Gliwice Scientific Meetings as a forum for discussion of research projects. Personal impressions

ABSTRACT

The article has been written for the occasion of 25 Anniversary of Gliwice Scientific Meetings (GSN). For this reason, I am going to present scientific contacts of the Institute of Oncology at Gliwice with the Institute of Human Genetics of the Polish Academy of Sciences at Poznań not only at conference occasions but also in regular research manner.

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DEDICATION

The article is dedicated to the memory of Mieczyslaw Chorąży and Ronald Hancock, two prominent scientists working on biology and genetics of human cancer

The Institute of Human Genetics at Poznań established at the year 1974 in the beginning it had to determine its research profile. Among the other proposals, we turned our attention to DNA fragments released into body fluids and to culture medium *in vitro*. Short DNA samples were seized for ca. 50 nucleotides and became known in the literature as free or extracellular DNA (exDNA). Preliminary results concerning characteristics and potential function [1] were presented and discussed in Gliwice. Discussions were supplanted by short internships in the Department of Tumor Biology at Gliwice. The main partners at that time besides Prof. Mieczysław Chorąży were Doctors: Stanisław Szala and Zdzisław Krawczyk. (Further, I will not use scientific titles as a majority of the mentioned persons have completed a full scientific carrier). Nevertheless, it was still difficult to rationalize if exDNA is a random artifact or a preparation having an exact biological role. The answer has appeared after the study done with Budapest partners that has shown a size distribution with a chain length of 6-60 nucleotides, a lack of specific deoxyribonucleoside monophosphates from the 5'-end that finally pointed at non-specific degradation of DNA excreted by stimulated lymphocytes [2]. With these results and a shortage of methods (DNA sequencing was not accessible at that time!) the project was abandoned.

Unexpectedly an interest in cell-free DNA (cf-DNA) has re-appeared massively recent years. cf-DNA extracted from blood and other body fluids was found to be a useful non-invasive tool for diagnosis of cancer and other ongoing diseases [3]. We have joined this stream and preliminary results on the application of estimation of microRNA in laryngeal cancer were presented by Joanna Janiszewska at GSN 2012. The study was confronted with the presentation of Prof. Mahvash Tavassoli (London, UK), one of the leaders of the miRNA topic [4] that resulted in invitation of J. Janiszewska to London to learn more about functional studies of miRNA. The stay contributed well to the publication on the oncogenic role of mir-1290 in laryngeal cancer [5]. Further studies on the role of miRNAs in laryngeal cancer, leukemia, and non-Hodgkin lymphoma as well as attracting clinicians to apply liquid biopsy in daily routine remain a target of our research activity [6].

Later on, our research interest embraced molecular epidemiology focused on oncogenesis. The studies on environmental and occupational exposure to carcinogenic agents pointed at biologically effective doses being a more reliable measure of risk as compared with the concentration of carcinogens in ambient air or consumed food products. Determination of carcinogen-DNA adducts was found at the end of the 20th century the best procedure to estimate the damage of genetic material that could be next followed by entering into oncogenesis [7]. The studies on the role of DNA adducts in preliminary steps of cancer progression were performed simultaneously in Gliwice and Poznań.

It has happened that Ewa Grzybowska (Gliwice) and myself landed in the laboratory of Prof. Kari Hemminki in Helsinki enjoying the work on DNA adducts. The most common although labor-consuming test of DNA adduct determination was the technique known as ^{32}P-postlabelling. We have been quite happy

to contribute to method improvement [8]. E. Grzybowska has published then her prominent study on seasonal variations of DNA adduct levels in Upper Silesia [9]. The paper has got a good background information on environmental pollution in Silesia established by Prof. M. Chorąży and coworkers [10]. On our side, we could point at the determination of bulky DNA adducts in postsurgical explants from laryngeal cancer. The paper indicated differences in DNA adduct levels in the tumor proper, adjacent tumor margin, and peripheral blood leukocytes. The results indicated ongoing carcinogenesis in tumor margin that by clinical and histopathologic methods was recognized as normal tissue [11]. Further, we wanted to find an explanation for much lower morbidity for laryngeal cancer in women that was not sufficiently explainable by sex differences in tobacco smoking and drinking, the main causative factors. Unfortunately, a low number of women with laryngeal cancer did not provide statistical power of results [12].

In some time, Prof. Hemminki decided to move to Karolinska Institute (Huddinge, Stockholm). To our satisfaction the decision was followed by the reconstruction of the research group, including two of us (E.G. and K.S) and also Pavel Vodička (Prague), and Asta Försti (Helsinki). Later on Rajiv Kumar (India) joined us to form together a core of Kari Hemminki research group. A couple of years later we had a friendly re-union at Gliwice (GSN 2018).

