COMPUTATIONALLY DESIGNED INHIBITORS OF THE LOW MOLECULAR WEIGHT PHOSPHATASE HCPTP

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One of the greatest challenges in the treatment of cancer is the control of metastasis. At the cellular level metastasis can be viewed as a disease of aberrant signal transduction, where elevated levels of tyrosine phosphorylation instruct metastatic cells to grow and survive in a foreign microenvironment. The human low molecular weight protein tyrosine phosphatase (HCPTP) is ubiquitously expressed as two isoforms in a wide range of human cells. Coimmunoprecipitation studies have suggested that HCPTP may regulate the phosphorylation state of the ephrin receptor tyrosine kinases. One of these kinases, EphA2, is overexpressed in a large number of metastatic human carcinomas. This potential regulation is significant, as EphA2 in malignant cells does not demonstrate any tyrosine phosphorylation, while in non-transformed epithelial cells it is phosphorylated. Modulation of activity for the two HCPTP isoforms can be demonstrated with a variety of purine molecules. Two nearly identical molecules, adenine and hypoxanthine, cause inverted modulation with adenine inhibiting one isoform while hypoxanthine activates it, and vice versa. We have solved the crystal structure of HCPTP-A, created a homology model for the HCPTP-B isoform, and performed molecular dynamics simulations on each with both adenine and hypoxanthine in the active site to determine which portions of the protein are most relevant in purine binding. This information is being applied in a rational drug design procedure incorporating both AutoDock and CHARMM to determine plausible leads. These leads will then be synthesized, tested for inhibition of either isoform of HCPTP as well as their effect on other tyrosine phosphatases, and evaluated in a complex with HCPTP using crystallographic methods. Several reasonable candidates have already been determined computationally and synthesized for testing as inhibitors.

Keywords: PHOSPHATASE COMPUTATIONAL DRUG DESIGN CANCER

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TEMPERATURE-DEPENDENT THREE-DIMENSIONAL SMALL ANGLE SCATTERING IN SEMICRYSTALLINE POLYMERS

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Many of the forming processes used to create useful materials from polymers lead to materials with strong orientation textures in both wide-angle and small-angle scattering. Protocols for characterizing the microstructure of such materials need to take account of this fact. In the small-angle scattering regime this is readily accomplished by simply collecting a series of 2-dimensional SAS patterns while the specimen is being rotated about an arbitrary axis. Interpretation is much simpler if the axis of rotation coincides with a symmetry axis.

Semicrystalline polymers offer a special feature in that the difference in thermal expansion coefficient gives rise to a very significant variation of scattering contrast with temperature. This phenomenon, which we have labeled 'Temperature Induced Contrast Variation' (TICV for short), provides a tool for separating contributions to SAS patterns associated with the phase-separated morphology attributable to crystallinity from other effects such as voids or molecular conformation. This leads to improved characterization of the phase-separated nanostructure.

Further specificity and linkage to crystallinity effects can be obtained from wide-angle scattering patterns. Semicrystalline polymers present special challenges in such studies because of their poor crystalline ordering, which tends to degrade the quality of pole figures. The above ideas will be illustrated by several examples from SAXS and SANS studies on High Density Polyethylene, Poly(4-methyl-1-pentene), poly(chlorotrifluorethylene), and fluorinated ethylene-propylene copolymer.

Keywords: SMALL ANGLE SCATTERING SEMICRYSTALLINE POLYMERS NANOSTRUCTURE