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REVIEW

Systems Oncology: Bridging Pancreatic and Castrate Resistant Prostate Cancer

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Abstract

Large investments by pharmaceutical companies in the development of new antineoplastic drugs have not been resulting in adequate advances of new therapies. Despite the introduction of new methods, technologies, translational medicine and bioinformatics, the usage of collected knowledge is unsatisfactory. In this paper, using examples of pancreatic ductal adenocarcinoma (PaC) and castrate-resistant prostate cancer (CRPC), we proposed a concept showing that, in order to improve applicability of current knowledge in oncology, the re-clustering of clinical and scientific data is crucial. Such an approach, based on systems oncology, would include bridging of data on biomarkers and pathways between different cancer types. Proposed concept would introduce a new matrix, which enables combining of already approved therapies between cancer types. Paper provides a (a) detailed analysis of similarities in mechanisms of etiology and progression between PaC and CRPC, (b) diabetes as common hallmark of both cancer types and (c) knowledge gaps and directions of future investigations. Proposed horizontal and vertical matrix in cancer profiling has potency to improve current antineoplastic therapy efficacy. Systems biology map using Systems Biology Graphical Notation Language is used for summarizing complex interactions and similarities of mechanisms in biology of PaC and CRPC.

Keywords Pancreatic cancer · Castrate resistant prostate cancer · Cancer marker · Systems oncology · Cancer profiling

Introduction

Current knowledge of cancer biology shows that all cancer types share a number of similarities in the mechanisms of their etiology and progression. On the one hand, such cancer biology poses a significant problem to the discovery of specific biomarkers for early detection of different cancer types. On the other hand, it provides an opportunity for another application of current antineoplastic therapy in those cancer types for which a form of therapy was not initially developed.

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Cancer initiation and progression is a complex network of mechanisms in which genome and epigenome alterations, receptor and hormone levels, glycosylation and immunological response pay crucial role. In order to make a horizontal comparison between two cancer types we selected PaC and CRPC due to (a) still unsatisfactory therapy options and low overall survival for both cancer types, (b) challenging similarities in the impact of sex hormones on their biology and (c) diabetes as a chronic disease which appears to have a significant role in both cancer types either in their etiology or as a side effect of therapy.

In men, prostate cancer (PC) is the 6th and PaC the 8th cause of death from neoplastic diseases worldwide [1]. The global incidence rate of CRPC and PaC is the same, 8 per 100,000 person years [2, 3].

Castration-resistant prostate cancer (CRPC) is an advanced form of PaC in which, despite deprivation of testosterone, progression occurs. Reactivation of AR in CRPC after testosterone deprivation may be explained by (a) mutations or splicing events to its ligand-binding domain, which facilitates the appearance of a promiscuous receptor that may be activated by other molecules including various steroid hormones and antiandrogens [4], (b) amplification of the AR gene, which

is detected in 30% of tumor samples, accompanied by an increase in AR stabilization [5], (c), high intraprostatic levels of testosterone [6–9] resulting in paracrine and autocrine supply of androgens sufficient for CRPC promotion.

Biology of PaC is poorly understood but it is associated with pancreatitis, smoking and stress [10]. It is a highly aggressive neoplasm. Although genomic instability, aneuploidy and mutations in KRAS, CDKN2A, TP53 and SMAD4/DPC4 are associated with PaC etiology and progression, these are nevertheless still poorly understood [11, 12].

Diabetes is one of landmarks, which links PaC and CRPC. Diabetes is a major systemic side effect of androgen deprivation therapy in CRPC and diabetes is a risk factor for development of PaC [13, 14].

Both CRPC and PaC are associated with poor survival rates due to limited therapy efficiency. PC incidence increases during aging, when serum testosterone levels decrease but estrogen level remains constant, which may suggest that the estradiol vs testosterone ratio, rather than serum levels of each steroid, is crucial in PC development [15]. Similarly, PaC's highest incidence has also been measured during postmenopausal period [16] but the impact of the estradiol vs testosterone ratio on PDAC's increased risk has never been studied.

Epithelial to mesenchymal transition, that means trans-differentiation, which involves AR mechanism – is another key mechanism in progression of both cancer types [17].

The aim of this study is to show a new concept based on system oncology [18], which may enable the mirroring of antineoplastic therapy between two entirely different cancer types. Biology of PaC and CRPC is compared using literature without any limits in terms of time of publication, with reliable statistical methods and study models. Case reports were not included.

