Journal of Steroid Biochemistry & Molecular Biology 166 (2017) 68–83

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry & Molecular Biology

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

Review

Stem cells and the role of ETS transcription factors in the differentiation hierarchy of normal and malignant prostate epithelium

Leanne K. Archer, Fiona M. Frame, Norman J. Maitland*

Cancer Research Unit, Department of Biology, University of York, York, YO10 5DD, United Kingdom

ARTICLE INFO

Article history:
Received 19 February 2016
Received in revised form 25 April 2016
Accepted 7 May 2016
Available online 14 May 2016

Keywords:
Prostate cancer
Cancer stem cells
ETS factors
Treatment resistance

ABSTRACT

Prostate cancer is the most common cancer of men in the UK and accounts for a quarter of all new cases. Although treatment of localised cancer can be successful, there is no cure for patients presenting with invasive prostate cancer and there are less treatment options. They are generally treated with androgen-ablation therapies but eventually the tumours become hormone resistant and patients develop castration-resistant prostate cancer (CRPC) for which there are no further successful or curative treatments. This highlights the need for new treatment strategies. In order to prevent prostate cancer recurrence and treatment resistance, all the cell populations in a heterogeneous prostate tumour must be targeted, including the rare cancer stem cell (CSC) population. The ETS transcription factor family members are now recognised as a common feature in multiple cancers including prostate cancer; with aberrant expression, loss of tumour suppressor function, inactivating mutations and the formation of fusion genes observed. Most notably, the TMPRSS2-ERG gene fusion is present in approximately 50% of prostate cancers and in prostate CSCs. However, the role of other ETS transcription factors in prostate cancer is less well understood. This review will describe the prostate epithelial cell hierarchy and discuss the evidence behind prostate CSCs and their inherent resistance to conventional cancer therapies. The known and proposed roles of the ETS family of transcription factors in prostate epithelial cell differentiation and regulation of the CSC phenotype will be discussed, as well as how they might be targeted for therapy.

Contents

1. Introduction . . . 69
2. Prostate cancer stem cells: the evidence . . . 69
   2.1. Epithelial composition of the prostate . . . 70
   2.2. Evidence suggests that a basal cell is the cell of origin of prostate cancer . . . 71
3. Cancer stem cells and treatment resistance in prostate cancer . . . 72
   3.1. Drug efflux transporters and anti-apoptotic molecules . . . 73
   3.2. DNA damage response . . . 73
   3.3. The tumour microenvironment and CSC niche . . . 73
   3.4. Other CSC targets . . . 74
4. Control of cell differentiation and the stem cell phenotype in prostate cancer: the potential role of ETS factors . . . 74
   4.1. ETS fusions . . . 74
   4.2. Aberrant expression of ETS factors . . . 76
   4.3. Regulation of epithelial-specific ETS factors . . . 77
      4.3.1. PDEF . . . 77
      4.3.2. ELF3 . . . 77
      4.3.3. ESE3 . . . 78
5. Targeting ETS factors in cancer . . . 78

* Corresponding author.
E-mail address: n.j.maitland@york.ac.uk (N.J. Maitland).

http://dx.doi.org/10.1016/j.jsbmb.2016.05.006
0960-0760/

5.1. Direct targeting of ETS factors . . . 78
5.2. Indirect targeting of ETS factors . . . 79
5.3. Expression of suppressive ETS factors . . . 79
5.4. Differentiation therapy . . . 79
6. Concluding remarks . . . 80
Acknowledgements . . . 80
References . . . 80

1. Introduction

Up to 40% of men with prostate cancer will develop metastases, most commonly to the bone [1]. Locally advanced and metastatic prostate cancer are generally treated with pharmacological drugs which aim to deprive the tumour of androgens which are essential for growth, known collectively as androgen-deprivation therapy (ADT). Patients undergoing ADT may initially show promising tumour regression and reduced prostate-specific antigen (PSA) levels. However, they will eventually become hormone resistant and the recurrent cancer is known as castration-resistant prostate cancer (CRPC). Therapy for CRPC includes treatment with cytotoxic chemotherapy agents such as docetaxel or cabazitaxel, which target rapidly dividing cells. Unfortunately, patients rapidly become resistant to chemotherapeutic drugs and the survival benefit with current agents is small [2]. The median life expectancy of a patient with CRPC is about 2 years despite the development of next generation therapies including abiraterone acetate, sipuleucel-T and enzalutamide, which only prolong life expectancy by a matter of months relative to a placebo [3–5]. These new agents target multiple routes of androgen deprivation, including powerful blockade of the androgen receptor (enzalutamide) as well as androgen synthesis (abiraterone acetate) [6].

