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Mini-review

Targeting apoptosis pathways in lung cancer

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ABSTRACT

Lung cancer is a devastating disease with a poor prognosis. Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) represent different forms of lung cancer that are associated with distinct genetic causes and display different responses to therapy in the clinic. Whereas SCLC is often sensitive to chemotherapy at start of treatment, NSCLC are less chemo-sensitive. In NSCLC different histological subtypes are distinguished and increasing efforts are made to identify subtypes that respond to specific therapies, such as those harbouring epidermal growth factor receptor (EGFR) mutations that have benefit from treatment with EGFR inhibitors. Targeting of the apoptotic machinery represents another approach that aims to selectively kill cancer cells while sparing normal ones. Here we describe different ways that are currently explored to induce apoptosis in lung cancer cells, specifically pathways controlled by TNF-related apoptosis-inducing ligand (TRAIL), BCL-2 family members and apoptosis inhibitory proteins (IAPs). Preclinical studies are discussed and for some agents results from early clinical studies and future perspectives are considered.

1. Lung cancer

Lung cancer is the leading cause of cancer related deaths worldwide. It has been estimated that more than 1 million people die with it annually and approximately 1.4 millions are diagnosed per year, 12% of which are new cases [1]. Lung cancers are divided into small cell lung cancer (SCLC) which comprises of 15–20% of total lung cancer cases and remaining 80–85% are attributed to the non-small cell lung cancers (NSCLC). On the basis of histological characteristics NSCLC is further divided into adenocarcinoma, squamous cell carcinoma and large cell

Abbreviations: ALK, anaplastic lymphoma kinase; BAX, B-cell lymphoma associated X protein; BAK, B-cell lymphoma antagonist/killer 1; BCL-2, B-cell lymphoma 2; BCL-XL, B-cell lymphoma-extra large; BH3, B-cell lymphoma-2 homology 3; BID, BCL-2 interacting domain; BIM, B-cell lymphoma 2 interacting mediator protein; BIR, baculovirus apoptosis inhibitory protein repeat; BRAF, B-raf proto-oncogene serine/threonine-protein kinase; cFLIP, cellular flice-like inhibitory protein; DcR, decoy receptor; DISC, death-inducing signaling complex; DLT, dose limiting toxicity; DR, death receptor; EGFR, epidermal growth factor receptor; EML, echinoderm microtubule-associated like protein; ERBB2, erythroblastic leukemia viral oncogene homologue 2; ERK, extracellular signal regulated kinase; FADD, Fas-associated protein with death domain; HDAC, histone deacetylases; IAP, apoptosis inhibitory protein; KRAS, Kirsten rat sarcoma viral oncogene; MCL-1, myeloid cell leukemia factor 1; MEK, mitogen activated ERK activating kinase; MET, mesenchymal epithelial transition factor; MOMP, mitochondrial outer membrane permeabilization; NSCLC, non-small cell lung cancer; OPG, osteoprotegerin; PARK2, Parkinson disease 2; PIK3CA, phosphoinositide-3-kinase, catalytic, alpha polypeptide; PUMA, *p53* upregulated modulator of apoptosis; rhTRAIL, recombinant human soluble TRAIL; SCLC, small cell lung cancer; SMAC, second mitochondria-derived activator of caspases; STK11, serine/threonine kinase 11; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand; TRAIL-R, TRAIL receptor; VEGF, vascular endothelial growth factor; XIAP, X-linked apoptosis inhibitory protein.

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lung cancer [2]. Smoking is the main causative agent in all types of lung cancers; it is strongest associated with squamous cell carcinoma and SCLC. The main histology in never smokers is adenocarcinoma. Although several attempts have been made to develop effective treatment strategies to combat lung cancer, still overall 5 years prognosis is less than 15% in NSCLC and for SCLC it is even lower [3]. SCLC's are neuroendocrine tumors and they differ from NSCLC in several aspects like biology, prognosis and response to therapy. SCLC is one of the most aggressive tumor types in man. At presentation patients most often have metastasized disease. SCLC's are initially sensitive to the chemotherapy, but even in limited disease with concurrent chemoradiotherapy and prophylactic cranial irradiation to prevent brain metastasis the 5 years survival is less than 15%. In most cases of lung cancer no symptoms or only a few are reported, and therefore most patients with lung cancer have advanced disease on diagnosis. The median survival in this group without therapy is 4 months [4].

New therapies are greatly needed for improving lung cancer treatment. Genetic analyses of NSCLC has identified both genetic and somatic mutations in EGFR and p53 genes, and somatic mutations in KRAS, BRAF, ERBB2, MET, STK11, PIK3CA and PARK2 genes. These mutations in genes have led to new strategies, aiming at these targets, such as for example mutated version of EGFR [5,6]. In this review we describe the progress made in the field of apoptosis targeted therapy for lung cancer.

