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Reprogramming to developmental plasticity in cancer stem cells

Caitlin O'Brien-Ball, Adrian Biddle*

Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, UK

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ABSTRACT

During development and throughout adult life, sub-populations of cells exist that exhibit phenotypic plasticity – the ability to differentiate into multiple lineages. This behaviour is important in embryogenesis, is exhibited in a more limited context by adult stem cells, and can be re-activated in cancer cells to drive important processes underlying tumour progression. A well-studied mechanism of phenotypic plasticity is the epithelial-to-mesenchymal transition (EMT), a process which has been observed in both normal and cancerous cells. The epigenetic and metabolic modifications necessary to facilitate phenotypic plasticity are first seen in development and can be re-activated both in normal regeneration and in cancer. In cancer, the re-activation of these mechanisms enables tumour cells to acquire a cancer stem cell (CSC) phenotype with enhanced ability to survive in hostile environments, resist therapeutic interventions, and undergo metastasis. However, recent research has suggested that plasticity may also expose weaknesses in cancer cells that could be exploited for future therapeutic development. More research is needed to identify developmental mechanisms that are active in cancer, so that these may be targeted to reduce tumour growth and metastasis and overcome therapeutic resistance.

1. Introduction

As tumours grow, they evolve through selection to adapt to their environment. Traditionally, this has been viewed as depending on genetic evolution (Greaves, 2015), but the role of phenotypic plasticity in driving tumour adaptation is increasingly recognised. The term 'phenotypic plasticity' describes the ability of cells to differentiate into multiple lineages, otherwise known as multipotency. In cancer, this ability is re-acquired by lineage restricted cells through reprogramming of their epigenetic state. This reprogramming may involve re-activation of developmental programs that can drive tumour adaptation, which will be the focus of this review. The precise molecular modifications underlying the epigenetic changes that enable re-acquisition of multipotency are reviewed elsewhere (Easwaran et al., 2014). Recent work has shed light on the relative contributions to tumour development of genetic selection *versus* phenotypic plasticity (Sottoriva et al., 2015; Williams et al., 2016). These studies demonstrated that, whilst some tumours are heavily dependent on genetic evolution, others undergo no further genetic selection after the early tumour-initiating mutational events and any further adaptation must occur through phenotypic plasticity. Reprogramming to plasticity by tumour-initiating mutations, and consequent reactivation of developmental programs, thus represents a potent mechanism whereby tumours may reversibly adapt to different environmental challenges in the absence of genetic evolution (Fig. 1).

The idea of phenotypic plasticity in cancer is now relatively well established, although the exact mechanisms behind this behaviour are still not well understood. It is believed that some cancerous cells undergo epigenetic reprogramming to induce metabolic and phenotypic changes which are often linked to behaviours giving the tumour the ability to become more invasive and resistant to treatment (Biddle and Mackenzie, 2012; Gupta et al., 2009; Lee et al., 2016), as well as increasing their lineage potential – the number of possible phenotypes that could arise from a cell. This behaviour is often described as phenotypic plasticity; the ability of a cell to change its phenotype, and in some cases do this multiple times (Biddle et al., 2011; Roesch et al., 2010). A well-studied example of plasticity is the ability to undergo epithelial-to-mesenchymal transition (EMT), a process normally seen in the developing embryo, where cells in a tumour of epithelial origin acquire the ability to express markers and behaviours associated with mesenchymal cells, becoming more invasive and less polarised (Hay, 2005; Yang et al., 2008).

There is significant evidence for the model of a cancerous tumour consisting of a heterogeneous population of different cell types (Fisher et al., 2013; Heppner, 1984). A particular subset of cells, the cancer stem cells (CSCs), has the ability to divide symmetrically and asymmetrically in order to initiate and maintain tumour growth (Dalerba et al., 2007), and is a source of phenotypic plasticity in the tumour (Lee et al., 2016). Within this loose definition of a CSC, cells that have undergone

* Correspondence to: Centre for Cell Biology and Cutaneous Research, Blizard Institute, 4 Newark Street, London E1 2AT, UK.
E-mail address: a.biddle@qmul.ac.uk (A. Biddle).