The evolution of research interest in human cancer has focused finally on head and neck cancer (HNC). Such a group formally exists in cancer classification but in fact is a heterogeneous one concerning biology, clinic, and treatment. To avoid this heterogeneity we stick mostly with laryngeal cancer dominated by squamous cell carcinoma (HNSCC). This topic has come from a close cooperation with the Clinic of Otolaryngology of Poznań Medical University headed first by Prof. Zygmunt Szmeja, next by Prof. Witold Szyfter, and recently by Prof. Malgorzata Wierzbicka. Access to well-characterized surgical material has given us a good advantage in our joined studies.

Initially, our methods were dominated by classical cytogenetics. Looking at chromosome aberrations we were expecting to find genes involved in the initiation and progression of HNC [13,14]. The partners from Gliwice were Jadwiga Michalska and Grażyna Motykiewicz [15,16]. A presentation of our results on the applicability bleomycin test to identify genetic risk to developing laryngeal cancer met a stormy discussion (GSN 2003) concerning the precise definition of chromatid breaks and chromosome aberrations. Anyway, the discussion helped to publish the results [17].

At almost the same time Gliwice and Poznań research teams undertaken studies on the genetic risk of cancer in relation to genetic polymorphism. Attention was paid to so-called low penetration genes as high penetration was much less numerous and usually not connected with neoplastic diseases of our interest. Thus, the studies were focused on genes responsible for chemical carcinogen activation, detoxication of carcinogens and removal of DNA damage by DNA repair process representing three consecutive steps in chemical carcinogenesis. Methods included genotyping of chosen genes by restriction fragment length polymorphism (RFLP) or other techniques confronted with such endpoints of carcinogen activity as DNA adducts [18], single or double DNA strand breaks [19] and finally with clinical/epidemiological data [20,21,22]. Step by step it was established that single low penetration genes do not contribute considerably to cancer risk.

However, a combination of gene variants responsible for low levels of carcinogen activation, poor detoxication, and low efficiency of DNA damage removal is effective enough to determine an increase in genetic risk [18,20]. The studies provided a good overview of risk and protective gene variants (GSN 1997).

The studies on genetic polymorphisms of the described genes above turned attention to DNA repair genes where the results concerning polymorphic risky (low effectiveness of DNA repair) and protective gene variants appeared to be more effective than those concerning activating and detoxifying genes [21,22]. In line with this observation, we performed a study on gene variant distribution in so-called young adults (age < 35 years) with laryngeal cancer. Average laryngeal cancer subjects are tobacco smokers and abusers of alcoholic beverages around 55-60 years old. Hence it was assumed that young adults having a much shorter time-period of carcinogen exposure would demonstrate a higher genetic predisposition to develop cancer. This supposition was shown in our study on polymorphism of XPD exon23, XRCC1 exon 10, and XRCC3 ex7 9 [21]. A similar conclusion was drawn in the study of Dorota Butkiewicz and coworkers [22].

Further studies on polymorphism of DNA repair genes have shown their impact is not limited only to entering oncogenesis. The publication of the Gliwice group demonstrated an association of polymorphism of DNA repair genes: XPA, XPG, XRCC1, and XRCC3 with survival of surgically treated patients suffering from non-small cell lung cancer [23]. A double-role DNA repair process entering into cancer, progression, and treatment was reviewed by us [24].

To complete the section concerning gene polymorphism related to human cancer I have to add a personal remark. Both Ron Hancock and myself were pipe smokers for decades. Each time when we met at Gliwice we arranged a pipe walk at lunch break. A habit of pipe walks emerged earlier at Huddinge when walking with Pavel Vodička. What did we discuss walking and smoking? The answer is quite obvious: Are our gene variants protective enough to enjoy puffing a pipe? Life has answered: YES.

Coming back to parallel studies performed in Gliwice and Poznań on DNA repair topic was not limited to gene polymorphism. At this point I stop at two papers published under almost the same title (GSN 2001, 2002). Both papers established a deficit of DNA repair capacity in cancer subjects as compared with healthy controls [25,26]. The question we posed later was an association between a rare congenital disease Fanconi anemia and laryngeal cancer. FA patients have a 500-700 times higher risk of head and neck

Table 1. The chosen findings concerning the involvement of particular genes in the progression of laryngeal cancer.

