Molecular and Cellular Endocrinology 457 (2017) 57–72

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

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

Recent views of heavy metals as possible risk factors and potential preventive and therapeutic agents in prostate cancer

Veronica Vella [a, 1], Roberta Malaguarnera [b, 1], Rosamaria Lappano [c], Marcello Maggiolini [c], Antonino Belfiore [b, *]

[a] School of Human and Social Science, Motor Sciences, University "Kore" of Enna, Enna, Italy
[b] Endocrinology, Department of Health Sciences, University Magna Graecia of Catanzaro, Catanzaro, Italy
[c] Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Rende, Italy

ARTICLE INFO

Article history:
Received 15 September 2016
Received in revised form
19 October 2016
Accepted 19 October 2016
Available online 20 October 2016

Keywords:
Prostate cancer
Metals
Androgens
Signal transduction

ABSTRACT

Prostate cancer is the most common cancer in men in many industrialized countries. A role for androgens in prostate tumor progression is well recognized, while estrogens may cooperate with androgens in prostate carcinogenesis. The incidence of prostate cancer is highly variable in the different countries, suggesting an important role of environmental factors. Heavy metals are common environmental contaminants and some of them are confirmed or suspected human carcinogens. Some metals are endowed with estrogenic and/or androgenic activities and may play a role as cancer risk factors through this mechanism. Moreover, prostate cancer may present alterations in the intracellular balance of trace metals, such as zinc and copper, which are involved in several regulatory proteins. Herein, we review the possible role of environmental heavy metals and of metal-dyshomeostasis in prostate cancer development and promotion as well as the potential use of some metals in the prevention and therapy of prostate cancer.

1. Introduction

Prostate cancer is the most common cancer in men, and the second leading cause of cancer death among men in western countries. The most frequent histotype, which accounts for about 80% of all prostate cancers, is prostate adenocarcinoma that arises from the secretory epithelial cells of the peripheral zone. The normal prostate gland can be divided in three parts: the peripheral zone that represents the 70% of the gland, the central zone (about 25%) and the transition zone (5%). Prostatic fluid is mainly produced from the cells of the peripheral zone. About 90% of prostate malignancy arises from this part of the gland, while about 10% origin from the transition zone.

Prostate specific antigen (PSA) is a tumor marker used for screening together with rectal exams. The detection of rising PSA markedly increases prostate cancer survival, partly due to overdiagnosis of early stage tumors (Neppl-Huber et al., 2012). The risk for prostate cancer increases with age, familiarity, and is elevated in African-Americans (Rishi et al., 2003). Prostate cancer has initially a slow growth rate, and early stages are characterized by androgens sensitivity and the ability to respond to androgen deprivation (medical or surgical castration). However, later stages are characterized by invasion of the adjacent organs and metastatic spread prevalently to lymph nodes and bones, together with unresponsiveness to androgenic suppression (castration resistance) and virtual resistance to the other available therapies (Attard et al., 2016).

Although prostate cancer pathogenesis is not well understood, several risk factors such as age, diet, ethnicity, and genetic/family history have been identified (Guo et al., 2007). In this review we will analyze the current knowledge regarding the role of heavy metals as possible carcinogens for the prostate and their potential role in prostate cancer prevention and therapy.

Several metals play a fundamental role in various biochemical processes in the human body, and dysregulation of these elements can affect health and may be involved in the development of various diseases including cancer (Tan and Chen, 2011). Other metals have no physiological role in the human body and may exert toxic effects mimicking or blocking the function of essential metals (Waalkes, 2000) or mimicking the effect of endogenous hormones,

* Corresponding author.
E-mail address: belfiore@unicz.it (A. Belfiore).
[1] VV and RM have equally contributed to the manuscript.

http://dx.doi.org/10.1016/j.mce.2016.10.020
0303-7207/

Abbreviations

cAMP	cyclic adenosine monophosphate
EGFR	epidermal growth factor receptor
ER	estrogen receptor
ERK	extracellular signal-regulated kinases
IGF-IR	insulin-like growth factor I receptor
GPER	G protein estrogen receptor
HIF-1α	hypoxia-inducible factor-1α
PR	progesterone receptor
VEGF	vascular endothelial growth factor
FGF	fibroblast growth factor
IL	interleukin
AR	androgen receptor
PSA	Prostate specific antigen
BPH	benign prostate hypertrophy
ROS	reactive oxygen species
NOC	N-nitroso compounds
SMR	standardized mortality ratio
SIR	standardized incidence ratio
MT	metallothionein
ZIP	Zrt-like Irt-like proteins
ZnT	Zn Transporter
TCA	tricarboxylic acid
PTP	protein tyrosine phosphatase
PI3-K	phosphatidylinositol 3-kinase
PKB/Akt	protein kinase B/Akt
TRAMP	Transgenic Adenocarcinoma of the Mouse Prostate
MAPK	mitogen-activated protein kinases
NF-kB	nuclear factor kappa-light-chain-enhancer of activated B cells nuclear
IGF-1	insulin-like growth factor-1
EGF	epidermal growth factor
DNMT3b	DNA methyltransferase 3b
TNF	tumor necrosis factor
TGF	tumor growth factor
TPEN	*N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-ethylenediamine
CTR1	Cu transporter 1

thus disrupting the endocrine homeostasis. Some of these metals are known or suspected carcinogens (Kim et al., 2015). Even though the molecular mechanisms by which heavy metals can cause cancer are not completely understood, studies concerning the carcinogenetic potential of non-essential metals but also of the dyshomeostasis of essential metals are of great importance for future cancer prevention and therapeutic strategies (Pasha et al., 2010).

