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Editorial

Sensitizing to apoptosis—sharpening the medical sword

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Hepatocellular carcinoma (HCC) is a growing clinical challenge. Poor results of current therapy put an increasing burden on researchers to intensify their efforts to better understand the biology of HCC. Usually arising from a cirrhotic liver—with an additional disease-specific risk of malignant transformation—cells of HCC are particularly resistant towards chemotherapy. Although the enigma of this particular resistance is only partially understood, a large body of data suggest that the process of oncofetal dedifferentiation enables hepatocytes to evade immune surveillance by refining their intracellular set of proteins which orchestrate the subtle balance of apoptotic death and survival.

Evading the immune surveillance by developing resistance to apoptosis is a classic principle which is of particular importance in a number of malignancies: the discovery of bcl-2 overexpression and cell death inhibition as the underlying principle of follicular B-cell lymphomas instituted a new look on mechanisms of immune escape of malignant cells [1]: overexpression of antiapoptotic proteins and subsequent interruption of the cell death pathway. The general idea was confirmed in different tumor entities such as colon cancer or HCC. However, reflecting nature's complexity, this principle comprises several apoptosis-modulating proteins. This includes the HCC, where increased levels of anti-apoptotic proteins such as FLIP [2] and survivin [3] or decreased levels of pro-apoptotic proteins such as FADD [4] have been described.

Transformation to malignancy goes along with changes in the expression profile of a given cell. Dedifferentiation, i.e. loss of the adult, cell-specific metabolic or functional profile, is an integral part of this process.

Having this in mind, intervention, or in medical terms, therapy, has two options: complete eradication of the malignant clones or refining the expression profile towards the initial differentiation status. So far most, if not all, chemotherapies exert their anticancer activity by induction of apoptosis. Resistance to apoptosis may be a major factor limiting the effectiveness of anticancer therapy. In the last few years, effort has been made to understand the biochemical alterations of apoptotic pathways in cancer [5]. Many of these alterations lead to a multidrug-resistant phenotype of the malignant cell. In this context, the new, recently developed anticancer therapies based on drugs that modulate apoptosis may have importance for the treatment of tumors that are scarcely responsive to the conventional anticancer chemotherapy.

Like a locally acting time machine, computer operating systems allow to reset the clock of the computer and thereby re-establish the status of a former time—before a severe error compromised intact function—how, if we could reset the clock of a cell back to a time when it was not dedifferentiated to malignancy?

Are there compounds which allow to reset a tumor cell? Several reports ascribe the group of histone deacetylase inhibitors such as sodium butyrate (SB), a potential to induce re-differentiation of malignant cells. In millimolar concentrations SB has long been known to be an inhibitor of histone deacetylases, cause reversible G0/G1 growth arrest and induce differentiation markers in cells from a variety of species and tissues. In addition, a number of studies demonstrated that SB is able to induce apoptosis by itself or increase sensitivity of malignant cell lines from different tissue origin towards receptor-induced apoptosis [6–8].

Acetylation of lysine residues on the NH_2-terminal tails of the histones neutralizes the positive charge of the histone tail and decreases its affinity to negatively charged DNA. The physiological and therapeutic effects of butyrate are thought to result primarily from core histone hyperacetylation, because chemically unrelated histone deacetylation inhibitors, such as trichostatin A or trapoxin, have been shown in several instances to mimic the effects of butyrate. Histone acetylation, in turn, has long been claimed to influence gene expression, a notion strongly supported by recent reports showing that components of the basal transcription machinery and several sequence-specific transcription

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factor coactivators have histone acetyl transferase activity, whereas corepressors often recruit histone deacetylases. Thus, histone hyperacetylation is thought to facilitate, and deacetylation to repress, individual gene expression (for review see Refs. [9,10]).

In the paper of Ogawa et al. [11] in this issue the authors demonstrate that SB increases sensitivity of hepatoma cells to CD95 (Fas receptor) induced cell death—by RNA chip analysis they could delineate that this effect is not simply attributed to changes in Fas receptor expression levels but is based on complex changes in the expression pattern of proteins involved in the intracellular death signaling cascade. Ogawa et al. underlined that particularly the modulation of members of the bcl-2 family changes susceptibility to receptor-induced apoptosis. This is in line with the observation that involvement of mitochondria—via caspase-8 induced cleavage of the bcl-2 family member BID—is of specific importance in hepatocyte apoptosis and reflects the concept of hepatocytes as type II cells [12].

How will the future therapy for patients with HCC look like? These days, only the surgical knife is sharp enough to cure patients from HCC, rarely by resection, often by liver transplantation. A subgroup of patients benefits from transarterial chemoembolization, basically a palliative approach interfering with tumor perfusion [13,14]. So, what are the medical treatment options? Classical chemotherapy almost completely failed; therapy with hormones such as octreotid [15] did not show a survival benefit. Taking the heterogenous genetics of HCC into account it seems clear that future treatment will not only be interdisciplinary but also calls for a combinatorial approach, e.g. the combination of apoptosis-inducing agents with others which tackle the status of resistance either by acting directly on gene expression or prompting cell death by antiangiogenic means. While SB itself seems not to be the ideal candidate due to its unfavorable pharmacokinetics, the principle to sensitize towards apoptosis by inhibiting histone acetylases merits further attention [16,17].

Of course, we need more in vivo data and we need substitutes for the pharmacologically poor acting SB: substances such as NVP-LAQ824 [18] or 7-[4-(4-cyanophenyl)phenoxy]-heptanohydroxamic acid [19] are promising new agents with histone deacetylation (HDAC) inhibiting activity; suberoylanilide hydroxamic acid was already tested in a phase 1 clinical trial with patients with advanced leukemias or solid tumors [20]. The class of HDAC inhibitors is about to step into clinical practice—although HCC patients are a heterogenous and difficult study population—they should not stand aside.

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