Rationale

Literature search revealed over 30 different molecules that are similar between PaC and CRPC [Table 1]. The profiling of pathways in which these molecules are involved clearly shows that androgen and estrogen receptors have a prevalent role in most of these and that diabetes is a chronic disease which may present a risk factor in both cancer types, either in their etiology or in progression.

Similarities in pathological processes between organs usually stem from their common embryology and developmental processes. From developmental standpoint, pancreas has endodermal origin [19]. Some of key regulator factors in pancreas development are Sox9+, Neurogenin3 (Ngn3), a basic helix-loop-helix (bHLH) transcription factor, Hedgehog system, the home box gene Pdx1, Wnt and Notch signaling [20–25]. In prostate cancer, which also originates from endoderm [26], during embryonal development Sox9+, Notch, bHLH and Hedgehog system also play a significant role [27–30]. Mechanisms and factors crucial for intrauterine development of both organs also take part in their carcinogenesis [27, 29, 31, 32]. Thus, for example, the progression of PaC and the transition of prostate cancer towards CRPC are orchestrated by an aberrant activation of Wnt, followed by enhanced expression of AR target genes [33–35].

PC and PaC are adenocarcinomas continuously dependent on a balanced axis between androgenic and estrogenic stimulation as evidenced by the presence of these receptors in all stages of these diseases [36, 37]. It is shown that estrogen can activate AR target genes, such as MMTV-long terminal repeat or prostate-specific antigen, in the presence of wild-type AR and the cofactor ARA70 (NCOA4) [38]. This synergistic effect may also be important in maintaining tumor androgen-receptor levels in pancreatic adenocarcinoma patients in whom circulating androgen levels are low and estradiol levels are raised compared to age- matched healthy controls [39, 40].

Both cancer types have an increased Prostate Specific Antigen (PSA), which belongs to the family of kallikrein [klk], and both klk3 (prostate) and klk7 (PaC) are androgen dependent [41–43]. The association of KLK7 expression and poor outcome of PaC suggests that inhibiting either KLK7 expression and/or activity could be a therapeutic strategy [43]. Gain in PC and PaC at 19q13, the location of klk3 and klk7 genes, and subsequent overexpression of the genes were associated with poorer survival [44–46].

Blockage of ARs does not inhibit growth of CRPC and PaC cells over a longer period of time [47]. The AR variant 7 (AR-V7) is a PC-specific AR isoform that is ligand independent [48]. There is still no data on the presence of AR-V7 in PaC. It is shown, however, that Polo-like kinase 1 (Plk1) inhibitor suppresses the growth of AR-V7 positive PC cells [49]. Plk1 is also a significant regulator of PaC cells proliferation [51, 52]. Thus it could be suggested that future investigations of PDAC should focus on the presence and interaction between AR-V7 and Plk1. Iinhibition of Plk1 enhances efficacy of antidiabetic drug metformin against the progression of androgen-dependent PC to its castration-resistant stage [50].

Same as in PaC, in PC high levels of 5α-dihydrotestosterone that activate AR and promote tumor progression have been observed [53, 54]. Both cancer types probably share the same mechanism of testosterone production bypassing, which in both cases have low levels [53]. The main route of dihydrotestosterone synthesis in CRPC, by which testosterone is bypassed, goes via 5α-reduction of androstenedione to 5α-androstenedione, aftermath converted to dihydrotestosterone [55].

There are three estrogen receptor types which are expressed in tumor tissue. In PaC, estrogen receptor alpha [ERα] is mostly stromal whereas estrogen receptor beta (ERβ) is differentially expressed in prostate epithelium during carcinogenesis [56, 57]. Estrogen receptor GPR30 expression is

Table 1 Similarities in receptor, membrane proteins and enzyme levels between PDAC and CRPC

