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The structure of conformational junctions in DNA and genomic instability

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The double helix of DNA, when composed of dinucleotide purine-pyrimidine repeats, can adopt a left-handed helical structure called Z-DNA. For reasons not entirely understood, such dinucleotide repeats in genomic sequences have been associated with genomic instability leading to cancer. Adoption of the left-handed conformation in parts of a long DNA-duplex results in the formation of conformational junctions: A B-to-Z junction is formed at the boundaries of the left-handed helix, whereas a Z-to-Z junction is commonly formed in sequences where the dinucleotide repeat is interrupted by single base insertions or deletions that bring neighboring helices out of phase. B-Z junctions are shown to result in exposed nucleotides vulnerable to chemical or enzymatic modification [1]. We determined and we will describe the three-dimensional crystal structure of a DNA Z-Z junction stabilized by Z α, the Z-DNA binding domain of the RNA editing enzyme ADAR1 [2]. We show that the junction structure consists of a single base pair and leads to partial or full disruption of the helical stacking. The junction region allows intercalating agents to insert themselves into the left-handed helix, which is otherwise resistant to intercalation. However, unlike a B-Z junction, in this structure the bases are not fully extruded, and the stacking between the two left-handed helices is not continuous. The structure captures a dynamic conformational state of the DNA double helix and provides a mechanistic explanation for DNA damage at CpG sites beyond methyl-cytosine modification. Moreover, the structure provides insights on the DNA-binding modes of Z-domains, a family of Z-DNA-binding domains found in interferon response proteins like the DNA sensor DAI and the RNA editing enzyme ADAR1.

[1] S.C. Ha, K. Lowenhaupt, A. Rich, Y.G. Kim, K.K. Kim, *Nature*, **2005,** *437*, 1183-1186. [2] M. de Rosa, D. de Sanctis, A.L. Rosario, M. Archer, A. Rich, A. Athanasiadis, M.A. Carrondo, *Proc Natl Acad Sci USA*, **2010** *107*, 9088-9092.

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Crystal structures of key components in toll-like receptor signaling

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The Toll-like receptor and IL-1 receptor superfamily (TLR/IL-1R) signals through a number of adaptor proteins and kinases, such as MyD88, IRAK4, IRAK2, TRAF6, and IKK β, to induce nuclear factor κB (NF-κB) activation. We here describe the crystal structure of the MyD88: IRAK4: IRAK2 (Myddosome) death domain (DD) complex, which surprisingly reveals a left-handed helical oligomer that consists of 6 MyD88, 4 IRAK4 and 4 IRAK2 DDs [1]. Assembly of this helical signaling tower is hierarchical, in which MyD88 recruits IRAK4 and the MyD88: IRAK4 complex recruits the IRAK4 substrates IRAK2 or the related IRAK1, consistent with the biology of pathway. Formation of these Myddosome complexes brings the kinase domains of IRAKs into proximity for phosphorylation and activation. Composite binding sites are required for recruitment of the individual DDs in the complex, which are confirmed by mutagenesis and previously identified signaling mutations.

IRAK activation in the TLR/IL-1R pathway leads to subsequent recruitment of the ubiquitin ligase TRAF6 and activation of IKK β. The latter phosphorylates IκB proteins leading to their degradation and liberation of NF-κB for gene transcription. We describe the crystal structure of inhibitor-bound IKK β [2]. The structure reveals a tri-modular architecture with the kinase domain (KD), a ubiquitin-like domain (ULD) and an elongated, α-helical scaffold/dimerization domain (SDD). Surprisingly, the predicted leucine zipper and helix-loop-helix motifs do not form these structures but are part of the SDD. We show that a) the ULD is required for catalytic activity; b) the ULD and SDD mediate a critical interaction with IκBα that restricts substrate specificity, and c) the SDD mediates IKK β dimerization, which is not important for maintaining IKK β activity, and instead required for IKK β activation.

Collectively, these structures highlight the involvement of high order oligomerization in TLR/IL-1R signal transduction.

[1] S.-Ch. Lin, Y.-Ch. Lo H. Wu, *Nature* **2010,** *465*, 885-90. [2] G. Xu, Y.C. Lo, Q. Li, G. Napolitano, X. Wu, X. Jiang, M. Dreano, M. Karin, H. Wu. *Nature* (in press).

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Atomic structure, electronic structure and optical response of metal nanoparticles

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Metal nanoparticles have unique optical properties due to their small size and they are of interest for a variety of applications in devices and materials, including sensing, photovoltaics and optoelectronics. Metal nanoparticles can be fabricated to bridge length scales from small molecular-like structures through to bulk materials in a continuous fashion. Although the optical properties of larger nanoparticles (>~2 nm) can be successfully described with classical electrodynamics, for small particles quantum effects become apparent.

This work presents first principles calculations of optimized structures, electronic structure and the optical absorption of gold clusters ranging in size from 10 to over 200 atoms. Ground state properties are calculated using density functional theory (DFT) and the optical response using time-dependent DFT (TDDFT), both within the Octopus code [1]. The largest clusters studied were ~2 nm size and so are in the region where our quantum based calculations should approach the classical results.

The calculations are performed over a discrete grid in real-space and time propagations for TDDFT are performed over discrete steps in real-time. Fully relativistic pseudopotentials were generated under the improved Troullier and Martins method [2] using the Ceperly and Alder local density approximation (LDA) for the exchange-correlation potential [3]. Ground state calculations were made using a Fermi-Dirac type electron smearing to simulate an electronic temperature and to ease convergence of open-shelled systems [4]. Propagations were performed under the LDA and used the approximated enforced time-reversal symmetry (AERTS) method [5]. Approximation of the