Bioorganic Chemistry - Bioactive Chemistry -

Prof
SUGIURA, Yukio
(D Pharm Sci)

Assoc Prof
FUTAKI, Shiroh
(D Pharm Sci)

Instr
NAGAOKA, Makoto
(D Pharm Sci)

Guest Res Assoc
PEI, Renjun
(D Sc)

Students

IMANISHI, Miki (D3)
HORI, Yuichiro (D1)
NOMURA, Wataru (M2)
NIWA, Miki (RS)
WAKAKO, Naoya (U4)
MATSUSHITA, Keizo (D3)
KIWADA, Tatsuto (M2)
KONDO, Yumi (M1)
ITAZU, Masako (U4)
SUZUKI, Tomoki (D2)
DOI, Yoshihide (M2)
SHIRAISHI, Yasuhisa (M1)
HAJI, Akiko (U4)
NOMURA, Akiko (D2)
NAKASE, Ikuhiko (M2)
HADA, Shintaro (M1)
YOSHIMOTO, Rei (U4)

Scope of Research

The major goal of our laboratory is to elucidate the molecular basis of the activity of various bioactive substances by biochemical, physicochemical, and synthetic approaches. These include studies on the mechanism of sequence-specific DNA cleavage by antitumor or carcinogenic molecules, studies on the DNA recognition of zinc-finger proteins, and model studies on the action of ion channels. In addition, artificial designed peptides have also been developed as useful tools in molecular biology and potentially in human medicine.

Research Activities (Year 2001)

Presentations

Multiconnection of identical zinc finger: implication for unit modulation of the three zinc finger domain, Nagaoka M, Kaji T, Imanishi M, Hori Y, Nomura W, Sugiura Y, Annual meeting, Pharm. Soc. Jpn., 28 March.

Design of artificial novel zinc finger peptides, Nagaoka M, Sugiura Y, 10th international conference on bioinorganic chemistry, 30 August.

Design of artificial multi zinc finger protein: regulation of DNA binding mode by alteration of linker sequence, Nomura W, Shiraishi Y, Nagaoka M, Sugiura Y, 11th symposium on the role of metals in bilogical reaction, biology and medicine, 25 May.

Translocation of various arginine-rich peptides and the potential of these peptides as carriers for intracellular protein delivery, Futaki S, Suzuki T, Ohashi W, Yagami T, Tanaka S, Ueda K, Sugiura Y, 2nd international peptide symposium, 10 June.

Argnine-rich peptides that translocate through cell membranes, Futaki S, Suzuki T, Nakase I, Niwa M, Ohashi W, Sugiura Y, 16th symposium on biofunctional chemistry, 20 September.

Grants

Sugiura Y, Architecture of transcription regulation: creation and functional analysis of multi-zinc finger, Grant-in-Aid for Scientific Research (B) (2), 1 April 2000 - 31 March 2002.

Sugiura Y, Regulation of cellular gene function by novel DNA bending finger, Grant-in-Aid for Scientific Research (B) (2), 1 April 2001 - 31 March 2004.

Futaki S, Creation and intracellular delivery of novel peptides for the regulation of transcription, Grant-in-Aid for Scientific Research (B) (2), 1 April 2000 - 31 March 2003.

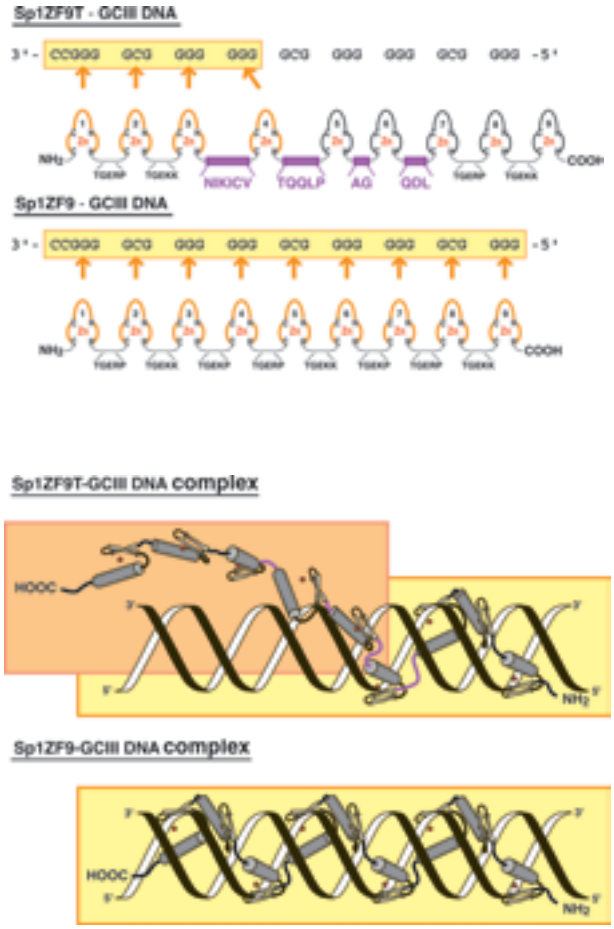
Futaki S, Design of membrane-current regulatory systems using assembly modulation of transmembrane peptides by extramembrane signals,Grant-in-Aid for Scientific Research on the Priority Area of Molecular Synchronization for the Design of New Materials, 1 April 2001 - 31 March 2003.