Hormon/Protein/Gen molecule characteristic	Pancreatic cancer	Castration-resistant prostate cancer	Reference
LHRH Luteinizing hormone	high	high (therapy)	[114]
Estradiol	high	high/low	[36, 115]
5 alpha reductase	high	high	[116, 117]
Androstenedione	high	high	[54, 118]
Testosterone	low	low	[40, 91]
5α-dihydrotestosterone	high	high	[53, 54]
Androgen receptor (AR)	high	high	[60, 119]
ERα (estrogen receptor alpha)	positive	low	[119, 120]
ERβ (estrogen receptor beta)	low	low	[119–121]
CYP19A1(aromatase)	high	high	[116, 122]
Kallikrein 3	high	high	[123, 124]
HER2	overexpressed	overexpressed	[88, 89, 125, 126]
SRC3	high	high	[65, 127]
GPR30	high	high	[37, 58, 128]
19q13	gain	gain	[44, 45]
IL-6	high	–	[67, 61, 129]
P300	caused by chemotherapy	present	[68, 69]
CDKN2A(p16)	inactivated	inactivated	[130, 131]
P53	loss	loss	[132, 133]
MUC1	expressed	expressed	[134, 135]
Sox9+	high	overexpressed	[136, 65]
STAT 3	activated	activated	[61, 137]
CTNNB1	present	present	[138, 139]
CXCR4	present	present	[140, 141]
FOXA 1	low	low	[52, 142]
WNT	aberrant activation	aberrant activation	[33, 34]
TWIST1	high	high	[143, 144]
IGFBP-1	high	high	[100, 145]

CYP19A1(aromatase) Cytochrome P450 family 19 subfamily A; **Kallikrein 3** (kallikrein related peptidase 3),KLK3, APS, PSA, hK3, KLK2A1; **HER2**,ERBB2 (erb-b2 receptor tyrosine kinase 2), CD340, TKR1, erb-b2; **SRC3** NCOA3 (nuclear receptor coactivator 3),ACTR, AIB1, RAC3, pCIP, AIB-1, CTG26, CAGH16, KAT13B, TNRC14, TNRC16, TRAM-1, bHLHe42; **GPR30** GPER1 (G protein-coupled estrogen receptor 1), mER, CEPR, GPER, DRY12, FEG-1, LERGU, LyGPR, CMKRL2, LERGU2, GPCR-Br; **IL-6** (interleukin 6); **FSH** (Follicule stimulating hormone); P300,(E1A binding protein), HGNC:3373, KAT3B, RSTS2;;**KRT18 keratin 18**, K18, CK-18, CYK18; **CDKN2A(p16)** (Cyclin dependent kinase inhibitor 2A), ARF, MLM, P14, P19, CMM2, INK4, MTS1, TP16, CDK4I, CDKN2, INK4A, MTS-1, P14ARF, P19ARF, P16INK4, P16INK4A, P16-INK4A; **P53** (TP53 tumor protein); **MUC1**(mucin 1, cell surface associated); **Sox9+**,(SRY-box 9), CMD1, SRA1, CMPD1, SRXX2, SRXY10; **STAT3** (signal transducer and activator of transcription 3); **CTNNB1** (catenin beta 1); **CXCR4** (C-X-C motif chemokine receptor 4); **FOXA 1** (Forkhead box A1), *HNF3A,TCF3A;* **WNT** (protein Wnt-2); **TWIST1** (Twist family bHLH transcription factor 1),*CRS, CSO, SCS, ACS3, CRS1, BPES2, BPES3, bHLHa38;* IGFBP-1 (Insulin growth factor binding proteins 1)

significantly higher in CRPC than in androgen-sensitive PC same as it is revealed that GPR30 levels are increased in PaC [37, 58]. Androgen depletion therapy does not destroy estrogen-dependent cells, which may have given rise to CRPC tumors. Thus, androgen depletion therapy is suggested to be insufficient and concurrent androgen and estrogen ablation is recommended, accompanied with the inhibition of selected steroid biosynthetic enzymes [59].

The activation of AR in PC occurs through IL-6, which increases the phosphorylation of transcription 3 signaling (STAT3) and MAPK, which in turn increases the activation of AR [60]. The IL-6 effect is mediated by the transducer and activator of STAT3, which is considered to have important oncogenic functions in PC [61]. The neuroendocrine pattern is more present in CRPC than in early stages of PaC [17, 62, 63]. In mice, it is shown that the isoflavonoid icaritin suppresses the development of neuroendocrine differentiation of PaC through inhibition of IL-6/STAT3 and Aurora kinase A pathways [17]. Other isoflavonoids, such as genistein, are shown to suppress metastatic progression of PaC [64]. Both genistein and icaritin are phytoestrogens [65]. IL-6/signal transducer and STAT3 are suggested to have important oncogenic functions in PC [61]. The IL-6/GP130/STAT3 pathway is crucial for tumorigenesis in multiple cancer types, including

PaC and presents a viable target for cancer therapy. STAT3 is one of the major downstream effectors of IL-6/GP130. Additionally, IL-6 also increases the expression of genes involved in testosterone biosynthesis in the absence of exogenous steroid precursors via *AKR1C3,* which is also a characteristic of PaC [55, 66]. Importantly, IGF-I and IL-6 may act in a synergistic manner in PaC cells [67].

