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Review

An Overview of Genetic Changes and Risk of Pancreatic Ductal Adenocarcinoma

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Abstract

The pancreatic carcinoma is a leading cause of death in cancer carriers worldwide. The early diagnostic is difficult due to late stage during diagnosis, lack of characteristic symptoms and also multifactor basis. In cancer development take part both, environmental and genetic factors, alone or in conjunction with each other. The nonspecific biomarkers of cancers are a reason for the search for more accurate factors which allow for fast and personalized diagnostics. Some of cancers have identified molecular (metabolic, biochemical or genetic) markers but in most cases the only clue is patient`s interview and abnormal levels of organ functions markers.

Possible genetic basis of cancer suggests to widen studies on connection between environmental factors with both, nuclear and mitochondrial, genes changes.

Key words: pancreatic carcinoma, polymorphism.

Introduction

The pancreatic carcinoma (PC) is one of the most frequent cause of death in patients suffering from cancer. The survival rate, with this extremely aggressive cancer, is drastically reduced from 25% of 1-year survival to below 5% in 5-year. Up to recognized a pancreatic cancer only 15-20% of patients are resectable [1,2]. In this group mortality and morbidity rates are reduced to almost 40% of 5-year survival [3]. Inclusion of chemotherapy also improves a survival ratio [4]. Additionally, pancreatic carcinoma is a highly metastatic tumor and therapy resistant [1,5]. This cancer is rarely diagnosed in middle-aged patients but its frequency increased with age and is most presented in patients between 60 and 80 years [6,7] with median age of 73 years [8]. The most common form of PC is pancreatic ductal adenocarcinoma (PDAC) amounts over 90% of pancreatic cancers [9].

Due to the sequence of certain events during pancreatic carcinogenesis its progression is referred to as early (with KRAS mutation and shortening of telomeres), intermediate (associated with inactivation of CDKN2A2 gene by mutations or epigenetic mechanisms) and late (connected with "switching off" mutations of p53 and SMAD4 genes) [2].

This paper is focused on genetic changes in PDAC.

Epidemiology of pancreatic cancer

Pancreatic carcinoma is related with both environmental and genetic basis. The environmental risk factors include smoking, high BMI and obesity [10-13], alcohol, diabetes mellitus presence [14], age (rare <45 years, cancer incidence increasing after 50 years) [15], race (being highest in New Zealand Maoris, native Hawaiians and Afro-Americans) [6, 11, 12, 15], gender (most common in men) [15] and also chronic or inherited pancreatitis [16]. Risk of pancreatic carcinoma decreases in group of former smokers and during diabetes mellitus duration [11]

with possible protective role of metformin and increased risk in insulin treatment patients [15, 16]. Allergies, in particular respiratory ones, are a risk reduction factor [12, 17].

The family history of PC is predisposing to increased risk in first-degree relatives, in particular in group with carrier siblings [11]. Also, presence of familial atypical multiple melanoma and mole (FAMMM) syndrome, hereditary pancreatitis, familial breast cancer, Peutz-Jeghers syndrome, Lynch syndrome and Fanconi anaemia increases the genetic susceptibility to pancreatic cancer [11, 18, 19].

Multiple genes were analyzed in context of increased risk of PC and carcinogenesis. Genes of methylation enzymes, DNA repair, oncogenes were suspected of taking part in carcinoma development [10] but also those which control cell cycle process, folate metabolism or inflammation-associated [11].

Diagnostic of pancreatic cancer

Diagnostics is very hard because of cancer late stage during first oncological visit and lack of characteristic symptoms. The imaging diagnostics is based on computed tomography (CT), ultrasound (US), endoluminal ultrasound (EUS), followed by positron emission tomography, magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography [3].

There are still no strictly specific markers of early diagnosis. Most laboratories are focused on intraoperative cancer pathological stage differentiation, biochemical factors of organ dysfunction and abnormal levels of biomarkers such as carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), gamma glutamyl transferase (GGT), bilirubin, lipase or amylase. All those factors, however, tells about present state, does not allow to detect the symptoms predisposing to the disease.