2. Epidemiologic studies

Several epidemiological studies have investigated the possible link between exposure to heavy metals and increased prostate cancer incidence and mortality. These studies have employed different study designs, have investigated exposure both directly and indirectly and have considered exposure in occupational and non-occupational settings.

2.1. Zinc

Zinc (Zn) is an essential trace element involved in important biochemical, metabolic, immunological functions. Diet is the main source of Zn and Zn levels in animal products depend on the soil and water concentrations, where the animals are raised. The recommended daily intake for men ranges from 5.2 to 16.2 mg/day (WHO Regional Office for Europe Air quality guidelines 2000; Agency for Toxic substances and Disease Registry, 2003) The main food sources are milk, flesh food, cereals, and vegetables. Serum Zn concentration is considered the only biomarker of Zn status in population, as recommended by WHO/UNICEF/IEA/IZiNCG, and it reflects Zn dietary intake and predicts responses to Zn interventions. Serum Zn levels in healthy individuals are maintained by homeostatic mechanisms, within a narrow range (12–15 μmol/l, 78–98 μg/dL) (Gibson et al., 2008). However, serum Zn values may vary day-to day, have a diurnal variation and may be affected by concurrent infection (Lonnerdal, 2000; Hambidge et al., 2005; International Zinc Nutrition Consultative, Brown, Rivera et al., 2004). Toenail clipping has been considered another possible indicator of Zn status as it may provide a more stable and integrated measurement of Zn exposure over the past several months (Garland et al., 1993). The use of hair Zn concentration as indicator of Zn status has been controversial (Hambidge, 1982) also because it could be affected by age, sex, season, hair growth rate, nutrition status, hair cosmetic products; thereby all these factors should be considered when interpreting the result of different studies.

Epidemiological studies have shown inconsistent results regarding the association between dietary Zn levels and prostate cancer risk. Possible beneficial effects, possible harmful or no effect have been described (Costello et al., 2004a,b,c; Costello et al., 2005) (Ho and Song, 2009; Andersson et al., 1996; Chan et al., 2005; Chang et al., 2004; Key et al., 1997; Kolonel et al., 1988; Kristal et al., 1999; Lee et al., 1998; Platz and Helzlsouer, 2001; Thomas, 1999; West et al., 1991).

Positive association between Zn dietary intake and prostate carcinogenesis was found in a large multicenter hospital-based case-control study conducted in Italy (Gallus et al., 2007). The Odds Ratio (OR) for the highest quintile of Zn intake (>15.65 mg/day), was 1.56 (95% CI = 1.07–2.26) with a significant trend in risk. For advanced and metastatic cancers the association was positively significant with the OR being 2.02 (95% CI = 1.14–3.59). These data suggest that Zn from food source may exert unfavorable effect on prostate carcinogenesis, although the study has been questioned for many aspects including the estimations of dietary intake, Zn levels and subgrouping of >2 mg/day. By contrast, Leitzmann MF et al. found that Zn contained in food sources was not associated with prostate cancer risk 2016 (Leitzmann et al., 2003).

Several studies have assessed the relationship between Zn serum concentration and prostatic cancer but, similarly to the association with dietary Zn intake, the current result are highly contradictory (Aydin et al., 2006; Feustel et al., 1989; Park et al., 2013; Rahman et al., 2012; Darago et al., 2011; Costello et al., 2004a,b,c; Christudoss et al., 2011; Chen, 2015; Ji, 2007; Li, 2006, 2015; Xu, 2002; Yao, 1977; Zhou, 2009; Liu, 1993).

A recent meta-analysis (Zhao et al., 2016) analyzed ten studies (Aydin et al., 2006; Feustel et al., 1989; Park et al., 2013; Darago et al., 2011; Christudoss et al., 2011; Li et al., 2005) (Chen, 2015; Li, 2006, 2015; Yao, 1977) investigating the correlation between serum Zn levels and prostate cancer (794 cancer patients vs. 1.359 controls) and found that in seven studies (Aydin et al., 2006; Darago et al., 2011; Christudoss et al., 2011; Chen, 2015; Ji, 2007; Li, 2006; Li et al., 2005) the serum Zn levels of prostate patients was significantly lower compared to control individuals Standard Mean Difference, SMD = −0.94 (95% CI = −1.57, −0.32). One study reported