

## Chapter 2

# Proliferation and Regeneration: Methodologies in Cancer Treatment and Post-Treatment Tissue Reconstruction

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### ABSTRACT

*There is an increasing tendency to use stem cells as potential therapeutics in various human diseases. This is a rapidly progressing field, believed to change the face of treatment and healing in the majority of human diseases. However, basic knowledge concerning the biology of stem cells and their use in various treatment protocols is inadequate, and there is still much to be learned. One of the “hot-spots” of stem cell research is their use in cancer treatment and post-treatment reconstruction. This chapter focuses on describing the main progress in the field of regenerative methods as far as cancer treatment is concerned. In addition, it reviews the up-to-date knowledge on the field of post-therapy reconstruction. Finally, the chapter mentions some aspects of proliferation and tries to give insight to the separation between proliferating tumor cells from proliferating stem cells.*

### INTRODUCTION

The key to develop novel and effective therapies goes through the understanding of cell growth mechanics and proliferation (Oviedo & Beane, 2009). On one hand, regeneration can be con-

sidered as the leading effect of cancer whether this is the “*aetion*” (cause) (Gr. *Αίτιον*) or the “*aetiaton*” (causative) (Gr. *Αιτιατόν*) remains to be elucidated. From the beginning of the century there was a connection established between tumor growth and embryological cell growth. This was

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first reported by Waddington where he mentioned and linked regeneration mechanisms as possible oncogenic mechanisms (Waddington, 1935). As he stated “...*the individuation field, then, is the agent which controls the growth of the different parts in a harmonious way so that a normal individual is formed. In later life, the individuation field splits up into smaller separate fields, such as leg fields, head fields, etc. These are the agents from whom cancerous growth has escaped...*” His work has been neglected in general in the literature as it states that uncontrolled growth could be linked to controlled developmental growth (Slack, 2002). In addition, it has been evident from the beginning of the century that proliferation and regeneration were two different things. This process, as it was observed in the embryogenesis of lower species, derived from experimental results of transplantation in frog embryos (Needham, 1936). Another aspect of regeneration, which involves pre-existing tissue remodelling, was also noticed from the beginning of the 20<sup>th</sup> century by Morgan, which was termed morphalaxis (Morgan, 1901).

This could indeed be true if we consider the following aspects: tumor growth occurs when normal differentiated cells transform and start to proliferate uncontrollably. Or maybe not? It appeared that not only somatic cells can differentiate, but also the adult stem cells can perform the same functions and become oncogenic.

In this process, we could separate the following terms: cancer ontogenesis, cancer progression and proliferation, tissue regeneration and cell proliferation, tumor regeneration. In the beginning, there is the event of a normal cell being transformed to a tumor cell. This cell could be a somatic cell or an adult stem cell, which could also be the later Cancer Stem Cell (CSC). After the tumor cell or cells emerge, then the proliferation steps start. At some point comes diagnosis of the tumor and the next step is therapeutic intervention. After therapy, there is in most cases a need for tissue reconstruction, which can occur probably only through the involvement of new stem cells that possess the ability to recognize the site of defect,

locate it and start the reconstruction. In general, a regenerative event always seeks to maintain or re-establish form and function, a process called morphostasis. Yet, at this point problems begin as regeneration is linked to cancer related cellular anomalies (Pellettieri, et al., 2010; Beachy, et al., 2004; Gurtner, et al., 2008; Schafer & Werner, 2008).

Further on, a contradictory topic concerns the fact that regeneration involves the emergence of abnormal growth, therefore, tumor growth. On this topic, two hypotheses were formulated: the regeneration process may bring invoke from an impaired or incomplete regenerative-proliferative process and the regeneration process itself may bring under control the autonomous growth of tumor cells. Probably the most difficult question to answer is which the etiology for tumorigenesis is. The problem is that tumor emergence differs from tumor to tumor. Epithelial tumors probably have different mechanisms of progression and ontogenesis than other tumor types.

Tumors have been considered as wounds that never heal. The connections between cancer, inflammation, and local tissue repair have been reported extensively. This is a very interesting topic, which brings about the fact that the different phenotypes of cellular pathology could probably emerge from similar gene regulatory mechanics.

## **TUMOR ONTOGENESIS**

The first consideration of cancer proliferation would come from the question on how a tumor develops. It is the hardest question to answer, since the reasons, on why tumors emerge are immensely diverse. Hence, tumorigenesis is the interconnection of thousands of factors acting simultaneously that brings about the malignant phenotype. Those factors focus mainly on genetic defects that take place during the influence of environmental factors. Yet, genetic factors are not the sole etiologies of tumorigenesis. Epigenetic alterations can also be held responsible for carcinogenesis. However,

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