena, highlight where there are discrepancies, and, when possible, provide alternative interpretations to reconcile the dissonance. Central to this is a comparison of the various models of cell competition. With our critical examination we seek to draw attention to future prospects in the field of cell competition. We believe that the elucidation of the interplay between loser and winner cells in the process of cell competition will provide new targets for the development of cancer therapeutics.

Contents

* Corresponding author. Tel.: +41 44 635 31 11.
E-mail address: konrad.basler@imls.uzh.ch (K. Basler).

http://dx.doi.org/10.1016/j.semcdb.2014.04.034
1084-9521/

Please cite this article in press as: Baillon L, Basler K. Reflections on cell competition. Growth, proliferation, morphogens and apoptosis. Semin Cell Dev Biol (2014), http://dx.doi.org/10.1016/j.semcdb.2014.04.034

1. Introduction

Just over ten years ago Decapentaplegic (Dpp) signaling was linked to the out-competition of *Minute* cells and renewed interest in the phenomenon of cell competition [1]. We are taking the opportunity of this issue of "Seminars in Cell and Developmental Biology" to review some of the past and present work done on the topic of cell competition. This intriguing mechanism was first discovered in *Drosophila melanogaster* imaginal discs nearly 40 years ago [2]. More recently it has also been observed in mammalian systems [3,4], and its potential implication in cancer development makes it a prime topic for further research.

Drosophila imaginal discs are the progenitors of most of the adult external structures with the exception of the abdominal epidermis [5]. In imaginal discs the elimination of one cell type ("loser cells") can occur in the presence of another cell type ("winner cells"), hence the name "cell competition" [2]. The loser cells in this archetype case were heterozygous for a mutant copy of a ribosomal protein gene, a so-called *Minute* mutant [2]. *Minute* cells are viable in a homotypic environment and are compatible with the development of a normally sized adult [6]. However, in a heterotypic environment the presence of non-*Minute* cells (i.e. wild-type cells) results in their loss. From this seminal study the core principle of cell competition emerged: the elimination is non-cell-autonomous.

In addition to its safeguard function (i.e. elimination of mutant cells) during development, a competitive interaction could promote the expansion of tumorous cells at the interphase with the wild-type tissue [7–12]. Cell competition therefore represents a promising target for future cancer therapeutics. However, more research is needed to gain a deeper understanding of the principles of cell competition and its core components.

The field of cell competition is challenging and therefore slowly progressing. Many answers still lag far behind the expectations of the research community. This discrepancy is also illustrated by the relative low number of "experimental" publications compared to the numerous reviews written on this topic. Though we present yet another review on this subject, we hope to be able to critically examine and compare the various contributions made in the field.

2. Classification of competitive interactions

Cell competition is being investigated with various experimental setups. An accurate classification of these different scenarios will help to compare and contrast the results. Cell competition can be described as the elimination of cells that are principally viable on their own, but are actively eliminated when intermingled with more competitive cells.

We will use the term "cell competition" as a generic term that includes all types of competitive interactions. Cell competition in this broad sense includes at least three types of competitive interactions: canonical competition, super-competition, and endogenous competition (see Section 2.1). The difference between these three types of competitions resides in the characteristics of the cells that are in competition.

2.1. Canonical competition, super-competition and endogenous competition

2.1.1. Canonical competition

In canonical competition wild-type cells outcompete mutant cells that have lost the ability to successfully compete with wild-type cells. The causative genetic modification can either be an inactivating mutation affecting, for instance, a *Minute* gene [2] or an activating mutation (e.g. leading to overexpression) that increases the function of a loser-specific determinant like *flower*^{lose} isoforms [13] (see Section 5.3).

2.1.2. Super-competition

Super-competitors are genetically altered cells that have acquired the ability to outcompete wild-type cells [7–12]. The genetic alteration, which makes these cells superior in a mosaic tissue, could either be an inactivating mutation affecting a growth-suppressor gene such as the gene *warts* [10] or an activating mutation in a growth-promoting gene, for example one that increases the activity of *dmyc* [8,9].

2.1.3. Endogenous competition

Endogenous competition has recently been described to take place within the mouse epiblast where cells naturally express variable levels of Myc [4]. The epiblast consists of pluripotent cells from which all three germ layers are derived: ectoderm, mesoderm and endoderm. In this embryonic tissue endogenous competition selects for epiblast cells with the highest levels of Myc and consequently the epiblast population is enriched for cells that have the highest growth potential. Note, to our knowledge this is the first example of non-experimentally induced cell competition among cells within a tissue.

In these three types of competition the exact nature of the stress experienced by the loser cells is still unknown. However a distinction can be drawn with respect to the origin of the stress experienced by the loser cells. In canonical competition one would assume that the stress originates cell-autonomously since these cells harbor a mutation. However, in super-competition loser cells are wild-type, therefore the stress these cells undergo originates non-cell-autonomously from the neighbors. Endogenous competition is not experimentally induced, which makes it difficult to unambiguously attribute the origin of the stress. It could lie within the continuum between canonical competition and super-competition. However, in all three cases, irrespectively of the origin of the stress, the elimination is triggered non-cell-autonomously.

2.2. Loser clones and winner clones

Various research groups have approached cell competition from different angles using different systems (see Sections 2.1–2.3). These different systems have their own specificity and sensitivity to experimental modifications (see below and Sections 3.3, 4.3, 4.4, 5.1 and 6.1). Therefore the conclusions reached with one system may not necessarily apply to the others and much consideration should be taken before drawing general conclusions.

Please cite this article in press as: Baillon L, Basler K. Reflections on cell competition. Growth, proliferation, morphogens and apoptosis. Semin Cell Dev Biol (2014), http://dx.doi.org/10.1016/j.semcdb.2014.04.034