There is still need for search more specific biomarkers and some genetic changes which could decide about increasing risk of PC, in particular in about 5 - 10% of patients who inherit predisposition to develop this kind of cancer. It seems that inherited risk might be connected with low penetrance of genetic variants [20].

Nuclear DNA changes

Structural genome changes

Aneuploidy and other changes within chromosome structure are represented in most solid tumors. The genes which could be associated with pancreas tumorigenesis are identified from single based substitutions (where missense changes are the most often followed by nonsense and changes of splicing sites), indels, deletions, amplifications and translocations [21].

Many cancers, including PC are characterized by polyploidy of DNA, therefore define a DNA ploidy and index of DNA in malignant cells pretend to be a good prognostic factors [9, 22].

Analysis of copy number of DNA in patients with pancreatic ductal adenocarcinoma indicate numerous regions in DNA where losses and gains of copies appears [23, 24]. The most frequent were identified gain change on 8q chromosome and most recurrent loss on 9p chromosome, which were present in almost 96% and 78% of analyzed patients, respectively. Those analyses also resulted in detection, probably unique, change for this type of carcinoma located in *SKAP2* gene (src kinase associated phosphoprotein 2, 7p15.2) and its overexpression identified in 67% cases but not in normal tissue. Additionally, analysis showed consistent presence of increased level of SKAP2 in all stages of carcinoma (I-IVb), which was statistically significant in correlation with copy number of DNA. It was also speculated possible role of *SKAP2* gene in regulation of cell cycle, by prolongation G1 phase, followed by differentiation of carcinoma cells. The most vulnerable to somatic mutations are regions connected with uniparental disomy [24].

Genetic instability is also a result of telomeres shortening during cell proliferation leading to neoplasm initiation. Enzyme telomerase, which should maintenance the telomeres stability is low expressed during early tumorigenesis, therefore the anaphase bridge-breakage-fusion cycles may occur [18, 23]. Those earliest genetic aberrations are observed in over 90% of pancreatic intraepithelial neoplasma (PanIN) lesions [8]. Telomerase activity in primary cancers, but not in benign ones, could be a differentiation factor for metastatic PC [25]. Human telomerase reverse transriptase (hTERT), a part of telomerase and crucial subunit for enzyme activity, pretend to be a marker of PDAC development. Its expression, even better than telomerase activity, predict low outcome in individuals with PC [26].

Another cause of genetic instability are genetic changes in genes engaged with DNA damage response starting with phosphorylation of ATM followed by the same process in histone H2AX. The last one, as a γH2AX is described as a marker of double-strand breaks in DNA. Those starting events could inhibit a proper DNA repair, results in accumulation of adverse changes in normal tissue as well as process control disorder of damaged cells on the path of apoptosis [27].

Polymorphic gene changes

Approximately all patients with PC carry one or more genetic changes connected with progression model in following genes.

First one is onkogene *K-ras* (kirsten rat sarcoma), which is present in chronic pancreatitis tissue [23], in almost 90% of cases of PDAC and occurs in an early stage of cancer development [3, 4, 10]. Its percentage increases during progression of carcinoma from 30-36% in PanIN-1 to 70-87% in PanIN-3 [8, 18]. Forster *et al.* even proposed a practical use of the detection of mutation (located in 12 codon) as a marker of contamination of islet cells for autotransplantation by pancreatic adenocarcinoma cells [28]. However, existing in most carcinoma cells, it requires additional factors to begin a carcinogenesis process. Researches indicates that K-ras copy number variations as well as mutation G12V could inhibit mitogen-activated protein kinase inhibitor treatment [29].

The second most common change concerns a tumors suppressor gene *p16*, which is connected with inactivation of *CDK* gene presented in almost 95% of tumors. The p16 is a regulator of the transition from G1 to S phase of cell cycle thus its inactivation, by homozygous deletion, loss the second allele or promoter methylation, leads to uncontrolled cell proliferation [3, 4, 8, 19]. It is characteristic from PanIN2 to PanIN 3 lesions [18].