Gene	Genome location	Change	Biological/clinical effect	Reference
CDKN2	9p21.3	homozygous deletion	TSG, tumor growth	[30]
CCND1	11q13	gain of gene copy number	oncogene, poor prognosis	[31]
CDK1	10q21.2	overexpression	oncogene, tumor growth	[32]
PPA1	10q22.1	protein upregulation	metastasis marker	[33]
CEACAM6	19q13.2	DNA hypermethylation, correlation with progression	TSG, tumor growth	[34]
FAM107A	3p14.3	downregulation, premalignancy marker	TSG, tumor development	[35]
PCDH17	13q21.1	homozygous deletion aberrant promotor methylation	TSG, tumor growth	[36]
DIAPH2	Xq21.33	hemizygous deletion, sequence variants	TSG, cellular motility, metastatic potential	[37]
CRKL	22q11	gain of gene copy number	oncogene, proliferation and migration	[38]
MAF mir1290	16q23.2	loss of function, promotor methylation, direct MAF-mir1290 interaction	TSG, tumor growth	[39]

squamous cell carcinoma (HNSCC) compared to the non-FA population. Using bisulfite pyrosequencing we analyzed the methylation profile of 13 FA genes in 64 laryngeal tumor samples and 13 relevant cell lines. It was established that the FANCA gene has got aberrant methylation level in 11/13 cell lines and in all studied tumor samples. It means the FANCA gene is the confounding factor in laryngeal cancer (GSN 2009) [27]. To keep balance with the Gliwice group I refer to the publication dealing with polymorphism of several DNA repair genes (XPA, XPD, XRCC1, APE1, NBS1) and cell cycle regulating gene CCND1 to associate studied polymorphisms with the risk of colon, head and neck and breast cancer. The most convincible results pointed to an association of some studied polymorphisms with colon cancer [28].

Recent years provided an abundance of laboratory techniques for accessible DNA and RNA sequencing, methylation profiling, genetic engineering by CRISP, and bioinformatics to list a few. To continue our involvement in chromosome studies we have been interested in turning conventional cytogenetics into molecular. As the FISH technique remains still in between [29] following progress in chromosome analysis including comparative genome hybridization (CGH), array CGH with gene expression analysis attracted us a lot (GSN 2005, 2009). We have received a battery of techniques providing an opportunity to study the involvement of particular genes in the progression of laryngeal cancer. There appeared several questions to be answered. The first one was connected with the common participation of genes in various tumors. The literature already provided the answer – establishing the role of an individual gene in the regulation of a given cancer is not necessarily transmitted to another one. It means the research area was broadly open. Therefore, we have undertaken research for a genetic background of such steps or processes as a tendency to develop multiple primary tumors, early undertaking metastasis to adjacent lymph nodes or to a distant location (the recent are not common in laryngeal cancer), developing recurrency, resistance to chemo- and radiotherapy, prognosis, and survival.

The chosen findings concerning the involvement of particular genes in the progression of laryngeal cancer are shown in Table 1.

The studies presented above have been started from a general (but still quite rough) supposition claiming that a gain of gene copy could indicate for oncogenic character of the gene and vice versa loss or silencing of a given gene could be connected with suppressing activity. Shortly, we have been looking for oncogenes and tumor suppressor genes potentially regulating laryngeal progression. The next step of these studies was to establish the mechanism(s) of gaining oncogenic or suppressing activity. The following points were taken under study: changes in gene copy number (GSN 1999), gene structure alterations (mutations, gene variants), epigenetic modulation of function, and interaction with miR. For some studied genes there were found two or more mechanisms responsible for the activity effect [36,37]. Interestingly, in a few situations, TSG recognized already in another cancer can have oncogenic activity in laryngeal cancer. The latter situation is more frequent in genes not coding proteins [39].

Going to the end I have to add two pieces of information not connected with research itself but still with scientific activity that is proving a constant cooperation between our institutions. Firstly, their professors serve as reviewers at procedures connected with academic carrier. Secondly, the founder of the Institute and its director and scientific leader prof. Antoni Horst deceased in 2003. A little time later to commemorate his role as a scientist it was decided to establish Antoni Horst Memorial Lecture. A prominent scientist working in genetics, medicine, or molecular biology is invited to give an annual lecture. In 2019 the lecture was presented by Prof. Mieczysław Chorąży, who passed away in less than two years at the age of 95 years. The Institute of Oncology at Gliwice immediately managed to introduce Mieczysław Chorąży memorial lecture. I assume the idea has come to Gliwice from Poznań.

Altogether, my reminiscences covered roughly half of the century of contacts and cooperation documented by frequent participation at Gliwice Scientific Meetings with multiple oral presentations and posters.

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