2. Apoptotic cell death

Apoptosis or programmed cell death is a physiological process that provides an effective, non-inflammatory way to remove redundant or damaged cells from tissues thereby securing tissue homeostasis [7]. Inhibition of apoptosis is considered as an essential step in tumorigenesis and is one of the hallmarks of cancer, allowing the survival of cells that accumulate oncogenic events that otherwise would have been removed by apoptosis [8]. A multitude of signals activated by variable triggers, such as growth factors, cell–cell interactions, changing nutrient conditions, hypoxic conditions, and cytotoxic damage affect the status of the apoptotic machinery [7]. The caspases, specific cysteine proteases, are instrumental in the initiation and execution of apoptosis. Two main caspase activation pathways have been identified the intrinsic or mitochondrial pathway and the extrinsic or death receptor pathway. The intrinsic pathway is triggered upon disruption of mitochondria, for example as a result of DNA damage inflicted by cytotoxic agents, resulting in the release of cytochrome c into the cytoplasm [9]. Cytochrome c and dATP are required for the assembly of the apoptosome consisting of Apaf-1 and procaspase-9 and the subsequent cleavage and activation of caspase-9. Mitochondrial disruption is regulated by the BCL-2 family proteins [10,11], comprising of anti-apoptotic members, such as BCL-2, BCL-XL, and MCL-1, and pro-apoptotic members, such as BAX and BAK. Together with BH3-only proteins, including BID, PUMA, and NOXA, which appear to be sensors for particular types of stress, interactions amongst the BCL-2 family members determine whether apoptotic thresholds are exceeded [12]. BAX and BAK then translocate from the cytoplasm to the mitochondrial membrane where they make pore-like structures resulting in mitochondrial outer membrane permeabilization (MOMP) and subsequently the release of cytochrome c, second mitochondria-derived activator of caspases (SMAC) and caspase activation.

The extrinsic or death receptor pathway is triggered via specific cell membrane receptors, such as Fas/CD95 TRAIL receptors, which after ligand binding can recruit FADD (Fas-associated protein with death domain) and procaspase-8 causing caspase-8 activation in a complex named the death-inducing signaling complex (DISC) [13]. Active initiator caspases-8 and -9 on their turn cleave and activate the effector caspases-3, -6, and -7 that result in the proteolytic disassembly of cells. Cellular flice-like inhibitory protein (cFLIP), a non-functional procaspase-8 homologue, can compete with procaspase 8 for FADD binding leading to suppression of apoptosis. The full activation of extrinsic apoptosis often requires the cross activation of intrinsic apoptosis that is mediated by caspase-8-dependent cleavage of BID and subsequent mitochondrial disruption [14]. The inhibitor of apoptosis protein (IAPs) family comprises proteins that can bind and inactivate caspases via one or more baculovirus IAP repeat (BIR) domains [15]. For example, X-linked IAP (XIAP) is known to inhibit caspases-3 and -9 and its anti-apoptotic activity is neutralized by the release of SMAC following MOMP [16].

3. Apoptosis as target for therapy

Standard cancer therapies such as chemotherapy and radiation eradicate tumor cells at least in part by indirectly activating the apoptotic machinery [17]. In this process the tumor suppressor p53 is an important effector that predominantly induces transcription-dependent mechanisms of apoptosis by upregulating pro-apoptotic genes such as PUMA, BAX and death receptors and subsequent activation of intrinsic and/or extrinsic apoptosis [18]. It is observed that around 50% of all types of lung cancers are associated with mutated *p53* [19]. In NSCLC and SCLC defects in the *p53* gene are observed generally caused by complete loss of one allele and point mutation in the other allele. Interestingly, G → T transversions are frequently observed that have been associated with the mutagenic activity of polycyclic aromatic hydrocarbons from cigarette smoke [19]. Non-functional p53 leads to less efficient apoptosis activation by conventional treatments. Therefore, the possibility to develop agents that directly target apoptotic mechanisms has generated a lot of excitement and could lead to more effective therapies with less toxic side effects. Currently, different apoptosis targeted therapies are being evaluated in preclinical and clinical studies in different tumor types. One may distinguish pro-apoptotic and apoptosis sensitizing strategies. Pro-apoptotic approaches aim to selectively trigger apoptosis in tumor cells such as for example by targeting tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptors. Sensitizing strategies, for example by neutralizing anti-apoptotic proteins like the inhibitor of apoptosis protein (IAPs) or BCL-2,