Another common change with lack of *SMAD4* gene (*DPC4* gene) is presented in almost 50% of pancreatic cancers and is connected with aberrant transforming growth factor β (TGFβ) signaling pathway [3, 4]. It is observed that individuals with *SMAD4* loss are characterized by significantly shorten survival connected with widespread metastasis. Together, SMAD4 and p53 changes are mostly observed in late stage of tumorigenesis, in PanIN 3 lesions [18]. The SMAD4 gene could be a predictive genetic marker of local progression or metastasis when it is a wild or mutant variant respectively [29].

The suppressor gene *TP53* (tumor protein p53) has also its share in PC through being inactivated in approximately 75% cases [3, 4, 10]. Approximately 90% of p53 mutations are localized in DNA binding domain sequence [27]. Inactivation leads to genomic instability through avoiding apoptosis via cell checkpoint passing by damaged DNA [3, 4]. It has been proven that the presence of Pro allele in TP53 Arg72Pro polymorphism reduces apoptosis through lower this tumor suppressor protein activity. The Pro72 form induce most frequent arrest of failure cell in G1 phase, but the Arg72 form is known as a more efficient inductor of apoptosis [30]. Here is revealed a twofold role of protein, which by affecting apoptosis and accumulation of cells with damaged DNA can lead to carcinogenesis but also to protect against cancer development by the lack of elimination of anti-cancer cells. DNA damage, metabolic products of smoking and drinking, accumulate during life and modify originally non anti- cancer process to increased risk of carcinoma development. Analysis of Japanese population showed that TP53Pro/Pro genotype is associated with increased risk of PC in over 65-year-old individuals, particularly in group of heavy smokers, excessive drinkers and male gender. In this case, it should be also taken into consideration fact that almost 50% of analyzed population have a deficiency in enzyme converting acetaldehyde, carcinogenic product of alcohol metabolism, to acetate and that the alcohol is indirect risk factor in PC [31].

It is worth noting that two homologues of p53 gene, p73 and p63, mostly unmutated in human cancers, could in their active forms (TAp73 and TAp63) direct the cell with damaged DNA on the path of apoptosis without functional p53, while the reverse situation is impossible [27].

Genes analysis of susceptibility to PC embraced also mainly connected with breast and ovarian cancer BRCA2 gene, PALB2 (partner and localizer of BRCA2 gene known from familial form of breast cancer), genes associated with autosomal and dominant forms of pancreatitis (SPINK1 and PRSS1 genes, respectively) [11, 15, 32]. Nearly 10% of PDAC patients are carriers of mutation of BRCA1, BRCA2, PALB and other genes engaged in DNA repair [2]. Analysis of sporadic and familial PC individuals showed almost 40% increased risk of cancer when there is PRSS1 mutation and long-standing hereditary pancreatitis. This risk is higher when patient smoke [33]. Some papers indicate also a role of ABO genes in increasing risk of PC, mainly in group of non-0-blood patients. Seropositivity for *H. pylori* additionally increases this connection [11, 15, 32].

Some genetic changes are connected with DNA mono or double strands breaks induced by radiation or chemoradiation treatment. Those damages are repaired mostly by base excision or homologous recombination [34]. The DNA damage repair is relevant not only for normal tissue but also for cancer one. Uncontrolled proliferation of cells may result in disruption of basic function of the cell [35].

Li *et al.* noticed possible influence of DNA repair genes: ATM serine/threonine kinase gene (*ATM*), ligase III-DNA-ATP-dependent gene (*LIG3*) and ligase IV-DNA-ATP-dependent gene (*LIG4*) which, in conjunction with other factors or alone, modify the risk of pancreatic cancer.

Homozygote *LIG3*-39AA, despite an intronic localization, and yet unknown function, seems to be a

protective genotype in PC. There is also an interaction, of statistically significance character, between *ATM* D1853N, *LIG4* C54T, diabetes and risk of pancreatic cancer [36].

