The ‘N-factors’ in pancreatic cancer: functional relevance of NF-κB, NFAT and Nrf2 in pancreatic cancer

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Pancreatic ductal adenocarcinoma (PDAC) represents one of the deadliest malignancies, with an overall life expectancy of 6 months. Despite considerable advances in the understanding of the molecular mechanisms involved in the carcinogenesis of PDAC, the outcome of the disease was not significantly improved over the last 20 years. Although some achievements in molecular-targeted therapies have been made (that is, targeting the epidermal growth factor receptor by erlotinib), which already entered clinical settings, and despite the promising outcome of the FOLFIRINOX trial, there is an urgent need for improvement of the chemotherapy in this disease. A plethora of molecular alterations are thought to be responsible for the profound chemoresistance, including mutations in oncogenes and tumor suppressors. Besides these classical hallmarks of cancer, the constitutive or inducible activity of transcription factor pathways are characteristic changes in PDAC. Recently, three transcription factors—nuclear factor-κB (NF-κB), nuclear factor of activated T cells (NFAT) and nuclear factor-E2-related factor-2 (Nrf2)—have been shown to be crucial for tumor development and chemoresistance in pancreatic cancer. These transcription factors are key regulators of a variety of genes involved in nearly all aspects of tumorigenesis and resistance against chemotherapeutics and death receptor ligands. Furthermore, the pathways of NF-κB, NFAT and Nrf2 are functional, interacting on several regulatory steps, and, especially, natural compounds such as curcumin interfere with more than one pathway. Thus, targeting these pathways by established inhibitors or new drugs might have great potential to improve the outcome of PDAC patients, most likely in combination with established anticancer drugs. In this article, we summarize recent progress in the characterization of these transcription-factor pathways and their role in PDAC and therapy resistance. We also discuss future concepts for the treatment of PDAC relying on these pathways.

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PANCREATIC DUCTAL ADENOCARCINOMA, CHEMORESISTANCE AND TRANSCRIPTION FACTORS

Pancreatic ductal adenocarcinoma (PDAC) represents the fourth leading cause of cancer-related death in western countries. Up to 90% of PDACs develop through premalignant precursor lesions, so called the pancreatic intraepithelial neoplasias-1 to -3. The remaining cases originate in mucinous cystic neoplasia or intraductal papillary mucinous neoplasia. A recent report comparing genetically engineered mouse models with human samples elegantly described an alternative pathway, which might be important especially in familiar pancreatic cancer. In this model, the ductal cancer cells arise in the centroacinar–acinar region, possibly through a process of acinar–ductal metaplasia. Several genetic alterations in pancreatic intraepithelial neoplasias and PDACs have been extensively described. The Kras oncogene has a central role in carcinogenesis and is mutated in nearly all PDACs. Other frequent mutations are found in the tumor suppressor genes p16INK4a, p53, SMAD4 and BRCA2. Despite advances in the understanding of the mechanisms of carcinogenesis, therapeutic options in pancreatic cancer are associated with very limited or no improvement in life expectancy. Because of a difficult and late diagnosis, only 15% of the patients have a disease localized to the pancreas, allowing a potentially curative resection. The majority of patients, having a locally advanced tumor status, receive radio- and or chemotherapy. Gemcitabine or 5-fluorouracil are the most often used drugs, but such as all other therapeutic interventions they fail to significantly improve the prognosis. Even the recommended first-line combination therapy with erlotinib and gemcitabine offers only a very limited gain in life expectancy compared with a monotherapy with gemcitabine. Recently, clinical trials showed that FOLFIRINOX, an aggressive combination therapy of several chemotherapeutic drugs, improves the life expectancy from 6–7 months with gemcitabine therapy to 10–11 months in the FOLFIRINOX group. Because of the higher rate of severe side effects and some problems in the group composition (a high proportion of pancreatic cancer localized in the tail of the pancreas), it still remains to be seen if FOLFIRINOX will indeed be the future gold standard in the palliative setting.

