FAST BREAKING PAPERS - 2008

August 2008

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Brian Kobilka talks with *ScienceWatch.com* and answers a few questions about this month's Fast Breaking Paper in the field of Biology & Biochemistry. The author has also sent along images of their work.

Article Title: High-resolution crystal structure of an engineered human beta(2)-adrenergic G protein-coupled receptor
Authors: Cherezov, V;Rosenbaum, DM;Hanson, MA;Rasmussen, SGF;Thian, FS;Kobilka, TS;Choi, HJ;Kuhn, P;Weis, WI;Kobilka, BK;Stevens, RC
Journal: SCIENCE
Volume: 318
Issue: 5854
Page: 1258-1265
Year: NOV 23 2007
* Stanford Univ, Sch Med, Dept Cellular & Mol Physiol, Stanford, CA 94305 USA.
(addresses have been truncated)

SW: Why do you think your paper is highly cited?

For at least two reasons:

1. Structural determination of membrane proteins in general, and human membrane proteins in particular, has proven very difficult. Therefore the paper is of interest from the perspective of membrane protein structural biology.

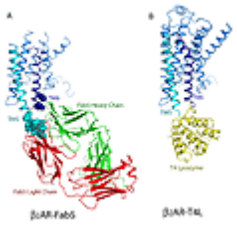
2. The ß2 adrenergic receptor (ß2AR) is representative of the large family of G protein-coupled receptors (GPCRs). GPCRs represent the largest family of receptors for hormones and neurotransmitters, and therefore the largest group of targets for pharmaceutical therapeutics. These proteins are consequently very interesting from a physiologic perspective, and there is hope that a better understanding of GPCR structure will lead to more efficient development of drugs for a very broad spectrum of diseases.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

This paper provides the first high-resolution picture of a hormone-activated G protein-coupled receptor. Crystallization of these membrane proteins is very challenging. The discovery was achieved by the application of several complementary methods. This paper and the companion *Science* article describe the use of protein engineering, lipid-based crystallography screens, and new microfocus X-ray technology that were required to obtain this structure. We were also able to obtain a structure of an unmodified ß2AR in complex with an antibody fragment, although at lower resolution (Rasmussen

et al., *Nature* 2007. See Figure.)

Figure 1: +details



SW: Would you summarize the significance of your paper in layman's terms?

The paper presents a high-resolution three-dimensional picture of a receptor for adrenaline. The adrenaline receptor is structurally similar to receptors for serotonin, dopamine, histamine, and many other hormones and neurotransmitters. The technology developed and applied to obtain the adrenaline receptor structure may be applied to obtain structures for other receptors. These structures may be useful for the development of more effective drugs for a broad spectrum of diseases.

SW: How did you become involved in this research, and were there any problems along the way?

I became interested in G protein-coupled receptors during my clinical training in internal medicine from 1981-84. In 1984 I joined the laboratory of Dr. Robert Lefkowitz at Duke University, and was part of the team that cloned the ß2 adrenergic receptor in 1986. Since that time I have been working to understand the structural basis of the function of this protein.

The major challenges to obtaining the crystal structure were to develop methods to produce and purify sufficient quantities of high-quality receptor protein for crystallography trials, and to develop methods to stabilize this otherwise fragile and flexible membrane protein and facilitate crystal formation.

This paper provides the first high-resolution picture of a hormone-activated G protein-coupled receptor.

SW: Where do you see your research leading in the future?

We are currently working on obtaining a structure of the active state of the ß2 adrenergic receptor in complex Gs, the G protein that becomes activated by the receptor and propagates the signal to other cellular proteins. We are also working on methods to study the dynamic properties of G protein-coupled receptors.

Crystal structures provide very useful information, but these structures represent only a snapshot of the many conformations that the protein assumes during its normal function in the cell. To fully understand how these proteins work, we need to characterize this dynamic behavior.

SW: Do you foresee any social or political implications for your research?

Only to the extent that GPCR structures help to develop more effective drugs at lower cost.

