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Should Deubiquitinating Enzymes be Targeted for Therapy?

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Effective, non-toxic therapies for many diseases, including malignancies, metabolic syndromes and age-dependent neurodegeneration remain elusive, though not for lack of effort from scientists all over the world.

To effectively treat a disease we need to understand what goes wrong at the cellular level, identify the molecular players involved and co-opt cellular pathways through targeted therapeutics. It is becoming increasingly clear that a large family of enzymes, the deubiquitinases or DUBs, play fundamental roles in health and disease. DUBs are cysteine- or Zn^{2+}-dependent metallo-proteases that fulfill their molecular duties by cleaving covalent bonds between the protein modifier ubiquitin and substrate proteins. Post-translational modification of proteins by ubiquitin regulates numerous cellular processes, including cell division, gene transcription, protein degradation, intra-cellular and inter-cellular communication. Ubiquitin-dependent pathways are dysregulated in many diseases.

Conjugation of ubiquitin to a substrate protein usually alters its interaction partners. By changing its interaction properties, ubiquitination can therefore change a protein's subcellular localization (e.g. send it to the nucleus, or internalize a trans-membrane receptor), target it for degradation by the proteasome or through autophagy, or change its activity (activation or inhibition). By cleaving off ubiquitin from substrates, DUBs regulate their fate and in turn control various cellular pathways.

A growing number of DUBs have been linked to cancer, either as oncogenes or as tumor suppressors. These include the DUBs BAP1, USP1, USP7 and CYLD [1-6]. Several DUBs have also been directly or indirectly connected to neurological diseases and neurodegeneration (examples include the DUBs ataxin-3 and USP14 [7]). Consequently, it seems suitable to focus on DUBs as therapeutic targets.

Nearly 90 DUBs are encoded by the human genome [8]. Although this large number would suggest functional redundancy, substantial evidence indicates that this is not the case [9-15]. Because of tissue- and substrate-specificity, DUBs are in fact attractive therapeutic targets. Current efforts to target DUBs for therapy in cancer and other diseases have largely focused on inhibitors of their catalytic activity; generation of activators has been problematic, even though there are DUBs whose catalytic activation could be therapeutically warranted. Therefore, researchers are working to identify inhibitors for DUBs whose activity or over-expression causes disease, mostly in cancer.

Perhaps the best example of the use of DUBs for therapy is USP7. Inhibiting the DUB activity of USP7 has the overall effect of stabilizing the protein p53, itself once hailed as the cure for cancer. Stabilization and activation of p53 leads to cell death, thus acting as a tumor suppressor. Several rounds of small molecule formulation and identification have led to USP7 inhibitors, including HBX41108, HBX19818, P22077 and P050429 [3,16,17]. A few compounds have passed the "proof of concept" test in mammalian cell culture, but their efficacy in patients is not yet known.

Another screen identified inhibitors specific to USP14, a proteasome-associated DUB. USP14 functions in synaptic development and maintenance by recycling ubiquitin. Recently, USP14 was also shown to rescue proteins targeted for degradation by deubiquitinating them at the proteasome. Consequently, cells that do not express USP14 show enhanced clearance of several disease-related proteins, including one that can cause familial Alzheimer's Disease [18]. This screen isolated 1-[1-(4-fluorophenyl)-2,5-dimethylpropyl-3-yl]-2-pyrrolidin-1-ylethanone (or IUI). Treatment with IUI enhances the clearance of aggregation-prone disease-causing proteins in cell culture [18], suggesting that this compound could alleviate neurodegeneration in patients. By inhibiting the catalytic activity of USP14, IUI would presumably prevent the rescue of some ubiquitinated proteins, leading to their degradation. Although the initial cell culture data are promising, it needs to be determined if IUI can prevent neurodegeneration in animal models.

More recently, a proteasome inhibitor was identified through cell-based screening. Unlike the drug Velcade®, that blocks the chymotrypsin-like activity of the proteasome, this inhibitor, called b-AP15, acts on two proteasome-associated DUBs, the aforementioned USP14 and UCH-L5. Interestingly, in contrast to inhibition of USP14 alone by IUI, b-AP15's inhibitory effect on both DUBs effectively blocks the proteasome by clogging it up with poly-ubiquitinated proteins [19]. b-AP15 was shown to inhibit tumor progression in *in vivo* models of solid tumors and in a model of acute myeloid leukemia [19]. This inhibitor, however, acts more generally instead of targeting a specific pathway or substrate.

Only a few other DUBs have been targeted with small molecule modifiers, including UCH-L1, which has been linked to Parkinson's disease. As the list of DUBs with oncogenic or tumor-suppressive properties continues to grow, the number of scientists designing molecules to control their activities or interactions will undoubtedly follow.

Yet, we need to be cautiously optimistic about the use of DUBs for therapy. We should be mindful of potential side effects from inhibiting or activating DUB's enzymatic properties. We recently showed that RNA-interference-mediated knockdown of most DUBs encoded by the model organism *Drosophila melanogaster* had negative physiological consequences during development or in adults [13]. Similarly, mutations or knockouts of several DUBs in mice, including USP14 [20-25] and USP7 [26-28], caused negative outcomes in the entire organism or in specific organ systems [7]. Perhaps targeted

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delivery can circumvent potential problems. Desired therapeutic effects might be achieved with limited inhibition of DUB activity.

Another concern stems from the designation of a DUB's activities as helpful or harmful. This is in part due to the fact that many DUBs investigated so far have more than one substrate. Also, most DUB studies are conducted in cell culture and need to be complemented by work in animals to fully understand their physiological importance, whether in a single pathway or to the entire organism. Without knowing the panoply of roles of a specific enzyme, inhibiting or increasing its activity might have no effect; worse, it might be detrimental.

Would DUBs make good drug targets? Presently, the answer is a cautious "Yes".

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