Thus, limitations in curative and, especially, palliative treatment options of PDACs demonstrate a need for new and gemcitabine-independent strategies.
NF-κB PATHWAY

The transcription factor NF-κB is involved in the regulation of expression of a variety of target genes. Among these are central regulators of apoptosis, the cell cycle and metastasis.18,19 NF-κB exists as a hetero- and homodimeric protein complex of members of the so-called Rel-family. RelA/p65, RelB and c-Rel harbor a transactivation domain along with the Rel homology domain. The Rel homology domain, also present in NF-κB1 (p50/p105) and NF-κB2 (p52/p100), functions as an interacting site for Rel-family members and confers DNA binding. In contrast, through the transactivation domain p65, RelB and c-Rel regulate the expression of their target genes. The most abundant NF-κB form is the heterodimer of p65 and p50. In the so-called classical NF-κB pathway, p65/p50 is anchored in the cytoplasm by the inhibitor of κB (IκB) proteins (Figure 1).6,18 In response to NF-κB-activating stimuli (Figure 2), the IκB kinase complex (IKK) consisting of two catalytic kinases (IKKα and IKKβ), together with the regulatory component IκKγ/NF-κB essential modulator, is activated by phosphorylation. Once activated, IKK phosphorylates the IκBs, which are subsequently polyubiquitinated and degraded by the 26S proteasome. The NF-κB dimer then translocates to the nucleus and regulates the transcription of its target genes.6,18,19

The number of NF-κB target genes is enormous and still growing.20 Among them are well-defined antiapoptotic genes like Bcl-xl, cIAP, Bcl-2 and c-Flip, which are able to inhibit the apoptotic cascade at several points, conferring resistance against chemotherapeutic drugs and death receptor ligands.6,21 Despite the fact that some reports indicate NF-κB activation can elicit proapoptotic functions,22,23 published data largely support a role for NF-κB as a central antiapoptotic factor.18,24 Meanwhile, there is firm evidence that the death receptor ligands TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) and Fas ligand induce NF-κB,17,25–27 and thereby inhibit their potential to eliminate pancreatic cancer cells. There is some controversy as to whether inducible or constitutive NF-κB activity is more important for PDAC resistance against TRAIL,30 but most reports indicate that in contrast to chemotherapeutic drugs (see below), the inducible activation confers resistance against death receptor ligands. Moreover, PDAC cells gain growth advantage by auto- and paracrine death receptor ligand loops either through secretion of the death ligands by tumor cells or by infiltrating immune cells.17,31 As already mentioned, some chemotherapeutic drugs like CPT-11 are able to induce NF-κB in a same manner as the tumor necrosis factor-α and TRAIL,32 but the studies supporting a critical role for a constitutive NF-κB activity in the resistance of PDACs against chemotherapeutic drugs are overwhelming.6,33–37 There is a multitude of mechanisms leading to this constitutive NF-κB activity. Chronic inflammation can induce NF-κB activation18,20,38 as observed in the course of chronic pancreatitis and acts as a risk factor for development of PDACs.39,40 In particular, proinflammatory cytokines, such as interleukin-1β,41 interleukin-1α42 and interleukin-8,43,44 either released by PDAC cells themselves or by immune cells, and the surrounding tissue—for example, myofibroblasts—in the course of chronic inflammation,45 can lead to the constitutive activation of NF-κB in tumor cells. As described, point mutations in Kras are present in up to 90% of PDACs and might be involved in constitutive NF-κB activation.46–49 In addition, NF-κB itself provides feed-forward loops, which are essential for pancreatic intraepithelial neoplasia and PDAC progression.47,48 Furthermore, the frequent overexpression and activation of members of the EGF/NGF signaling pathway might contribute to NF-κB-dependent tumor progression and invasive phenotype of PDACs.50–52

So far, the NF-κB target genes involved in PDAC chemoresistance, either through interference with death receptor signaling or in association with chemotherapeutic drugs, have remained elusive. There are some reports indicating that classical inhibitors

Figure 1. Scheme of unstimulated state. Depicted are the key factors of the three transcription factor pathways. Transcription factors (in blue) and the corresponding inhibitors (in red) as further outlined in this review. P, phosphorylation; Ub, ubiquitin.
mediated approaches are currently not feasible for broad clinical application. As small interfering RNA (siRNA) or other transcription factors such as STAT3 have been extensively used for pharmacological NF-κB inhibition in preclinical and clinical studies. Nevertheless, the proteasome is not only part of the NF-κB pathway, but also is a central target for therapeutic options in PDAC treatment. The proteasome is involved in the NF-κB activation pathway by degradation of IκB and is therefore extensively used for pharmacological NF-κB inhibition in preclinical and clinical studies. Nevertheless, the proteasome is not only part of the NF-κB pathway, but instead a central regulator of a variety of regulatory pathways involved in cancer initiation, progression and chemoresistance, making the proteasome a promising target in PDAC therapy, but without clear conclusions on the role of NF-κB in this context.

