Prostate (Cancer) Stem Cells

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Summary

The prostate stem cell concept described in this chapter was studied in our laboratory, where we provided experimental immunophenotypic evidence of the presence of keratin, androgen receptor, neuroendocrine markers, and c-Met protooncogene in unique populations of normal developing and malignant human prostate epithelial cells. The characteristic responses of these stem cells to growth factors and neoadjuvant hormonal therapy supported the cancer stem cell concept, and, if successfully applied to human prostate cancer specimens, could reveal new therapeutic targets.

Key Words: Androgen receptor; cancer stem cells; c-Met protooncogene; hepatocyte growth factor/scatter factor; HGF/SF; immunophenotype; keratin 14, 5, and 18; neuroendocrine factors; primary; recurrent and metastatic prostate cancer; serotonin and chromogranin A.

1. INTRODUCTION

Solid tumors are heterogeneous, typically containing varied populations of cells that differ in the specific proteins or phenotypic markers they express. The cancer stem cell (CSC) hypothesis suggests that neoplastic clones are maintained exclusively by a rare fraction of cells with stem cell properties (1,2). As early as in 1976, Fialkow (3–5) identified the CSC for chronic myelocytic leukemia, and further evidence was obtained independently by others (5). For leukemia, the CSC hypothesis is now generally accepted (6). For solid tumors in general, significant progress has been made in recent years. A candidate CSC population was identified in breast cancer (7–9). For brain tumor, initiating cells were isolated and characterized (10,11). Singh and colleagues (11) described how they isolated a minority population of human brain cancer cells based on the expression of a cell surface marker called CD133. They report that, when injected into the brains of mice, this subpopulation of CD133+ cells could, by itself, drive tumor growth and dissemination. As few as 100 of the CD133+ cells formed tumors that could be serially transmitted from mouse to mouse, whereas tens of thousands of cancer cells lacking CD133 failed to do so. When tumors that arose from the injected CD133+ cells were examined, the cellular heterogeneity and architecture closely resembled that of the human tumors from which the cells had originally been taken.

In the normal brain, neuronal stem cells as well as early progenitor cells, but not their fully mature progeny, express the CD133 marker. In the brain tumors examined, Singh et al. (11) found distinct subpopulations of cells that expressed either CD133 or various markers of mature brain cells. Thus, the cellular architecture of the brain tumors may be a caricature of that of the normal brain, with brain CSCs, probably derived from normal CD133+ stem or progenitor cells, giving rise to aberrantly differentiated progeny.

Stem cells have two unique properties that make it likely that they are involved in cancer development. First, they are often the only long-lived cells that have the ability to replicate in a tissue. Mul-
tiple mutations, occurring over many years, are necessary before a cell becomes cancerous. Thus, the implication is that cancer-inducing mutations accumulate in the long-lived, normal stem cells. Second, through a process called self-renewal, stem cells generate new stem cells with similar proliferation and differentiation capacities as their parental cell. By contrast, with each round of replication, progenitor cells become progressively more differentiated and are eventually destined to stop proliferating. Predictably, self-renewal is an essential property of some cancer cells, and at least some genes that regulate normal stem cell self-renewal also do so in cancer cells (12,13). There seem to be common signaling pathways implicated in stem cell expansion and CSC growth, such as wingless (14,15), and hedgehog (16); for a review see Rizvi (17). Interestingly, Beachy and colleagues have recently provided evidence for hedgehog involvement in normal and malignant prostate development (18,19). This suggests that cancers arise either from normal stem cells or from progenitor cells in which self-renewal pathways have become activated.

These observations provide a mechanism by which breast and prostate cancer patients with cancer cells in their marrow can remain progression-free for a prolonged time (20,21). One explanation for tumor dormancy is that the microscopic clusters of cancer cells did not contain CSCs and therefore, like the CD133+ brain cancer cells, were unable to grow further. Taken together with the observation that circulating cancer cells in the blood are an indicator of prognosis in breast cancer patients (22,23), this suggests that the use of markers to reveal CSCs could help in making decisions regarding treatments. The identification of CSCs is a significant step in the fight against these dreaded diseases. Because self-renewal is essential if tumors are to grow, agents that target such cells may be effective treatments. A possible complication is that the mechanisms known to regulate CSC self-renewal also regulate the same process in normal stem cells. Unlike normal stem cells (24,25), however, the expansion of CSCs is not tightly regulated, implying that there are significant differences between normal and cancerous self-renewal pathways. This gives hope that the isolation of CSCs, coupled with our knowledge of the mutations causing cancer, will result in ways to eliminate cancer cells while sparing normal tissues. The identification and functional characterization of CSCs can contribute significantly to improved methods for prognosis, better treatment decisions, and new treatments for cancer.

2. PROSTATE EPITHELIAL STEM CELLS

The existence of prostate epithelial stem cells and their putative role in prostate cancer development was proposed by Isaacs and Coffey (26–28). The stem cell model described in this paper is very similar to the one described above. Prostate cancers arise from prostate secretory acini. These acini are characterized by two cell layers that can be discriminated morphologically as undifferentiated basal cells and luminal cells primarily composed of terminally differentiated exocrine (prostate-specific antigen producing) cells. The neuroendocrine cells are found “supra” basally, with protrusions through the epithelium. The first evidence for a hierarchical relation between the basal cells and the luminal cells was provided by our group (29,30), using keratin antibodies as differentiation markers. We and others found further indications that the neuroendocrine and exocrine cells have a common progenitor, termed the transiently amplifying (TRANSIT) cell (31–34).

Clearly, most of these studies are descriptive and enable discrimination between the various cell types based on specific immunophenotypes. The location of the cells, as well as hormone manipulation studies (30), suggest a hierarchical relation between the basal cells and the luminal cells. The early and late progenitors are characterized by “intermediate” immunophenotypes (Fig. 1; Table 1). The first evidence for a hierarchical relation using primary epithelial cell cultures was described by our group (35). More recently, Collins and colleagues succeeded in isolating a purer candidate prostate epithelial stem cell, using CD133 selection (36). Thus, a very specific immunophenotype of the stem cell, the early and late progenitor cell populations, and the terminally differentiated exocrine and neuroendocrine cells emerges (see Table 1).