Protein Engineering Enables A Fragment-Based Drug Design Platform To Inhibit The Anti-Apoptotic Protein MCL1

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Evasion of apoptosis is a hallmark of cancer that allows tumor cells to survive stresses that would kill a normal cell. Cell death-inducing mitochondrial permeabilization is prevented by tight sequestration of membrane-localized proteins by anti-apoptotic members of the BCL-2 family, which include BCL-2, BCL-XL, BCL-W, A1, and MCL1. MCL1 is among the top 10 most frequently amplified genes in human cancer. Consistent with its frequent amplification, MCL1 is highly expressed in many tumor types, and high expression levels of MCL1 contribute to tumor development and resistance to chemotherapy. There has been intensive effort to inhibit MCL1 and other anti-apoptotic members of the BCL-2 family with small molecules designed to release pro-apoptotic proteins from their sequestered state. Many MCL1-ligand structures display ligand/protein contacts both within and across adjacent crystallographic units, indicating that the crystallization of MCL1 is highly ligand-dependent. This also explains why fragment-bound structures of MCL1 have been intractable by crystallography despite considerable effort from several groups. Here we describe the development of a general and robust crystallography platform for MCL1, using a combination of protein fusion and engineering strategies. This novel system has led to the first apo structure of MCL1 by x-ray crystallography and has also enabled fragment-based lead generation that has previously eluded structural characterization.