

# **Workshop on Cancer and Inflammation: Promise for Biological Therapy**

## **Genetic Polymorphisms and Factors which Modulate Inflammation and Cancer**

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Oct. 30 , 2008

# Introduction

- Chronic infection or inflammation lead to 20% of all human cancers
- Chronic inflammation has been related to the occurrence of cancers of the bladder, stomach, colon and rectum, prostate, lung, skin, and liver, etc.

De Marzo et al. Nature Reviews Cancer 2007

Coussens et al. Nature 2002

# Prostate Cancer

## USA

- The **most common** non-skin cancer in men
- The **2nd** cancer cause of death
- **42%** of prostate cancer cases up to age 70 years can be explained by **heritable factors** (**cf.** colorectal cancer: 35%; breast cancer: 27%)

Lichtenstein et al. NEJM 343(2) 2000

# 1. Candidate Gene Approach (Hypothesis Driven)

# Inflammatory-Related Candidate Genes in Prostate Cancer

- RNASEL
- MSR1
- **TLR** (1, 4, 6, 10)
- MIC1
- TNF- $\alpha$ , TNF- $\beta$ 1
- IL1 $\beta$ , IL6, IL8, IL10, IL1RN
- VEGF
- **COX2**

De Marzo et al. Nature Reviews Cancer 7 2007  
van der Poel et al. Critical Review in  
Oncology/Hematology 61(2) 2007

# Compare Two Association Studies

<b>TLR4 and Prostate Cancer</b>		
	<b>Zheng et al. Cancer Research 64(8) 2004</b>	<b>Chen et al. Cancer Research 65(24) 2005</b>
<b>Population</b>	<b>Swedish</b>	<b>US Caucasian (94%)</b>
<b>Design</b>	<b>Population-based case-control study</b>	<b>Nested case-control study</b>
<b>Time period</b>	<b>2001-2002</b>	<b>1993-2000</b>
<b>Sample size</b>	<b>Prevalent case: 1,383 Control: 780</b>	<b>Incident case: 700 Control: 700</b>
<b>SNP genotyped</b>	<b>8 SNPs</b>	<b>16 SNPs (4 SNPs overlap with Zheng et al.)</b>
<b>Gleason 8+</b>	<b>17%</b>	<b>8%</b>
<b>Significant findings</b>	<b>1 SNP (↑ PCa) 0 haplo</b>	<b>10 SNPs (↓ PCa) 1 SNP (↑ PCa) 1 haplo (↓ PCa) 1 haplo (↑ PCa)</b>

# Flip-Flop Phenomenon

(1) For the same ethnic groups → spurious findings

(2) For different ethnic groups

- Different **linkage disequilibrium (LD) pattern** b/w populations when test non-causal variants
- Different **environment**

(3) **Publication bias/Reporting bias**

(4) Fail to account for **multilocus effect** or **correlation with causal SNPs**

Lin PI et al. Am J Hum Genet 2007, 80: 531-538.

## **2. Pathway Analysis (Hypothesis Driven)**

# Inflammation Pathway and PCa

- A Swedish case-control study

## Stage 1:

- 200 familial cases and 200 controls
- 9,275 SNPs in 1,086 genes (Microarray)

## Stage 2:

- 1380 cases and 780 controls
- 26 SNPs in 26 genes

Zheng et al. The Prostate 66:1556-1564, 2006.

- Results:

- *CRLF1* (rs7250623)

- *FCER2* (rs753733)

- *CIDEB* and *LTB4R2* (rs2144493)

→ Not the most significant SNPs and represent a **small fraction** of true associated SNPs.

→ Additional SNPs with **lower significance** level may contain true associated SNPs.

# **3. Genome-Wide Association Study (Hypothesis Free)**

ORIGINAL ARTICLE

## Cumulative Association of Five Genetic Variants with Prostate Cancer

S. Lily Zheng, M.D., Jielin Sun, Ph.D., Fredrik Wiklund, Ph.D., Shelly Smith, M.S., Pär Stattin, M.D., Ph.D., Ge Li, M.D., Hans-Olov Adami, M.D., Ph.D., Fang-Chi Hsu, Ph.D., Yi Zhu, B.S., Katarina Balter, Ph.D., A. Karim Kader, M.D., Ph.D., Aubrey R. Turner, M.S., Wennuan Liu, Ph.D., Eugene R. Bleecker, M.D., Deborah A. Meyers, Ph.D., David Duggan, Ph.D., John D. Carpenter, Ph.D., Bao-Li Chang, Ph.D., William B. Isaacs, Ph.D., Jianfeng Xu, M.D., D.P.H., and Henrik Grönberg, M.D., Ph.D.

- Genotyped **16 SNPs** that were significantly associated with PCa from previous **genome-wide association studies**.

SNP	Chomosomal Region	Alternative Alleles
rs4430796	17q12	T, C → TCF2
rs1859962	17q24.3	G, T
rs16901979	8q24	C, A
rs6983267	8q24	G, T
rs1447295	8q24	C, A

No gene

Joint PAR of 5 SNPs plus family history =46%

	<b>Candidate Gene/Pathway Analysis</b>	<b>Genome-Wide Association Study</b>
<b>False Positive Rate</b>	<b>Lower</b>	<b>Higher</b>
<b>Cost</b>	<b>Lower</b>	<b>Higher</b>
<b>Interaction</b>	<b>Gene-gene Subpathways</b>	<b>Not significant Not applicable</b>
<b>Sample Size</b>	<b>Smaller</b>	<b>Larger</b>
<b>Consistency across different populations</b>	<b>Not ideal for low-penetrance genes</b>	<b>Good*</b>

Loza et al. PLoS ONE 10 2007.

\*Xu et al. Clin Cancer Res 14(18) 2008. 14

# Future Directions

- Pathway analysis or genome-wide association study?
- **Interactions** between pathways, G and E
- Data from **multiple levels** (DNA, RNA, and protein)
- Studies across different **ethnic groups**