Another genes polymorphisms analyzed as modifying risk factors, were three genes related in the same DNA repair pathway. The X-ray repair cross-complementing group1 gene (*XRCC1*) polymorphism Arg194Trp, could increase PC risk only in combination with other changes in apurinic/apyrimidinic endonuclease 1 (*APE1*) Asp148Gln or O^6-methylguanine-DNA-methyltransferase (*MGMT*) Leu84Phe polymorphisms [37, 38]. Some of mutations, for example Arg399 in XRCC1 gene, could pretend to be a risk factor and have an influence on therapeutic response. Also mutation which inhibit an activation of APE1 gene are connected with better results of gemcitabine treatment [35]. Previous analysis of *XRCC1* variants (Arg194Trp and Arg399Gln) found them to be protective against tobacco based cancers (194Trp genotype) and as a risk factor in light smoking but protective in heavy smoking (399Gln) individuals [39].

A controversial role of *OGG1*(Ser326Cys) polymorphism was also debated in many papers including meta-analysis. It is suggested that this particular change is present in many cancers and has different impact on them. However, in PC, only dominant model of heterogeneity could be associated with susceptibility of cancer and has not race-specific character [40].

Some authors hypothesized that genetic variants in DNA repairing genes may affect therapy and prognosis through influence on radiosensitivity. Analysis indicates genetic variants of *RecQ1* (A159C), *RAD54L* (C157T) and *ATM* genes as an independent predictors of survival [5]. Li *et al*. described helicases as a group of proteins taking part in DNA repair process in disorders connected with chromosome instability and predisposition to malignancies. The RecQ family of helicases is involved in controlling of proper cell cycle and further functioning of tumor suppressors. The *RecQ1* gene is located in the same region of genome as *K-ras* gene and is associated with DNA mismatch repair. Another member of helicases family, *RAD54L*, is involved in DNA repair via homologous recombination and is described as a tumor suppressor gene. Both genes (*RecQ1* and *RAD54L*) homozygotic variants decrease survival almost of 6 months, considered their significant role in overall survival [34].

Couch *et al*. analyzes 33 polymorphic gene sites in correlation with pancreatic cancer risk. Two of single nucleotide polymorphisms (SNPs), in *APC* (adenomatous polyposis coli gene) and *NIN* (ninein gene) genes, were statistically significant and associated with an increased and decreased risk, respectively. Other genes and their variants were significant taking into consideration BMI or smoking habit (for example *MCPH1* gene polymorphism associated with increased risk former and ever smokers) [20]. Jang *et al*. confirmed a reducing character of *NIN* polymorphisms on PC risk [41].

A few more factors indicate a similar influence with interaction with cigarette smoking: *FYN* (tyrosine protein kinase Fyn), *SNW1* (SNW domain containing protein 1) and *PRKCA* (protein kinase C alpha). In group of increasing risk polymorphisms were *PLK2* (TopBP1, polo-like kinase 2) and *MCPH1* (microcephalin). The last analyzed polymorphic site was in high linkage disequilibrium with those described by Couch *et al*. [41]. Interesting was also analysis of β-catenin signaling cascade, which is overexpressed in over 65% of pancreatic tumors, and possible participation of genetic variants in *AXIN2* gene (axin2 gene) [20].

In the meta-analysis of Mazaki *et al*. concluded, that potential gene variants in genes candidates connected with carcinogenesis (*CYP1A1, GSTM1, GSTT1, NAT1, NAT2, UGT1A*) did not result in influence on risk of PC [10]. However, previous analysis showed such relation between *NAT1*(N-acetyltransferase 1 gene) and *CYP1A2* (cytochrome P450, family 1, subfamily A, polypeptide 2 gene) genotypes in heavy smoking females [42].

Earlier investigation of Vrana *et al*. suggest a role of *CYP1B1* (cytochrome P450, family 1, subfamily B, polypeptide 1 gene) polymorphism Val432Leu, located in heme-binding domain of enzyme, in lower risk of PC when Val/Val genotype is presented in Slavic population, however its significance do not allow to be a prognostic factor [43].

Analysis on connection of GSTs (glucotransferases, mu *GSTM1*, pi *GSTP1* and theta *GSTT1*, group of detoxification genes) considered an association between the null-genotype of *GSTT1* gene and increased risk of PC in Asians but no in Caucasians, Africans or Japanese [44-46].