Beyond these chemical compounds, a growing number of natural products like curcumin, epicatechin gallate and catechin gallate have shown the potential to block NF-κB and sensitize PDACs for apoptosis without severe side effects, and might be beneficial in combination with chemotherapy drugs and death ligands. Other herbal compounds include thymoquinone, sulforaphane, dihydroartemisinin or 3,3-dimethoxybiphenyl, which block both constitutive and anticancer drug-induced NF-κB activity, and have been successfully tested in preclinical experiments for sensitization of PDAC cells against chemotherapy.

**THE NFAT PATHWAY**

The NFAT family of transcription factors is a group of calcineurin-responsive, inducible nuclear proteins. Originally described in the context of T-lymphocyte activation, increasing evidence exists showing a crucial role of this transcription factor family in the regulation of cell growth and apoptosis. Four calcium-responsive isoforms named NFATc1 (NFATc1/NFATc2, NFATc2 (NFATc1/NFATc2, NFATc3 (NFATc1/NFATc4), NFATc4 (NFATc3) are members of a family, which is under the control of a Ca(2+)-/calcineurin signaling pathway. Under unstimulated conditions, NFAT is anchored in the cytoplasm through phosphorylation of a number of serines within its highly conserved regulatory domain, which masks the nuclear localization sequence. After dephosphorylation by calcineurin, which exposes the nuclear localization sequence and masks a nuclear export sequence, NFAT enters the nucleus and regulates the transcription of target genes by dimerization with NFAT family members, but also with other transcription factors, such as activating protein-1 and NF-κB (Figure 2 for classical activation pathway and Figure 3 for interaction of the pathways). Termination of NFAT activity is mediated by multiple mechanisms, including inhibition of calcineurin and phosphorylation of NFAT by nuclear kinases. Hereby, NFAT is rephosphorylated, the nuclear export sequence unmasked and the nuclear localization sequence masked. In addition to the still growing number of regulating kinases and phosphatases, other regulatory mechanisms including sumoylation, ubiquitination and de novo expression of NFAT members exist. Thus, as in the case of nearly all other signaling pathways, the oversimplified linear model of a merely Ca(2+)-/calcineurin-dependent signaling pathway must be revised to reflect a complex regulatory network. Recent reports indicate a crucial role of NFATc1/NFAT2 and NFATc2/NFAT1 in different steps of PDAC carcinogenesis and chemoresistance. NFATc1/NFAT2 is activated by serum in PDAC cells and binds to a serum-responsive element within the proximal c-myc promoter, initiating p300-dependent histone acetylation, which creates a local chromatin structure permissive for the inducible recruitment of Ets-like gene (ELK)-1. This NFATc1/NFAT2-dependent pathway...
results in the promotion of c-myc-dependent growth of PDAC cells. Recently, the same group elegantly delineated an NFATc2/NFAT1-driven pathway in PDACs, which, by targeting a p15(INK4b)-mediated fail-safe mechanism, promotes pancreatic cancer growth.

However, besides this well-documented role of NFAT in pancreatic cancer development and growth regulation, there are only very limited data on the suitability of NFAT as a molecular target in pancreatic cancer therapy. For other malignancies, preclinical and limited clinical data exist (Figure 3). Cyclosporin A and FK506 represent two structurally unrelated, clinically established, potent inhibitors of calcineurin. These are widely used immunosuppressive agents that prevent NFAT nuclear translocation by interfering with calcineurin activation, thus resulting in the blockade of dephosphorylation of numerous other substrates in addition to NFAT. The long-term clinical experience with these drugs in transplantation medicine demonstrates a significant increase in cancer incidence in patients subject of long-term cyclosporin A and FK506 treatment. On the one hand, this might be due to the interference of these drugs with calcineurin- and NFAT-dependent immunosurveillance, and on the other hand, oncogenic effects of calcineurin inhibition might result from NFAT-independent mechanisms of cyclosporin A and FK506. Therefore, more selective NFAT targeting strategies are currently being developed. VIVIT, a peptide that interferes with the calcineurin–NFAT interaction, potently blocks dephosphorylation and nuclear translocation of NFAT, and has been shown to attenuate breast cancer cell invasion. Thus, VIVIT administration might be a specific measure to block the oncogenic effects of NFAT in PDACs. As the delivery of the VIVIT peptide to the tumor in an in vivo setting could be difficult other small molecule inhibitors like L-732531, an analog of FK506, and ISATX247, a potent and less toxic analog of cyclosporin A, are promising. However, up to now sufficient in vivo data of the capacity of NFAT inhibitors to reduce chemoresistance and tumorigenesis, beyond their well-documented activities in immune suppression, are missing—especially for pancreatic cancer.