Nagaoka M, Design of metallofinger with novel functions: transcription regulation based on the metal substitution in zinc finger, Grant-in-Aid for Encouragement of Young Scientists (A), 1 April 2001 - 31 March 2003.

Topics

Effect of linker sequence on DNA recognition by multi-zinc finger protein

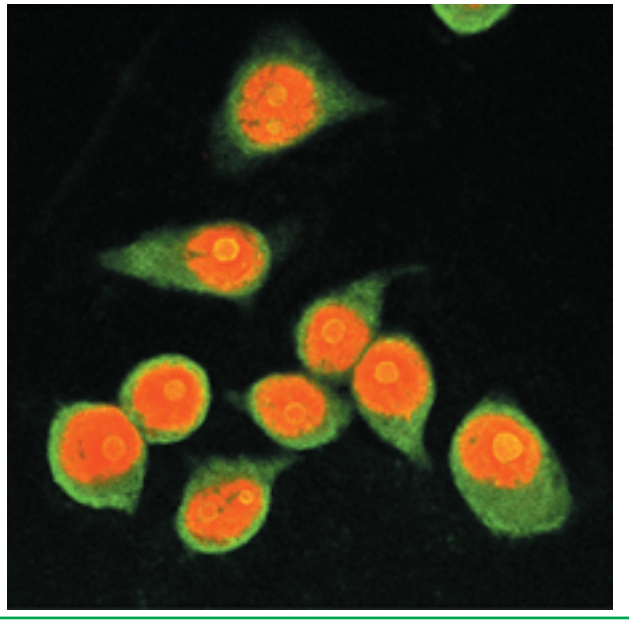
The unique linker sequence of the native nine zinc finger transcription factor IIIA (TFIIIA) appears to significantly affect its novel DNA recognition mode. An artificial new nine zinc finger peptide Sp1ZF9T has been created by connecting three units of the three zinc finger domains of Sp1 with the TFIIIA-type linker [1]. The DNA binding characteristics of Sp1ZF9T were evaluated and compared with those of the previous Sp1ZF9 with a Krüppel-type linker [2]. Sp1ZF9T forms two complex species, a short-lived species (B-2) and a long-lived species (B-1), with GCIII DNA (5'-GGG GCG GGG GGG GCG GGG GGG GCG GGGCC-3'). The B-2 complex dissociated into the free peptide and DNA, whereas the B-1 complex was stable even after 72 h. In the B-1 complex, 3'- and central portions of GCIII DNA are recognized by Sp1ZF9T. The present DNA binding mode of Sp1ZF9T is evidently different from that of Sp1ZF9. Namely, fingers 1-5 participate in the DNA contact of Sp1ZF9T, and fingers 1-9 in that of Sp1ZF9. Therefore, the linker sequence among the zinc finger domains has a significant effect on the specific DNA recognition by the multi-zinc finger proteins. To estimate the DNA contacts of the natural multi-zinc finger proteins and to design artificial zinc finger peptides with desired sequence specificity, the present results will provide useful information.



1. M. Nagaoka, W. Nomura, Y. Shiraishi, Y. Sugiura, *Biochem. Biophys. Res. Commun.*, **282**, 1001-1007 (2001).
2. T. Kamiuchi, E. Abe, M. Imanishi, T. Kaji, M. Nagaoka, Y. Sugiura, *Biochemistry*, **37**, 13827-13834 (1998).

Intracellular protein delivery using arginine-rich basic peptides

Basic peptides derived from the HIV1-1 Tat protein and Drosophila Antennapedia protein have been reported to have the ability to translocate through the cell membranes and to carry exogenous molecules into cells. We have demonstrated that various arginine-rich RNA or DNA-binding peptides such as HIV-1 Rev-(34-50) and flock house virus (FHV) coat-(35-49) were also membrane permeable and have the ability to bring proteins into cells [1]. These results suggested that there seems to be new types of ubiquitous transmembrane mechanisms for the arginine-rich peptides. Using these peptides as carrier, establishment of novel concepts for the intracellular protein and drug delivery is expected.



1. S. Futaki, T. Suzuki, W. Ohashi, T. Yagami, S. Tanaka, K. Ueda, Y. Sugiura, *J. Biol. Chem.*, **276**, 5836-5840 (2001).