In the paper of Mazaki *et al*. were also analyzed methylation gene *MTHFR* (methylenetetrahydrofolate reductase gene, two polymorphic variants), DNA repair gene *XRCC1* (four genetic variants), pro-inflammatory gene *TNFa* (tumor necrosis factor α, a promoter variant in position -308), *ALDH2* gene (aldehyde dehydrogenase) participating in alcohol metabolism and two polymorphic variants of *SPINK1* gene (serine peptidase inhibitor, Kazal type 1 gene). None of analyzed variants was associated with risk of pancreatic carcinoma. However, analysis indicated on

some connections between genotype *MTHFR* 677TT in group of smoking Caucasians and increased risk of PC as well as significant increased risk in polymorphic variant *ALDH* 2*1*2 [10].

In the other hand, another meta-analysis concludes that above polymorphism in *MTHFR* is associated with risk of pancreatic carcinoma in East Asians but not in Caucasians [47]. None of above conclusions does not interfere with reduced cancer risk in the case high intake of folate from plant food sources [31].

There are evidences that dietary intake of variant floral compounds (grains, fibre, fruits and vegetables) in association with variable genes polymorphisms could have an influence on risk of PC. The group of increasing risk changes includes catalase (*CAT*) and *GSTP1*, while to those with reducing character belongs glucosidase alpha acid (*GAA*), *UGT2B4* (UDP-glucuronosyltransferase 2 family, polypeptideB4) and *MT1E* (metallothionein 1E) [48].

Polymorphic site could have also a prognostic character which proved Avan *et al*. analyzing *XPD*-Lys751Gln presence in pancreatic ductal carcinoma patients combine with chemotherapeutic treatment. In gemcitabine treated group was no association between polymorphism presence and risk of death or tumor progression, but it was in group treated four-drug regimens. It is connected with different ways of DNA repairing. Polymorphism examination, before starting chemotherapy, could help in personalize treatment [49]. Gemcitabine preoperative treatment individuals, with resectable PC, in connection to combined genotypes of gemcitabine metabolism genes, described by Okazaki *et al*. considered an association with toxicity and tumor response, as well as overall survival [50].

Inflammation and pancreatic cancer

In non-pathological conditions, immune system and accompanying cytokines secretion is a first-defense reaction of organism. Process of inflammation, with migration of immune cells, presentation of foreign as well as own, but failured antigens, and production of multiple pro- and anti-inflammatory factors is a part of healing. However long maintenance of pathological inflammation, caused by for example chronic pancreatitis, can form connection between inflammatory process and carcinogenesis, and such chronic inflammatory basis is present in almost 15% of cancers [51]. When damage tissue is repaired, inflammatory signals of survival and proliferation can promote growth of both, normal and tumor cells [52]. Cytokines, an integral part of inflammation, play role in this process as well as in metastasis formation and cancer growth.

Some cytokines expression such as transforming growth factor β (*TGFβ*), tumor necrosis factor α (*TNFa*), Toll-like receptor 4 (*TLR4*), nuclear factor κB (*NFκB*) or hypoxia inducible transcription factor 1 (*HIF1*) increased in pancreatic cancer.

Under normal conditions TGFβ plays suppressive role in carcinogenesis, influences on cell growth regulation and apoptosis process. In most PC tissues, however, occurs the genetic TGFβ loss or disturbances in its pathway. In cancer tissue *TGFβ* is expressed by tumor cells and then stimulates expression of factors responsible for cells survival or suppressing some immune reactions which could be toxic for tumor [51, 53]. Overexpression occurrence indicate on poor outcome, correlated with progression of cancer, metastasis as well as angiogenesis process [51, 53, 54].

Tumor necrosis factor α (*TNFa*), associated with pro-apoptotic abilities [55], is also overexpressed in cancer tissues, especially in advanced tumor stages. As *TGFβ*, is correlated with poor outcome and reduced survival rate. The *TNFa*-308A genotype is showed as a factor increasing the protein expression which could be related with nuclear protein binding differences [53].