Androgen receptor co-activators SRC3 and p300 are overexpressed in PaC [68, 69]. The role of p300 in PaC is still not elucidated but it is shown that SRC is a significant mediator of oncogenic hormone receptor signaling in pancreatic cancer where it promotes the expression of ER or AR [70]. Activation of SRC kinase has been linked to androgen-independent cell growth, inhibition of anti-apoptotic pathways, cell migration and adhesion, and tumor invasion, among other aspects of PC cell biology [68].

There is an interplay between diabetes, PaC and PC, which is one of the risk factors for PaC [71] and PC. It is even suggested that prostate cancer is one aspect of the insulin resistance syndrome [72]. Patients with diabetes progress faster to CRPC than those without diabetes [73]. Homozygous GG carriers of the sex hormone binding hormone +5790 G > A, which is suppressed by insulin have increased risk of developing CRPC [74, 75]. Androgen deprivation therapy in PC patients is associated with an increased risk of diabetes [76]. Metformin, an oral diabetes medicine, which is already shown to be promising in treatment of PaC is also candidate for treatment of CRPC. In both cancer types metformin acts via activation of the AMP-activated protein kinase (AMPK) [77–79].

Hypothyroidism is associated with a higher risk of PaC and antiandrogen therapy in CRPC [80, 81]. A significant increase in TSH and a decrease in FT4 serum level were detected in PC patients under testosterone deprivation therapy [82]. Additionally, an increase in TSH is a biomarker of good response to antiandrogen therapy in PC patients [83].

HER-2 (erbB-2) belongs to the family of Type I receptor tyrosine kinases and its overexpression is important in the pathogenesis and progression of many tumors [84]. Androgen-independent sublines of LAPC-4 PC cells express high levels of HER 2, which activates the AR pathway at low levels of androgen and increases AR signaling [85]. In PaC, overexpression of HER 2 is observed and correlates with lymph node metastases [86]. It is interesting that activation of HER 2 causes suppression in insulin signaling [87]. HER-2 overexpression in patients with PaC is an independent factor for a worse prognosis, while men with PC HER-2 (+) cells are resistant to treatment [88, 89].

Male PaC patients are reported to have increased levels of FSH LH and estradiol and lower levels of progesterone and testosterone while female patients have increased levels of estradiol and lower levels of LH, FSH and progesterone, than the controls. These results show dysfunction of the hypothalamic-hypophysial-gonadal axis in PaC [40, 90, 91]. In PC, higher levels of FSH are a predictor of faster transition towards CRPC [92]. This suggests that FSH may have a mitogenic effect on PC cells [93], while low LH is caused by LHRH antagonist therapy [94] and this shows similar importance of hypothalamic-hypophysial-gonadal axis as found for PaC.

The transcription factor FOXA 1 modulates ER and AR during embryonal development of prostate and pancreas [95] and in PC it directly inhibits AR expression. The loss of FOXA 1 enables aberrant AR activation in the very low androgen environment [96]. In PaC, low FOXA 1 launches epithelial-to-mesenchymal transition [52]. Additionally, Aurora kinase A [AURKA]-Twist1 is a significant axis in promoting epithelial-to-mesenchymal transition and chemoresistance in PC [97].

The TWIST1 methylation level is significantly higher in PaC compared to non-neoplastic pancreatic tissues [98]. Oxidative stress caused by castration seems to promote AR overexpression through Twist1 overexpression, which may result in a gain of castration resistance [99]. By activating STAT3 and Twist1, the insulin growth factor induces PC pathogenesis [100]. Additionally, Twist1/AR signaling is augmented in CRPC pointing to a significance of crosstalk between epithelial-mesenchymal transition and castration resistance [101].

