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Inducing apoptosis: mind the natural killer cells ▼

The elegant and timely review by Los *et al.* [1] lists numerous novel apoptosis-related drug targets, many of them seemingly suitable for further development as anticancer drugs. The list is expected to continue growing as data mining of the published human genome sequence continues to yield potential drug target candidates. Yet, one wonders how to select the most likely to succeed anticancer candidates among so many new apoptosis targets for further research and development. After all, the cost of drug development for an entirely new drug target is often prohibitive. Moreover, failures during advanced phases of clinical trials could create serious financial problems even for larger biotech companies.

We would therefore like to use this platform to offer a word of advice for the creative minds in academia and in the pharmaceutical industry who are looking for premium new anticancer targets. When searching for apoptosis-inducing anticancer drug targets, look for those that are least likely to obstruct the performance of the human immune system. Above all, beware of possible interference with the immune system's most vital innate cancer-fighting counterpart, the natural killer (NK) cells [2,3]. Indeed, inhibition of NK cell activity has often been linked to tumor development. For example, it has been suggested that stress-induced inhibition of NK cell activity is a key player in metastasis [4], and appears to involve the release of catecholamines from the adrenal glands [5].

The reason for this concern is that numerous apoptosis control pathways are apparently implicated in the intricate and delicate regulation of immune responses, fine-tuned by evolution to ensure accurate control of self-immunity. The drug-induced activation of some of these pathways in immune cells of cancer patients might inhibit the native immune attack on their cancer tissues, thereby potentially causing more harm than benefit at certain stages of the battle against cancer.

Moreover, identifying the novel apoptotic pathways employed by NK cells during their intrinsic attack on cancer cells, and harnessing these signals so that they can be enhanced by apoptosis-promoting anticancer drugs, might be a key approach for developing this innovative class of drugs. For example, activation of nitric oxide synthesis was implicated in cancer-cell-killing by NK cells [6]. Thus, it is likely that anticancer drugs capable of enhancing this particular activity in cancer cells could be particularly beneficial in battling cancer. In conclusion, while the long list of apoptosis-related drug targets implicated in killing cancer cells keeps growing, only selected targets might be activated without interfering with the patients' innate immune system. Moreover, only a handful of anticancer drugs might have the added benefit of augmenting NK cell action *in vivo*, and such drugs seem to have a potential advantage for cancer pharmacotherapy.

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Taking the lead? ▼

None of us needs reminding that the spiraling costs of bringing a drug to the market are primarily due to the alarming attrition rate of new drug candidates, a failure rate that few other research-based

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