Hypoxia-inducible transcription factor 1α (*HIF1a*) is overexpressed in hypoxic cancer conditions, being regulator of other genes and thus influence on cancer biology. Lipopolisacharide (LPS) can induce NFκB activation on TLR4/MyD88 pathway which enhances cellular invasion [56]. LPS also may cause accumulation of HIF1α and TLR4 dependent effect. Nuclear factor κB is required in TLR signal pathway and thus may modulate the HIF1α protein. In case of *HIF1a* and *TLR4* expression of their mRNA in cancerous tissues is correlated with tumor size, pathological stage of tumor, lymph node involvement and venous invasion. Overexpression of both factors reduces patient survival for almost 8 and 7 month, respectively [57].

NFκB, with interleukin 8 (IL8) are mediators of inflammation in chronic pancreatitis, the first one being activated in cancer tissue inhibits apoptosis and induce progression of pancreatic cancer [55, 58].

Every genetic change, which up- or down regulate inflammatory-associated genes expression, as well as those which influence on their proper structure and function, may modulate risk of PC.

Mitochondrial DNA changes

Investigations on possible molecular basis are focused not only on nuclear DNA changes but also on mitochondrial ones. The polyploidy of mitochondrial genome connected with a presence of many

mitochondria in one cell, gives rise to hypothesis of the incidence of heteroplasmy (co-existing of wild and mutant copies of mtDNA in one cell) which seems to be very decisive. Impact of mutation depends on amount of mutated mtDNA and its proportion to wild variant [59]. Heteroplasmic mutations seems to have a subtle influence on oxidative phosphorylation. Most of mutated variants have a missense or silence character [60].

Mitochondrial genome is able to independent (to nuclear DNA) replication [59], however some connections with cell cycle are suggested [61]. Inheritance of this genetic material is strictly maternal [62, 63]. Mendelian-population genetic approach is not able to explain an inheritance *de novo* mutations in mitochondrial DNA and appearance of clinical presentation among the one family members [64, 65].

Mitochondrion is equated with the energetic centre of the cell. It has also its impact on apoptosis, as well as carcinogenesis and can play a crucial role in anticancer defensive processes. Mitochondrial participation in diseases is normally associated with nervous and muscles tissue disorders and is not age-dependent [61]. The proximity of oxidative products have an influence on frequency of mutations, while lack of histones or efficient repair systems increasing risk of accumulation of damaged or mutated sequences. This events often accompanying different types of cancers, indicates the presence of numerous changes in mitochondrial DNA (mtDNA).

Speaking of crucial role of mitochondria in apoptosis, any alterations in their function may lead to carcinogenesis. Especially vulnerable sequences for mutations, are in triple-stranded mtDNA structure, known as (D)-loop, which contains origin of replication sites and transcription promoters. Mutations in this region does not occur often in PC, being rather some epiphenomena. One of them, T16519C, reduces life expectancy and increases risk of PC-associated diabetes mellitus [39, 66].

Pancreatic carcinoma is however no exception of presence changes of mtDNA. Coding or regulatory sequences demonstrates a homoplasmic mutations (domination of mutant mtDNA) in complexes I, III, IV and V of mitochondrial genes [59]. Changes could be detected in the early stages of cancer and confirm a multistep progression of carcinogenesis process [59, 67].

Wang *et al*. studied 24 mtSNP (mitochondrial single nucleotide polymorphism) sites and their possible association with cancers. Three of them, mtSNP11719 (rs2853495) in coding region of *ND4* gene, mtSNP3010 and mtSNP1719 both in coding sequence of 16SrRNA appear to be associated with PC, taking into consideration covariates like age, gender etc. [7].

Conclusions

Excluding any other reasons but genetics, there is almost impossible that pancreatic carcinoma could have a monogenic basis. It should be rather classified as a multigene-based disease, where each gene has an additive impact of its course. Up to now, all studies indicate that the disease could be related to genetic material dysfunction, both nuclear and mitochondrial DNA, however, most relations are significant only in consideration of environmental factors, which predispose to PC development.

At the moment, the only reasonable solution, is further, continuing, maybe multi-centre study of PC genetics. Only in such studies could be found a specific "switch on" or "switch-off" gene or, what is more possible, group of genes, characteristic for pancreatic carcinogenesis.

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Competing Interests

The authors have declared that no competing interest exists.

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