**THE NRF2 PATHWAY**

Nrf2 is a transcription factor belonging to the family of cap'n' collar basic leucine zipper protein family, and represents a key regulator of the cellular defense against oxidative stress. Under homeostatic conditions (Figure 1), Nrf2 is anchored in the cytoplasm through kelch-like ECH-associated protein 1 (Keap1). Keap1 is an E3 ubiquitin ligase mediating polyubiquitination of Nrf2, thereby tagging it for degradation by the 26S proteasome. In addition, Keap1 can terminate the Nrf2 activation through retrieving the transcription factor from the nucleus. Similar to IκB in NF-κB signaling, Keap1 represents a classical feedback regulator itself, being a target gene of Nrf2.

Nrf2 is activated by numerous cellular conditions and stimuli (Figure 2). In general, through modifications of critical cysteine residues of Keap1 and of Nrf2 the interaction of both molecules is disturbed, leading to the nuclear translocation of Nrf2. In the nucleus, Nrf2 interacts with small v-maf musculoaponeurotic fibrosarcoma oncogene homolog (sMAF) regulator proteins and binds to antioxidative response elements in the promoters of a plethora of target genes. For a long time, Nrf2 was considered an attractive and quite hopeful target for chemopreventive strategies to maintain cellular redox balance. Through induction of antioxidative target genes, Nrf2 could protect non-transformed cells against DNA damage and, thereby, may prevent mutagenesis. However, there is growing evidence that Nrf2 activation can lead to tumor development and enhanced chemoresistance once a malignant transformation occurred. Stable overexpression of Nrf2 results in enhanced resistance of cancer cells to chemotherapeutic
agents, whereas targeting Nrf2 renders cancer cells more susceptible to these drugs.  

Interestingly, the strategy of using Nrf2 inhibitors (Figure 3) to increase the efficacy of chemotherapeutic agents is not limited to certain cancer types or anticancer drugs and may be beneficial during the course of chemotherapy in general.  

Besides direct regulation of expression of phase-II enzymes and transporters for xenobiotics and drugs accounting for direct detoxification of anticancer drugs, Nrf2 is a crucial regulator of proteasome activity by transcriptional control of several subunits of the proteasome  

and conferring resistance against a wide variety of apoptotic stimuli.  

Through a plethora of alterations, such as gain-of-function mutations of Nrf2 itself or, more frequently, through loss-of-function mutations, promoter hypermethylation, miR targeting or succination of the Nrf2 inhibitory protein Keap1  

activity is upregulated in several types of solid cancers, for example, in colonic, thyroid, endometrial, lung, ovarian, breast and pancreatic cancer.  

Beyond these genetic alterations, inflammatory carcinogenesis is characterized by increased levels of metabolic and oxidative stress, leading to an exaggerated Nrf2 activity in tumors.  

As a consequence of the increased Nrf2 activity, tumor cells acquire protection from apoptosis  

and are more capable to proliferate, both conditions favoring tumorigenesis on the one hand and making tumor cells more resistant to chemotherapeutic agents.  

The small interfering RNA-mediated inhibition if Nrf2 activity sensitized the cell lines for chemotherapeutic drugs.  

Another group showed that increasing Nrf2 by overexpression or through induction on endogenous Nrf2 conferred protection of PDAC cell lines against apoptotic stimuli, leading to the conclusion that strategies to pharmacologically manipulate the levels and/or activity of Nrf2 may have potential for PDAC therapy.  

Several strategies for induction of Nrf2 activity to prevent cancer development were propagated over the last couple of years.  

Most of these strategies used food compounds like sulforaphane and triterpenoids.  

