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PLENARY SESSION 3

New targets and inhibitors

38 INVITED

The lysosomal cell death pathway

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Transformation is associated with a decreased stability of lysosomal membranes and an enhanced sensitivity to lysosomal cell death pathways induced by various anti-cancer drugs. This sensitization is at least partially brought about by the increased cysteine cathepsin expression and activity and cathepsin-mediated degradation of lysosomal membrane stabilizing proteins LAMP-1 and LAMP-2. On the other hand, the cancer-associated translocation of heat shock protein 70 (Hsp70) to the lysosomal lumen stabilizes the lysosomal membranes and thereby promotes the survival of cancer cells with high levels of cathepsins. Here, we show that Hsp70 stabilizes lysosomes by enhancing the activity of lysosomal acid sphingomyelinase (ASM). In acidic environment Hsp70 bound with high affinity and specificity to bis(monoacylglycero)phosphate (BMP), an essential co-factor for ASM, thereby facilitating the binding of ASM to BMP and stimulating ASM activity. The inhibition of the Hsp70 − BMP interaction by BMP antibodies or a point mutation in Hsp70 (W90F) effectively reverted the Hsp70-mediated stabilization of lysosomes. These data prompted us to investigate whether the lysosomal ASM could serve as a direct target for cancer therapy. Oncogene-driven transformation enhanced the sphingomyelin degradation significantly as evidenced by an increased ASM enzyme activity and a dramatic decrease in the cellular sphingolipid content. Importantly, the enhanced ASM activity in transformed cells was associated with a striking sensitization to the lysosomal cell death induced by structurally different pharmacological inhibitors of ASM as well as genetic depletion of ASM. Furthermore, ASM inhibition effectively re-sensitized therapy-resistant cancer cells to various anti-cancer drugs. Thus, the lysosomal ASM may have a great potential as a target for future cancer therapy.

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Update on polo-like kinase inhibitors in early clinical testing

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Background: Polo-like kinases (PLKs) are a group of highly conserved serine/threonine protein kinases that play a key role in processes such as cell division and checkpoint regulation of mitosis. About 80% of human tumors of various origins, express high levels of PLK transcripts. PLK mRNA is mostly absent in surrounding healthy tissues. Overexpression of PLK is associated with a poor prognosis in several tumor types and a lower overall survival rate. PLKs are overexpressed in human tumors, but not in nondividing cells. PLK inhibitors interfere with different stages of mitosis, such as centrosome maturation, spindle formation, chromosome separation, and cytokinesis. They induce mitotic chaos and severely perturb cell cycle progression in preclinical models, eventually leading to cancer cell death. Several PLK inhibitors are in preclinical and early clinical development and are currently undergoing evaluations as potential cancer treatments.
Materials and methods: This update, based on published evidence and information provided by pharmaceutical companies, provides a comprehensive overview of PLK inhibitors in early and more advanced stages of clinical testing, and the outcome of reported dose-finding trials and disease-specific studies in patients with solid tumors and hematologic malignancies, with a focus on the safety, toxicity, and efficacy of these compounds either as single agent or in combination with other antineoplastic drugs.
Conclusions: PLKs are attractive, selective targets for cancer drug development, and various PLK inhibiting agents are currently studied in dose-finding and exploratory early clinical trials. The definitive role of these drugs is yet to be defined.

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Metformin: What are the targets of this potential anti-cancer agent?

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There is growing interest in a potential role of metformin in both cancer risk and prevention. Recent epidemiologic evidence has demonstrated lower rates of cancer incidence and mortality in diabetics receiving metformin (as compared to those receiving other diabetes therapy); these effects have been seen overall as well as in specific types of cancer (eg. breast, pancreas). Observational clinical data provide evidence that diabetic breast cancer patients receiving metformin have enhanced rates of complete response to standard neoadjuvant chemotherapy (versus diabetics not receiving metformin or non-diabetics).
Metformin is unusual among cancer agents in that it may target both host and tumor factors, exerting anti-cancer effects through insulin dependent and/or insulin independent mechanisms. Insulin dependent mechanisms have received the most attention clinically. Obesity and/or the associated high circulating insulin levels associated with obesity have been linked to poor cancer outcomes, particularly in breast cancer. Insulin receptors, notably the fetal insulin receptor, are overexpressed on many solid tumors; they commonly hybridize with IGF1R (also over-expressed). In breast cancer cell lines, activation of these hybrid insulin/IGF-1 receptors by insulin has been shown to stimulate mitogenic pathways and it has been hypothesized that the fetal IR may act as a molecular switch, shifting insulin signaling from metabolic to mitogenic pathways. Observations that metformin lowers insulin levels in non-diabetic breast cancer survivors by 22% provide support for insulin mediated effects.
A growing body of preclinical work suggests metformin may also act through insulin independent mechanisms, notably intra-tumoral LKB1 mediated activation of AMP-activated protein kinase (AMPK), a cellular energy sensor, leading to mammalian target of rapamycin (mTOR) inhibition and subsequent downstream reduction of protein synthesis and proliferation. Emerging work suggests metformin may also inhibit aromatase activity (leading to reduced estrogen levels, particularly relevant in breast cancer), that it may alter expression of cell cycle related genes, reduce cyclins D1 and E, lower HER2 expression in breast cancer and preferentially impact stem cells.
Ongoing and planned clinical trials in the neoadjuvant “window of opportunity” and metastatic settings are examining effects of metformin (alone or in combination with standard anti-cancer treatment) on insulin/glucose physiology, clinical cancer response and/or tumor biology. Differentiation of the relative importance of insulin dependent and independent effects is a major focus of these studies; this work should assist in defining patient and tumor characteristics associated with metformin benefit. A Phase 3 adjuvant study of metformin (versus placebo) in breast cancer has recently been activated (NCIC CTG MA.32); embedded correlative research will explore insulin dependent and independent predictors of metformin benefit. Additional studies in breast and other tumor types are planned.

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Applications of the inhibition of Mdm2 function in Cancer Therapy

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The activation of p53 has been proposed as a novel anti-cancer treatment in two distinct contexts. In the first activation of p53 in tumour cells can promote apoptosis and senescence and enhance the anti-tumour activity of cytotoxic chemotherapeutic drugs. In the second application activation of p53 in normal tissues can cause a reversible cell cycle arrest that can be used to protect normal cells and tissues from the action of anti-mitotics and anti-S phase specific drugs. In this cyclotherapy role p53 mutant tumour cells are not arrested and remain sensitive to anti-mitotics and anti-S phase drugs. The advent of specific p53 activating molecules such as nutlin-3 has encouraged both approaches. We have used fragment based screens and extensive biophysical analysis to better understand the p53 mdm2 and p53 Mdm4 interactions. We have carried out extensive investigations of drug combinations and timing of addition in cell based systems to optimize these concepts. We have sought for a clinically approved drug that can mimic nutlin-3. Following a cell base p53 reporter screen of a natural product library we were surprised to find that low doses of actinomycin D mimic nutlin-3 in the highly specific activation of p53 dependant transcriptional activation and repression examined using gene expression arrays, in the induction of a reversible protective growth arrest in normal cells and in the enhancement of the activity of chemotherapeutic drug induced killing of p53 positive human tumour cells. While high doses of actinomycin D reveal its more non-specific activities, low doses of the drug will allow exploration of