A metabolic code for signaling

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Proteins are typically classified by structural or sequence similarity, but many drugs disregard these associations and boundaries, exhibiting profound off-target activity and polypharmacology. From this activity emerges their side effects, but also often their therapeutic efficacy.

Here we ask whether we can use ligand polypharmacology to organize coherent pharmacologically related targets. Comparing ligand-based and sequence- and proteomic-organizations of proteins and signaling networks, we find drug targets that are often unrelated by biological metrics, but neighbors by ligand similarity. Because this method is articulated by specific molecules, it is readily tested, and on experiment we find several pairs of unrelated targets that can be modulated with a single small molecule ligand, with potencies ranging from nanomolar to micromolar. Ligand similarities among these targets reflect the conservation of identical signaling molecules among sequence-unrelated receptors, which often respond in different time domains to an identical chemical signal. The evolutionary origins of this polypharmacology of endogenous signaling molecules, and the drugs that imitate them, is considered, as are applications to the discovery of new signaling networks and of therapeutics with designed and specific polypharmacology.