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Chemotherapeutics - Where to Now?

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As insights into the molecular pathways governing cell growth and cell death have been gained, so have the identities of specific components regulating those pathways and their promise as targets for cancer therapy. The rationale behind targeting individual components, ideally those uniquely expressed (selectively over-expressed) or heavily relied upon in cancer cells/tumors, is that cytotoxicity will be selective/specific for such cells, thus limiting potentially harmful side effects. Although there is great merit in this line of reasoning, as evidenced by the successes that have been achieved, it may be that this approach is also, in itself, a limitation to drug development. Let us address the question as to which direction(s) research advancing drug development might prove more productive by examining examples of the more successful current therapeutics and their limitations. As such, this note will not be all-inclusive nor is it intended to court favor of one therapeutic over another. It is also noted this will express the view of one researcher who has yet to figure out how cells die.

Many of the currently used drugs acknowledge the growth advantage of many cancer cells and thus have been designed to kill rapidly dividing cells. Such would be the case of inhibitors of DNA synthesis/repair, drugs that disrupt the dynamics of microtubule formation/dissociation or those that target components necessary for cell cycle progression, as examples. Since some healthy cells undergo rapid division, such treatments also elicit significant side-effects. Newer approaches target specific proteins in growth factor signaling that are over-expressed or otherwise overly-active in cancer cells. For example, high expression levels of EGFR and its family members in a number of cancers led to the development of drugs designed to selectively inhibit those receptors. This would include monoclonal antibodies like Herceptin to inhibit the Her2 receptor over-expressed in breast and ovarian cancers or Cetuximab to target the EGF receptor in colorectal cancer. Small molecule inhibitors of the tyrosine kinase activity of these receptors are also being developed and evaluated. Gleevec, the inhibitor of a receptor-independent transforming kinase has shown success in the treatment of chronic myeloid leukemia. Although these drugs have remarkable effects on patient survival, they are also accompanied by significant resistance e.g. approximately 70% of patients undergoing EGFR-directed treatment will become resistant after 8-12 months.

Although the underlying cause of this resistance can be variable, it generally arises from secondary mutations resulting from clonal selection and/or the genetic variability of tumors. For many patients, subsequent treatment involves higher drug doses and/or their incorporation into some sort of combination regime. In this light, many initial treatments may involve drug combinations designed to avoid/minimize the development of drug resistant cancers. Although outcomes have improved, all of these approaches have associated toxicities.

The goal of many of these treatments is to elicit apoptosis either via the intrinsic or extrinsic pathway. Drug resistance, however, limits their effectiveness since most tumor cells have acquired mutations that restrict apoptosis. For example, >50% of cancers harbor mutations in p53, a tumor suppressor, the absence of which renders cells resistant to apoptosis. Approaches are now designed to activate, stabilize, or provide pro-apoptotic proteins, or to inhibit anti-apoptotic components. Another therapeutic approach is to induce death via an alternative mechanism. But the limited scope of action of such drugs/approaches presents problems similar to those previously discussed--their efficacy against subsets of cancers with the requisite genetic background and the frequency of acquisition of drug resistance. Again, to deal with such limitations, patients often receive high-density combination drug therapy, but a high incidence of drug resistance still occurs. Another strategy is needed. A drug that disables multiple anti-death pathways and/or activates multiple pro-death pathways would represent a significant advance in patient treatment. This would turn attention from pathways to cellular processes as a means of maximizing cell death and minimizing resistance. This idea is proving of merit as exemplified by the combination of temozolomide and PARP1 inhibitors. The former results in DNA damage/lesions as a result of DNA base alkylation. PARP1 is required for base-excision repair and its absence results in enhanced temozolomide cytotoxicitye. An important corollary to this example is that drug efficacy depends upon the acquired importance of PARP1 as a result of temozolomide treatment.

With the above discussion in mind, it is not a significant leap of faith to acknowledge that emphasis on cell death pathways (processes), with its inherent limitations, overlooks an important class of drugs that could be effective due to their ability to inhibit survival mechanisms. It would seem that if a drug produced a stressed metabolic state that could not be compensated for by the cell's adaptive processes, then cell death would ensue via its default mechanism(s). Such a drug would be an effective cytotoxic agent independent of the genetic background producing the cancer phenotype i.e. of the mechanism by which the cancer has modulated the death pathway to maximize growth/survival. So, what would be important survival pathways of a "stressed" cell? Many stressed metabolic states are associated with the production of abnormal proteins, leading to enhanced utilization of the endoplasmic reticulum associated degradation (ERAD), the ubiquitin proteasome (UPS) and/or the autophagic pathways to eliminate potentially toxic misfolded/aggregated proteins. Limiting such pathways would be expected to enhance the toxicity of any such stress-inducing drug. In support of this premise, we note the effectiveness of the proteasome inhibitor, bortezomib, shown to reduce myeloma growth and IL6 production. Its lack of general cell cytotoxicity i.e. normal cells and other types of cancers do not seem to be killed by this treatment, has been attributed the general importance of the proteasome in preventing toxic protein build up and aggregation in myeloma cells. This idea is in keeping with the premise that targeting a survival pathway (in this

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case the UPS in cells dependent upon this pathway) is a productive approach toward drug development. However, a more effective alternative would be to inhibit the process of protein degradation, as cells often induce alternative pathways for protein degradation when one pathway becomes non-functional.

Such an approach to drug development would redirect attention to processes, rather than specific components, or even pathways, in particular, processes by which cancer cells restore homeostasis and "normal" function as a result of chemically (drug) induced stress. In this vain, drug/drugs that inhibit protein degradation via UPS, ERAD and autophagy should be effective against all types of cancers and unlikely to be readily reversed so as to lead to drug resistance. This approach to drug development would be highly successful and widely applicable since all cancers would have maintained, or may have even amplified, their survival pathways.

It is also recognized that such drugs would likely be toxic to both normal and cancer cells. Thus, the task will then be to selectively target these drugs to the appropriate cell type. Current technologies allow this to be accomplished either by direct application/injection e.g. in the case of skin tumors or prostate cancer, or via targeted delivery via liposomes, conjugation to peptides/apatamers etc that have selective affinities for tumor cells. As research along these lines continues, more effective and selective means of targeting cancer cells are expected to develop.