As is increasingly acknowledged that once premalignant or tumor cells acquired a persistent Nrf2 activity tumorigenesis and chemoresistance are substantially promoted, new strategies for inhibition of these pathways are under intensive investigation. Recently, retinoic acid receptor-β or estrogen-related receptor-β have been described to inhibit Nrf2 activation, but in PDAC cell lines estrogen-related receptor-β is not detectable and retinoic acid up to now failed to improve the outcome of PDAC patients due to profound molecular resistance mechanisms.  

Thus, besides genetic modification and or small interfering RNA-mediated knock down of Nrf2, pharmacological strategies using natural compounds have been identified to directly inhibit Nrf2. The alkyloids luteolin or tricinoline would be attractive tools for sensitization of tumor cells to apoptosis, in particular, as they have already been used in clinical trials (for example, diabetes). Intriguingly, tricinoline was shown to have great potential to inhibit PDAC tumor growth in vitro and in vivo.  

A recent screening of pharmacological inhibitors identified 4-(2-cyclohexylethoxy) aniline (IM3829) as highly potent in the inhibition of Nrf2. IM3829 greatly enhances the radiosensitivity of human lung cancer cells in vitro and in vivo, and this compound may also be effective in chemosensitization of PDAC cells.

THE THREE 'NS': INTERACTION OF THE PATHWAYS

As already mentioned NF-κB, NFAT and Nrf2 are influencing each other through direct interaction and/or modification of their signaling pathways (Figure 3). For instance, NF-κB and NFAT are members of a superfamily of transcription factors. They share similar DNA-binding domains, and especially the regulation of COX-2 expression depends on parallel activation of both pathways. In line with this, full activation of the BLYS promoter requires parallel constitutive activity of NF-κB and NFAT in aggressive B-cell lymphoma.  

Despite the well-established role of NFAT and NF-κB in regulating COX-2, and the importance of COX-2 for chemoresistance of PDAC, up to now evidence is missing that the two pathways directly interact with each other in PDACs.  

An interaction of Nrf2 and NF-κB is increasingly described. Most of the reports concentrated on the effects of oxidative stress induced Nrf2 activation, leading to alterations in NF-κB signaling. In this context, Nrf2 activation can inhibit NF-κB-dependent proinflammatory signaling by an unknown mechanism and epigallocatechin-3-gallate elicits at least some of its anti-inflammatory properties by Nrf2-mediated NF-κB inhibition.  

However, the opposite effect is evoked by Nrf2-mediated transcription of proteasome subunits that leads to an exaggerated activity of the 26S proteasome, and thereby facilitates the release of NF-κB from IκB. As dendritic cells from Nrf2 knockout mice exhibit no change in basal NF-κB activity, it remains unclear if the proposed interaction of both pathways is of functional relevance in epithelial cells of PDACs. Keap1 seems to be a central regulator of both pathways.  

Through the double glycine repeat domain, Keap1 can bind to other proteins directly or indirectly, and IκB is destabilized by Keap1, which resulted in inhibiting NF-κB-derived tumor promotion. Besides these Nrf2 effects on NF-κB, this central mediator of PDAC chemoresistance can influence Nrf2 activity. A recent report showed that the NF-κB subunit p65 directly interacts with Keap1, leading to inhibition of Nrf2 activity.  

Finally, varieties of natural compounds modulating Nrf2 also affect NF-κB and vice versa. Especially, curcumin, which is reported to be a chemosensitizer of PDAC, affects NF-κB and Nrf2, or sulforaphane, which is a well-known inducer of Nrf2 but has been described also as an inhibitor of NF-κB, taking into account the tumor- and chemoresistance-promoting role of NF-κB just evoked over the last couple of years, it will be interesting to analyze whether the Nrf2 activation of many of these compounds is responsible for the failure of clinical trials in PDACs and whether a combination with Nrf2 inhibitors, such as tricinoline, can improve the outcome in NF-κB-inhibiting strategies.

CONCLUSIONS

Among the rising number of promising molecular targets in PDAC therapy, the transcription factor pathways of NF-κB, NFAT and Nrf2 are of potential interest for several reasons:

(1) All three of these pathways have been shown to be altered in PDACs in vitro and in vivo, leading to PDAC development, migration, invasion and chemoresistance.

(2) They interact with each other, and especially the counteraction of Nrf2 and NF-κB might explain some problems in targeted therapies.

(3) A battery of natural and chemical compounds with well-known clinical safety exist, making it possible to target these pathways in upcoming clinical trials for PDAC therapy in the near future.

CONFLICT OF INTEREST

The authors declare no conflict of interest.
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