The activated Ack1 (TNK2), an oncogenic kinase which regulates the activity of AR, correlates with the severity of

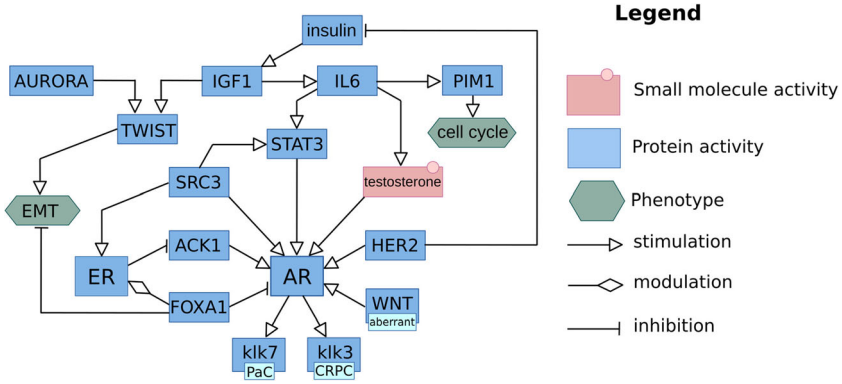

Fig. 1 Common pathways in PaC and CRPC related on AR using Activity Flow language of Systems Biology Graphical Notation

PDAC and supports development of CRPC [102]. The absence of ER, as seen in a triple negative breast cancer or CRPC, increases expression of ACK1 via SIAH2 [103].

In both CRPC and PaAC, L-type amino-acid transporter 1 (LAT1) is overexpressed [104, 105]. In CRPC, this is caused by androgen deprivation and decreased androgen signaling but the mechanism in PaC is unknown [105].

The proviral integration site for Moloney murine leukemia virus-1 PIM kinases belongs to a family of serine/threonine kinases and its downregulation causes cell cycle arrest, increased apoptosis and decreased gemcitabine and intrinsic irradiation resistance in pancreatic cancer cell lines. Pim 1 is increased both in PC and PaC [106, 107] and it is shown to be activated by IL6 in pancreatic cell line models [108]. Both PIM-1 isoforms promote PC cell growth under low-androgen conditions [109, 110], which is also reported in an animal model in which androgen deprivation significantly increased PIM 1 levels [111].

Aryl hydrocarbon receptor (AhR) is active in CRPC and in the most invasive sub-type of PaC cells (QM-PDA). Its inhibition reduced growth and the selective modulators inhibited invasion through a non-genomic AhR pathway [112].

In order to summarize the collected data on the common pathways in PaC and CRPC related on AR are presented using Activity Flow language of Systems Biology Graphical Notation (Fig. 1) [113]. Map shows the interaction of AR with other molecules described in this paper, known to have a significant role in the aetiology and progression of PaC and CRPC.

Conclusion

All cancer types share a large number of common mechanisms such as disturbance of estrogen levels and its receptors, polymorphisms of genes associated with DNA repair or cytokine levels. A growing body of evidence indicates that there are more similarities than differences in cancer biology, which is an advantage for therapy but a disadvantage for diagnostics and follow-up of patients after completed therapy. During the last decade, chemotherapy development has shown slowing down in terms of new solutions and immunotherapy due to still unforeseen long and short term side effects and hence it still does not offer a reliable new approach. Large number of biomarkers, key molecules that are positioned at cancer check points, are in the process of investigation but their roles in different cancer types are anecdotally rather that systematically compared. Such a significant gap in horizontal profiling of cancer biology may hide new options for understanding better the efficacy of the application of available therapy types.

This study suggests that PC due to androgen deprivation therapy evolves to CRPC, a cancer which has significant similarities with PaC, as well as with diabetes, a common chronic disease in their etiology or progression. PaC and CRPC share a number of common mechanisms and metabolic disturbances such as levels of estrogen and androgen receptors, growth factors, membrane proteins, and genetic profile. Such similarities give rise to the investigation of the application of pancreatic cancer therapy also to CRPC and vice versa. The proposed matrix of similarities between these two cancers provides a tool for similar analysis of other cancer types. It may also significantly add value and cut costs in the pharmaceutical industry and oncology.

As an important additional conclusion, which should be stated, data collection was troubled by the change in proteins' and genes' nomenclature during the past few decades. Development of unified nomenclature is crucial as all future studies sharing a similar concept will be done by software which requires clear semantics.

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Compliance with Ethical Standards

Conflict of Interest Authors declare no conflict of interest.

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