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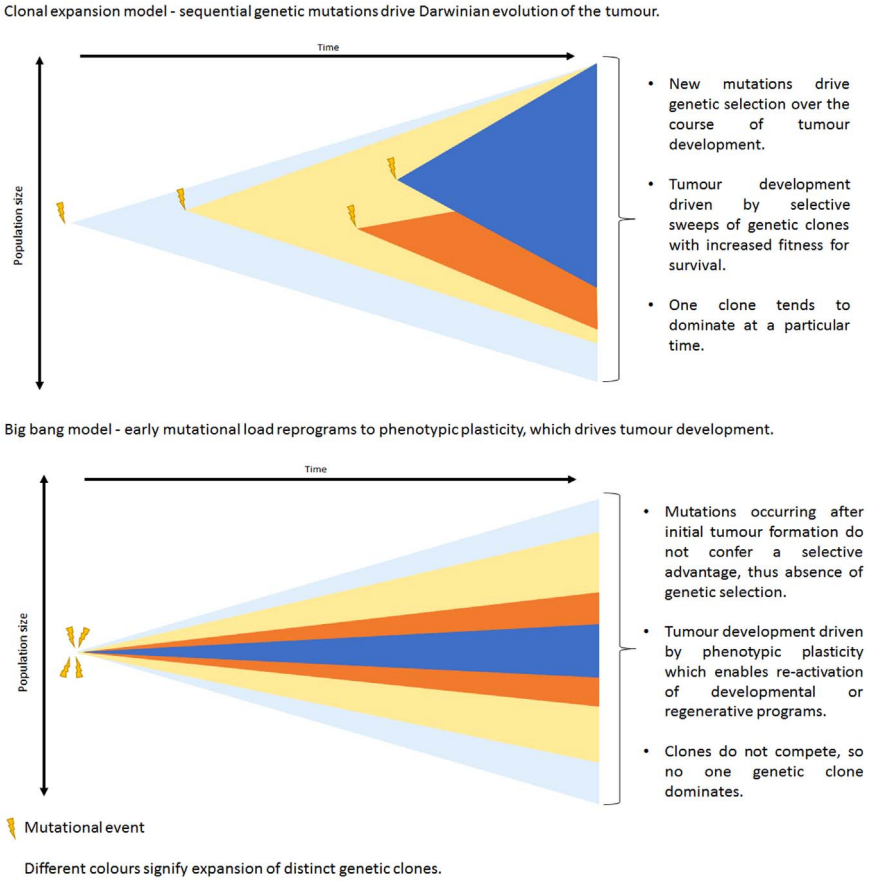

Fig. 1. Two different models for genetic *versus* epigenetic contributions to tumour progression (Sottoriva et al., 2015).

EMT have received particular attention owing to their therapeutic resistance (Gupta et al., 2009) and their ability to survive in a hostile environment to more efficiently seed tumours in immunocompetent mouse models (Gjerdrum et al., 2010). However, it is clear that stem cell characteristics such as self-renewal, phenotypic plasticity and tumour-initiating potential are also shared (if to a lesser degree) by epithelial tumour cell sub-populations that have not undergone EMT (Biddle et al., 2011). The phenotypic plasticity of both EMT and epithelial sub-populations enables regeneration of each by the other, as has been seen in the spontaneous production of EMT cells by isolated epithelial sub-populations from mammary tumours (Chaffer et al., 2011). This is sometimes referred to as 'de-differentiation', although it is unlikely to involve terminally differentiated cells re-acquiring a stem cell state. Instead, it is more likely the case that partially-differentiated sub-populations retaining some degree of stem cell characteristics can act to regenerate more undifferentiated stem cell sub-populations. Even within single genetic clones, CSCs diverge on an epigenetic and phenotypic level, leading to multiple phenotypic sub-populations within a single tumour (Biddle et al., 2011; Hermann et al., 2007; Kreso et al., 2013).

Plastic CSCs may play an important role in tumour progression and therapeutic resistance, as they have an increased ability to adapt to challenges presented by drug therapy, and the tumour microenvironment (*e.g.* hypoxia) (Biddle et al., 2016; Gammon et al., 2013; Kreso et al., 2013). Plasticity may also enable resistance to stresses encountered during metastasis, including detachment from the ECM and increased oxidative stress (Piskounova et al., 2015). Once at a metastatic site, plasticity enables restoration of the cellular heterogeneity characteristic of the primary tumour (Thiery, 2002). Therefore, plastic CSCs have become an attractive target for cancer therapy (Biddle et al., 2016) and for assessment of patient prognosis (Lee et al., 2016).

Phenotypic plasticity is essential for successful human development, so perhaps it is not surprising that cancer cells hijack these mechanisms to drive their own development. Developing embryos rely on the ability of cells to change phenotype and alter their epigenetic state. Many crucial processes in development require these behaviours; for example in neural tube formation (Green et al., 2015). There is also some continuing limited phenotypic plasticity in adult human tissues. In many adult tissues, there exists a population of stem cells whose purpose is to steadily replicate and produce the differentiated cells required in that particular tissue (Lei et al., 2014) whilst retaining some limited regenerative capacity. This has been observed in the intestinal epithelium (Buczacki et al., 2013), skeletal muscle (Moss and Leblond, 1970) and breast tissue (Shackleton et al., 2006) to name a few examples. Although mammals are not capable of the extraordinary regenerative ability of organisms such as salamanders and hydra, they do have the ability to regenerate some tissues when damage occurs, for example in the liver, where stem cell-mediated regeneration can occur depending on severity of injury (Riehle et al., 2011). Some specialised mammalian cells do however have the ability to reprogram their epigenetics with the goal of returning to a totipotent state – these are the gametocytes. The global epigenetic landscape is considerably altered in these specialised cells so that the resulting fertilised egg can go on to generate an entire organism (Cantone and Fisher, 2013; Teperek et al., 2016).

2. Phenotypic plasticity and lineage potential

2.1. Plasticity in development

During development, the single fertilised egg from which the embryo will form is said to be totipotent – able to produce any cell type, both embryonic and extra-embryonic (Morgani and Brickman, 2014). As embryogenesis progresses, the zygote develops into a