

Focusing on men's health

Guest Editors: Maria Pasic, Vathany Kulasingam and Eleftherios P. Diamandis

Men and women are genetically extremely similar, with women having a 46XX and men a 46XY chromosomal composition. Sex differentiation is driven by a single gene on chromosome Y known as sex-determining region Y (SRY). Despite these similarities, women suffer from some unique disorders, such as breast cancer, while men suffer from others (e.g. prostate cancer). These two cancers represent the most frequently diagnosed and two of the most common causes of death in females and males, respectively. A few years ago, we reviewed the many common features between breast cancer in females and prostate cancer in males (1).

Women's health has attracted more attention and more funding than men's health (e.g. the January 2014 special issue of the journal "Clinic of Chemistry" is focusing on women's health) (2). In this issue of eIFCC we focus on men's health with special emphasis on prostate cancer. We also include some other health issues exclusive to men such as androgen replacement therapy and male infertility. We have also included one chapter on bladder cancer which is common in both men and women.

A lot has been written already about prostate cancer screening by using prostate specific antigen (3-4). Despite the fact that the long-awaited prospective clinical trials on the usefulness of prostate cancer screening have already been published (5,6), the issue is still widely controversial. The US Preventive Services Task Force issued recommendations which do not support widespread prostate cancer screening. Dr. Carsten Stephan and colleagues review the issue of prostate cancer screening and examine novel biomarkers which may increase its effectiveness. The same topic is examined by Dr. Ulf-Hakan Stenman and colleagues but from a different angle.

MicroRNAs have emerged as major players of gene regulation and a Nobel Prize has been awarded for their discovery (7). More recently, the family of non-coding RNAs has been greatly expanded (8). In addition to mechanistic aspects related to transcription and translation, an emerging field is to use microRNAs as cancer biomarkers (9). The application of these markers to the clinic is still remote but efforts are continuing with a fast pace. Yousef and colleagues review the use of microRNAs as candidate biomarkers of prostate cancer.

The majority of prostate cancers do not kill the patient and many do not even need treatment, but a new form of therapy coined "active surveillance" (10). Prostate cancer is not lethal, unless it becomes

metastatic. Why do the vast majority of patients respond initially very well to various forms of therapies but relapse within 2-3 years with distant metastasis? This is usually due to the establishment of androgen independence. Although some mechanisms of androgen independence are known (11) we still do not understand the fine details or how to reverse it. Keith Jarvi and colleagues review the currently known mechanisms of androgen independence and describe the clinical importance for finding new therapies.

Mass spectrometry is a powerful technique not only for measuring various types of analytes such as hormones, metabolites, proteins and nucleic acids, but also as a discovery tool for novel biomarkers (12, 13). While most researchers focus on identifying genomic or proteomic biomarkers for cancer and other diseases, it is also possible to investigate small metabolites as potential biomarkers, which can be found in either serum or urine. Recently, some highly promising metabolomic biomarkers for prostate cancer (such as sarcosine) have been described (14, 15). Robert Wolfert and colleagues examine how mass spectrometry can be used to study the metabolome and on how to use this information to derive clinically relevant prostate cancer biomarkers.

Kallikreins are a group of serine proteases that are encoded by 15 genes located in tandem on human chromosome 19q13.4 (16). Two members of the kallikrein family, prostate specific antigen (PSA; KLK3) and KLK2 are expressed only in the prostate and are used widely as biomarkers for prostate cancer screening, diagnosis and monitoring (17). KLK3 and KLK2 are not the only prostatic specific kallikreins; at least another two (KLK4 and KLK15) are also almost exclusively expressed in prostate (18). It is likely that these prostate specific kallikreins, which have been found to participate in semen liquefaction (19), could find important applications as individual or combined biomarkers. Judith Clements and colleagues review the status of kallikreins in prostate cancer and suggest on how this group of enzymes can be used in clinical practice.

The genetics of prostate cancer are relatively obscure (20). While there is a familial form of the disease (21), the majority of prostate cancers have not been associated with specific cancer predisposition genes. Recently, whole exome sequencing revealed candidate genes associated with the disease (22). Also, previous genome-wide scans established genetic loci that are associated with prostate cancer predisposition such as those on chromosome 8q (23). Dr. Robert Nam and colleagues review the genetics of prostate cancer and outlines the known genetic components of this disease.

With increased life expectancy, more men live longer while remaining sexually active. There is currently a debate as to the existence of male andropause (24). However, it is also widely accepted that a proportion of aging men lose potency and have other symptoms of possible testosterone deficiency such as fatigue, weakness, loss of motivation and mood swings. Testosterone replacement

therapy is an effective way to reverse these symptoms. However, this therapy may have important side effects (25). Dr. Ethan Grober and colleagues bring us up to date with the status of testosterone replacement therapy and outline advantages and disadvantages.

Stem cells represent one of the most rapidly growing areas of research as they promises to revolutionize regenerative therapies for many diseases (26). Inducible stem cell technologies enjoyed dramatic improvements over the last two years and they are highly promising. Dr. Kirk Lo and colleagues review the status of testicular stem cells and propose important applications in male infertility and other testicular diseases.

Infertility affects approximately 5-10% of all couples and is due to disorders of both partners (50% each). While female infertility has received much attention, male infertility is a less researched area. In men with azoospermia, the question is whether the infertility is due to obstruction of the vas deferens (this is equivalent to vasectomy) or to a non-obstructive cause. Non-obstructive azoospermia is further divided into three major categories (maturation arrest, hypospermatogenesis or Sertoli cell-only syndrome). The most viable current way of establishing if a non-obstructive azoospermic man may be able to have children, is to retrieve sperm from his testes and proceed to artificial insemination. Retrieving sperm from the testes requires testicular biopsy followed by a surgical procedure, testicular semen extraction (TESE). This procedure is invasive, painful, has serious side effects and on many cases does not lead to sperm extraction. Dr. Keith Jarvi and colleagues recently described a new biomarker, TEX101, which may have the potential to discriminate between obstructive and non-obstructive azoospermia, as well as, of various forms of non-obstructive azoospermia (27). Their review is an update on TEX101 and other seminal plasma biomarkers for male infertility.

Last but not least, Dr. Alex Zlotta and colleagues address a cancer that is found in both males and females, bladder cancer. There is an urgent clinical need to identify biomarkers not only to diagnose bladder cancer early, but also to discriminate between low-grade and high-grade bladder cancer since these two forms need different types of treatment.

All-in-all, this compilation covers a wide spectrum of clinical questions and aims to bring the readers up-to-date with new developments in prostate cancer and other areas related to men's health. We thank all authors for their efforts but the Co-Editors assume responsibility if this special issue falls short of expectations.

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