Although the principal focus of drug design has been on androgen depletion, resistance suggests that androgen receptor (AR) positive cells are not the only cell type within the tumour. Current prostate cancer drugs target androgen responsive luminal cells which comprise the bulk of a tumour, whilst overlooking the AR negative basal cell populations which includes a stem-like population. Cancer stem cells (CSCs), and similar populations, have been identified in a number of cancers, including AML [7], glioblastoma [8], bladder [9], pancreas [10], breast [11], lung [12], colon [13] and prostate [14]. This rare population possesses similar characteristics to normal tissue stem cells. Stem cells are able to undergo asymmetric division, resulting in self-renewal and a progeny cell with the ability to differentiate. This gives stem cells the distinct ability to reconstitute a tissue following injury, which poses the hypothesis that a cancer stem cell can reconstitute a tumour following treatment and thus promote resistance and recurrence [14–18]. The extended life span of a stem cell also presents the possibility for accumulation of the mutations required to develop cancer, but this is currently unproven. A likely candidate founder mutation in prostate cancer, namely fusion of TMPRSS2 to ERG, is found in 50% of prostate cancers and is rarely considered in the context of CSCs [16,19]. ERG is an ETS family transcription factor, a family which is critical for controlling and regulating a variety of cellular processes [20–22]. The dysregulation of ETS factors *via* aberrant expression or repression, various mutations and their involvement in fusion genes in both leukaemias and solid tumours, including prostate, highlights them as significant factors influencing tumourigenesis [23]. Furthermore, as many ETS factors are also involved in epithelial cell differentiation it is important to consider the consequences of their expression in the individual cell populations found in a prostate tumour [24–26].

2. Prostate cancer stem cells: the evidence

The CSC hypothesis proposes that only a subpopulation of cells within a tumour is able to initiate, propagate and maintain tumour growth. In addition to self-renewal and multipotency, CSCs also have dysregulated proliferation and differentiation. Thus a CSC can maintain itself, whilst also differentiating into the distinct heterogeneous cell types that constitute the bulk of a tumour (Fig. 1). These tumour bulk populations are considered non-tumourigenic, although it should be noted that CSC properties may not only be originally acquired by normal tissue SCs but also by a more differentiated cell type within the hierarchy. The original cell type which is targeted for genetic mutation and transformation, whether or not it is a stem cell, is known as the cell of origin. Since CSCs are the only cells capable of driving tumour growth, these cells therefore require targeting to achieve long term cancer therapy. However, consistent with normal tissue SCs, CSCs possess inherent resistance mechanisms which allow them to evade standard cancer treatments including chemotherapy and radiation [27–29].

Multiple studies, going back over a hundred years had implied the existence of CSCs [30]. The first “modern age” evidence presenting CSCs as the cause and maintenance of cancer was elegantly demonstrated in acute myeloid leukaemia (AML) by John Dick’s laboratory in 1994 [31]. Since then our understanding of CSCs has been refined and their identification in multiple other leukaemias and solid tumours has supported the CSC hypothesis of cancer [32]. However, accumulating evidence for the CSC hypothesis has posed significant challenges, including the identification of markers that can accurately distinguish CSCs and expedite isolation of these relatively rare cells from a complex tumour environment. The two functional caveats for identifying CSCs are that they must (1) be tumourigenic, forming heterogeneous tumours reminiscent of those from which they were derived and (2) be serially transplantable when xenografted in mice. An array of markers, including CD133, CD44, CD24 and ALDH1, have been used to isolate CSCs from different solid tumours. Moreover, as there is no single CSC marker for each tumour type, multiple markers are generally used to isolate as homogeneous a population as possible. These markers usually include normal stem cell markers of the same tissue [33]. Whilst it has previously been hypothesised that CSCs constitute a rare population of tumour cells, studies in melanoma have shown that the current models could be significantly underestimating the size of the CSC population. In NOD/SCID mice the proportion of cells with tumourigenic capacity was 0.1–0.0001%, which rose to 25% in more immunocompromised NOD/SCID/IL2Rγ^{null} mice [34]. However, the original hypothesis seems true in tumours of other tissues such as human pancreatic adenocarcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and head and neck squamous cell carcinoma. In these tumours, the CSC population only accounted for 0.0028–0.04% of total tumour cells in NOD/SCID/IL2Rγ^{null} mice [35]. The proportion of tumour cells with a CSC phenotype is therefore likely to be a quality that is dependent on tissue of origin and cancer subtype within that tissue, and in some cases tumour grade may also be important [36,37]. Although serial