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Structural Biology of Cysteine Cathepsins

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Proteolytic activity is important for normal functioning of an organism and must be rigorously controlled due to its potential danger. Failure in biological control mechanisms of proteolytic activities may result in a disease. Emerging biological roles of lysosomal cysteine proteases are bringing them in the focus of drug discovery research. They are expressed in variety of organisms from bacteria to humans (for the group of mammalian homologues the term cysteine cathepsins is used). Cysteine cathepsins are lysosomal proteases involved in processing and digestion. These enzymes have rather short active site cleft, comprising of only three well defined substrate binding subsites (S2, S1 and S1') and rather broad binding areas (S4, S3, S2', S3'), which makes them distinct from other protease classes such as serine and aspartic with six and eight substrate binding sites, respectively. There are eleven human enzymes currently known (cathepsins B, C, F, H, L, K, O, S, V, X and W). Exopeptidases (cathepsins B, C, H, X), in contrast to endopeptidases (such as cathepsins L, S, V and F), provide features, which facilitate binding of N- and C- terminal groups of substrates in the active site cleft. Besides clear preference for free chain termini in the case of exopeptidases, the substrate binding sites exhibit no strict specificity. Their subsite specificity is rather exclusive than limiting. Our study of their interactions with protein inhibitors addresses their roles in the endosomal pathway of the immune system response. During this process foreign proteins are degraded to peptides of appropriate length, which must be delivered at the moment when the last piece of invariant chain (CLIP peptide) leaves the binding groove of the MHC class II molecules and makes it available for peptide binding and antigen presentation.

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Bridging phases in high-response piezoelectric materials

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Ferroelectric perovskites hold the largest observed piezoelectric responses. In particular, lead titanate in solid solution with several other lead oxide perovskite compounds show astonishingly large piezoelectric coefficients that can reach 2.5nm/V. It is well known that this behavior is associated to the existence of quasi-vertical phase boundaries in the temperature-composition phase diagrams, the so-called morphotropic phase boundaries (MPB) [1], and with phase transformations between rhombohedral and tetragonal states under the applied electric field[2]. It is of great technological importance to understand these processes in order to be able to design better and more enviromentally-friendly materials with similar behavior. In the last years this understanding has improved considerably, in large part due to detail structural characterization and parallel theoretical calculations on these complex oxide systems. Specifically, low monoclinic symmetries that bridge the rhombohedral and tetragonal phases, have been observed by diffraction techniques at the MPB's [3]. All observed monoclinic phases have space groups Cm or Pm, with no principal symmetry axis. In ferroelectrics this unusual situation translates into a lack of symmetry-determined polar axis and a larger freedom for the polarization to deform under the electric field, not only by elongating or contracting, as in most piezoelectrics, but also by rotating within the mirror plane. These phases have been confirmed, and some times predicted, by phenomenological and first-principles calculations[4,5]. The calculations have also demonstrated that huge electromechanical responses are indeed expected around monoclinic phases, when polarization rotation takes place[5-7]. The former picture is, however, largely simplified. It is known since the work of Glazer et al.[8] that the average distortion observed by diffraction techniques does not completely reflect the local structure. First principles calculation have shown that indeed the chemically disordered nature of the solid solution produces atomic shifts that vary from site to site[9]. Moreover, small domains and strain effects will also have an effect at the mesoscale. Therefore, at present, developments in the field aim to obtain a consistent picture of the phenomena observed at the different length scales, as revealed by different techniques. Finally, it will also be shown in this presentation, how this understanding can be used to improve the response of chemically simple thin ferroelectric films, in which the strain imposed by the substrate rotates the polar axis, and how this can be observed by Grazing Incidence Diffraction[10].

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