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LABORATORY — CLINICAL INTERFACE

Novel therapeutic targets in lung cancer: Inhibitor of apoptosis proteins from laboratory to clinic

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Summary Lung cancer is the leading cause of cancer death worldwide. Despite the introduction of new agents and schedules, chemotherapy still obtains unsatisfactory overall response rates, rare complete remissions and responses of relatively short duration. The inhibitor of apoptosis proteins (IAPS) are a family of caspase inhibitors that selectively bind and inhibit caspases-3, -7, and -9. As caspase activation is central to apoptosis, novel therapeutic drugs that target IAPs enabling apoptosis to occur have potential as a treatment of malignancy. Several agents that target core components of the apoptotic signalling pathway are currently at an early stage of development. This review reports the progress being made in characterising the IAP family, with a focus on the available data relevant to the treatment of lung cancer.

Introduction

The World Health Organisation estimates that there are currently 11 million new cases of cancer per year and this will rise to 16 million by 2020.[1] Lung cancer is the leading cause of cancer death worldwide (17% overall, 23% in males and 11% in females), with the major histological types being small cell lung cancer (SCLC), adenocarcinoma, squamous cell carcinoma and large cell carcinoma, the latter three of which are collectively referred to as non-small cell lung cancer (NSCLC). Unfortunately, the presentation in the majority of patients is with advanced, metastatic disease for which there is currently no cure. Chemotherapy, most commonly a platinum agent in combination with another cytotoxic, e.g. gemcitabine, vinorelbine or a taxane for NSCLC or etoposide for SCLC can prolong survival and palliate symptoms.[2] However, even with modern chemotherapy most patients survive for less than two years following diagnosis. Therefore, new therapeutic approaches for lung cancer are urgently required.

Tumour formation is a multistep process involving the progressive transformation of normal human cells into highly malignant derivatives. Six alterations in cell

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physiology form the hallmarks of malignant growth: self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis.[3] Chemo- and radiotherapy have traditionally been central to cancer therapy and work by causing irreparable genomic damage. However, the usefulness of such agents is limited by off-target effects on normal rapidly proliferating cells which cause dose-limiting toxicity. Improved understanding of the molecular mechanisms underpinning tumour development has led to an era of targeted therapies that selectively modulate critical molecules driving malignancy. Over recent years erlotinib and bevacizumab, that block epidermal growth factor and vascular endothelial growth factor signalling, respectively, have demonstrated efficacy in patients with lung cancer.[4,5] Despite such advances, the tumour response rates and survival times achieved remain modest. Here we review the inhibitor of apoptosis (IAP) family of proteins with respect to their functions, expression and clinical significance in lung cancer, and the current strategies in development to exploit them for therapeutic control.

Apoptosis

The term apoptosis describes a form of programmed cell death by which multicellular organisms remove damaged, potentially harmful or excess cells, in order to maintain cellular homeostasis.[6] With a few exceptions, all cell types appear to have the capacity to undergo apoptosis, and large numbers of cells are eliminated every day by this process without activating a local or systemic inflammatory response. In fact, apoptosis can be thought of as a default processes requiring receipt of appropriate survival signals to prevent its occurrence.[7]

Pathologically, evasion of apoptosis facilitates proliferation of mutated cells. This proliferation and a low rate of cell attrition eventually results in tumourigenesis. Additionally, failure to execute apoptosis in response to chemotherapy, radiotherapy and immune surveillance, provides neoplastic cells with a survival advantage.[8,9] Theoretically, apoptosis-targeted therapies will target cancer cells as, by virtue of the fact these cells are abnormal, they are under continual proapoptotic stresses and survive as they are unable to couple this stress to initiation of the cell death process. If these cells are perilously teetering on the verge of apoptosis by lowering apoptotic resistance, tumour cells may be able to initiate their own demise.

The ultimate effectors of apoptosis are a family of intracellular cysteine proteases termed caspases which are activated during apoptosis, in a proteolytic cascade, by two distinct but convergent pathways[10–12] (Fig. 1). The intrinsic mitochondrial pathway of caspase activation results in cytochrome *c* release from the mitochondria into the cytosol where it binds Apoptotic Protease Activating Factor-1 (Apaf-1).[13] Pro-caspase-9 associates with Apaf-1 to form the apoptosome complex and, in the presence of ATP, autoactivates releasing mature caspase-9.[12,14–16]

The extrinsic death receptor pathway of caspase activation begins with ligand binding to the extracellular domain of the TNF family of cytokine receptors. This recruits the protein FADD (Fas associated death domain/Mort-1) to the

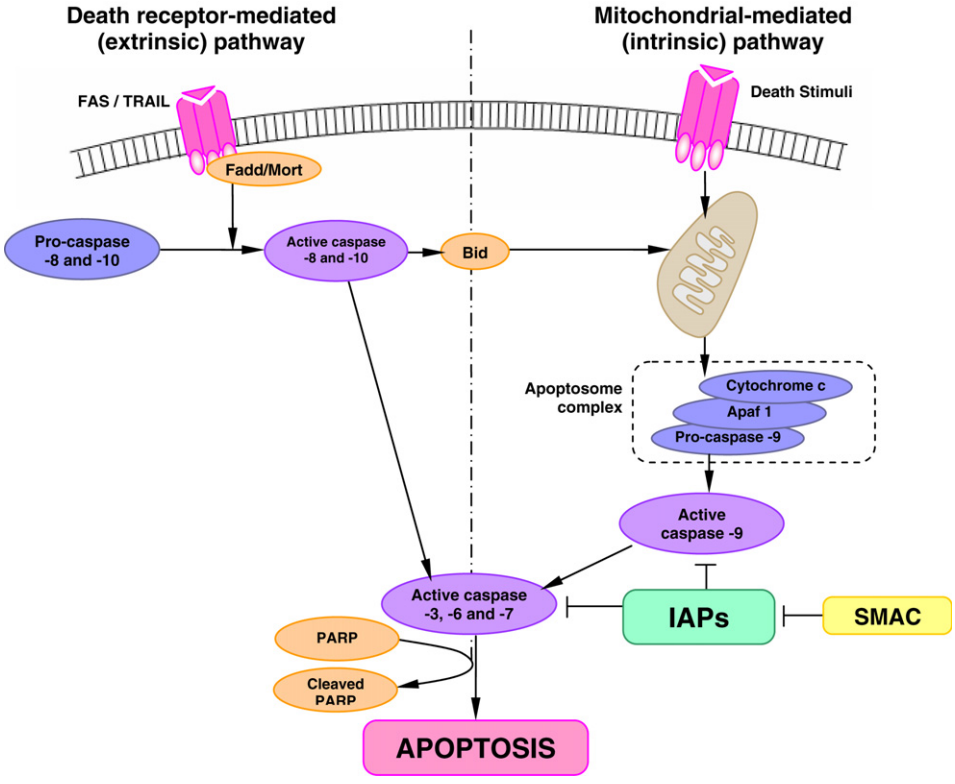

Figure 1 Intrinsic and extrinsic pathways of apoptosis.