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References:

Rasmussen SGF, Choi HJ, Rosenbaum, DM, Kobilka TS, Thian FS, Edwards PC, Burghammer M, Rratnala VRP, Sanishvili R, Fischetti RF, Schertler GFX, Weis WI, Kobilka BK, "Crystal structure of the human beta 2 adrenergic G protein coupled receptor," *Nature* 450: 383-7, 2007.

Rosenbaum DM, Cerezov V, Hanson MA, Rasmussen SGF., Thian FS, Kobilka TS, Choi HJ, Yao XJ, Weis WI, Stevens RC, Kobilka BK, "GPCR Engineering Yields High-Resolution Structural Insights into beta 2-Adrenergic Receptor Function," *Science* 318: 1266-73, 2007.

Cerezov V, Rosenbaum DM, Hanson MA, Rasmussen SGF, Thian FS, Kobilka, TS, Choi HJ, Kuhn P, Weis, WI, Kobilka BK, Stevens RC, "High-Resolution Crystal Structure of an Engineered Human beta 2-Adrenergic G Protein–Coupled Receptor," Science, 2007. 318: 1258-65.

Keywords: B2 adrenergic receptor, B2AR, G protein-coupled receptors, GPCRs, GPCR structure, GPCR structures, protein engineering, lipid-based crystallography screens, microfocus X-ray technology, adrenaline receptor, serotonin, dopamine, histamine, neurotransmitters, crystal structures.

PDF

back to top

2008 : August - Fast Breaking Papers : Brian Kobilka

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Return to interview.

Figures and descriptions:

Figure 1:

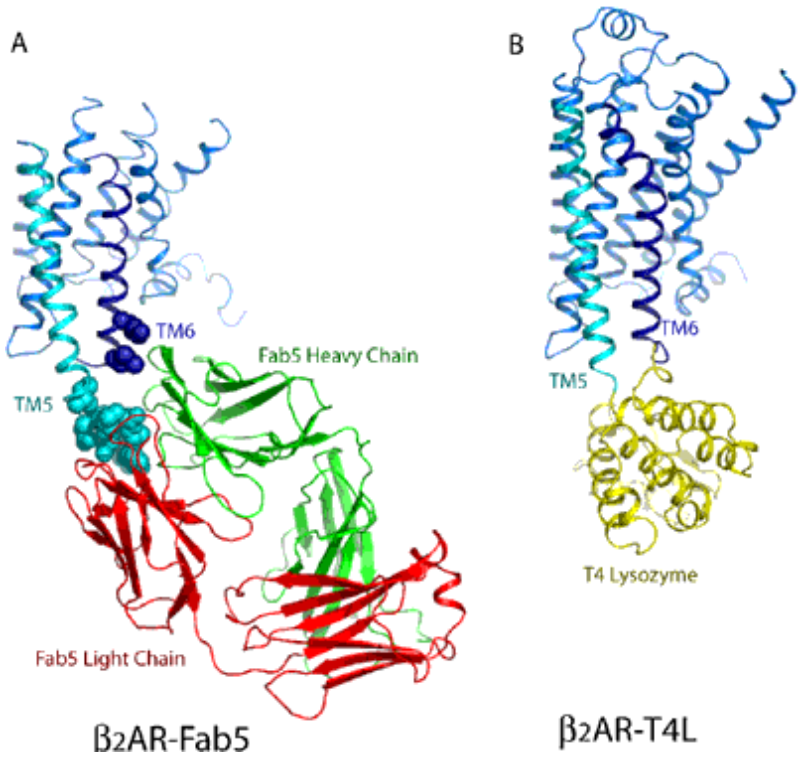

Figure 1:
Structures of the ß2AR. Crystals of the ß2AR have been grown using two different approaches: (a) Wild-type ß2AR in complex with Fab5 (Rasmussen et al.). (b) Engineered ß2AR-T4-lysozyme fusion protein (described in Rosenbaum et al, and applied in Cherezof et al). Fab5 and T4 lysozyme sever similar functions in these two crystal structures. They both stabilize interactions between TM5 and TM6, and provide additional polar surface area for crystal lattice contacts. TM, transmembrane segment; ICL2, second intracellular loop.

Return to interview.

PDF

back to top

2008 : August - Fast Breaking Papers : Brian Kobilka - Figures & Descriptions

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