A Chemoproteomic Platform to Quantitatively Map Targets of Lipid-derived Electrophiles

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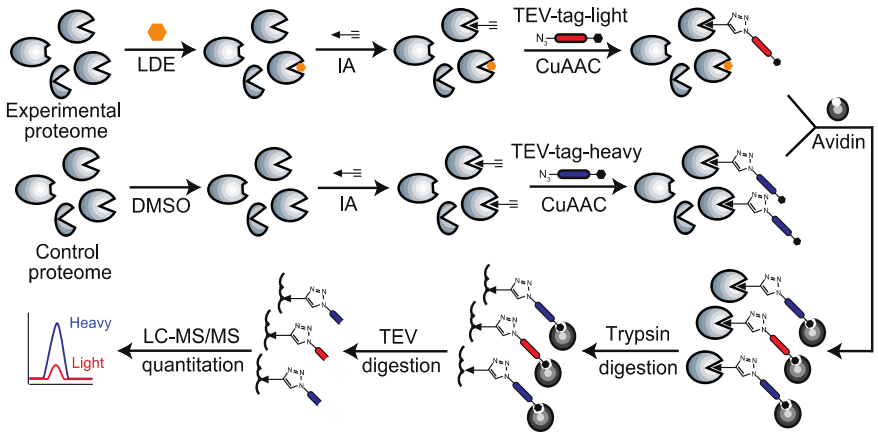
Cells produce electrophilic products with the potential to modify and affect the function of proteins[1]. Chemoproteomic methods have provided a means to qualitatively inventory proteins targeted by endogenous electrophiles[2]; however, ascertaining the potency and specificity of these reactions to identify the sites in the proteome that are most sensitive to electrophilic modification requires more quantitative methods. Here we describe a competitive activity–based profiling method (ABPP[3,4]) for quantifying the reactivity of electrophilic compounds against >1,000 cysteines in parallel in the human proteome (**scheme 1**). Using this approach, we identified a select set of proteins that constitute 'hot spots' for modification by various lipid-derived electrophiles (LDEs), including the oxidative stress product 4-hydroxy- 2-nonenal (HNE)[5]. We show that one of these proteins, ZAK kinase, is labeled by HNE on a conserved, active site–proximal cysteine and that the resulting enzyme inhibition creates a negative feedback mechanism that can suppress the activation of JNK pathways normally induced by oxidative stress[5].



Scheme 1: Quantitative profiling of LDE-senstive cysteines in proteomes

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