Programmable DNA Binding Oligomers for Control of Transcription in angiogenesis

Sarah Furqan

EMAN Research and Testing Laboratory, Department of Pharmacology, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia

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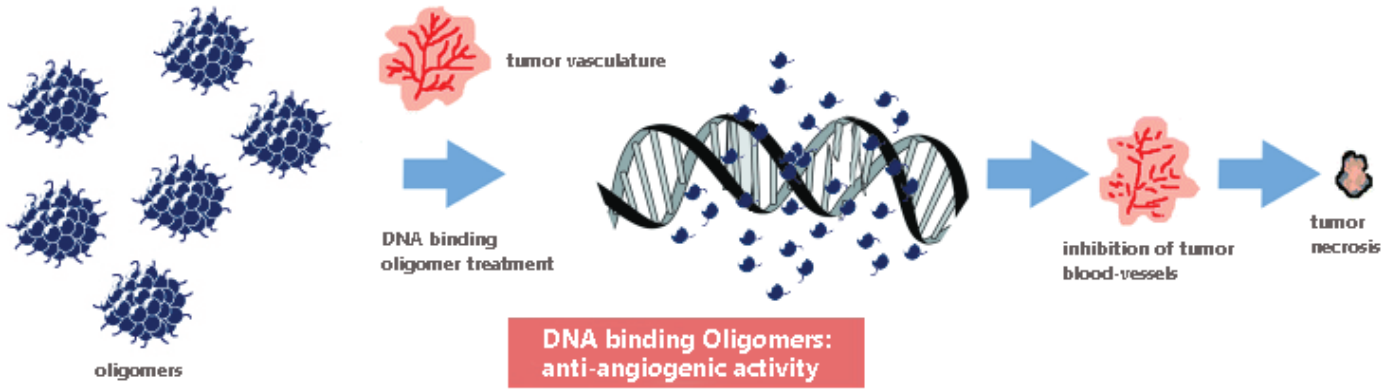
Graphical Abstract



*Correspondence: EMAN Research and Testing Laboratory, Department of Pharmacology, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia. E-mail: sara.creed89@yahoo.com

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Sarah Furqan

Abstract

The drug discovery opportunities with chemistry, biology and human medicine are increasing by mapping and sequencing the genetic blueprint of humans, mice and other organisms. The realization of the function of 25,000 genes of humans and understanding the biological circles that control these genes will be a crucial starting point for new chemistry technologies. The cellular events that lead to cancer and diseases in human involve aberrant gene expression. Small molecules that can be programmed to mimic transcription factors could be useful tools in biology and potentially in human medicine as they could bind a large repertoire of DNA sequences in the human genome.

Keywords: Transcription, Oligomers, DNA, Chromatin, Drug Discovery, Angiogenesis

Abbreviations: VEGF, vascular endothelial growth factor

Introduction

Polyamides are synthetic oligomers that can be programmed to read the DNA double helix. They bind chromatin and have been shown to regulate endogenous genes in cell culture. They are cell permeable. (To bind chromatin is not necessarily to bind DNA. Binding chromatin means to bind DNA/histones/proteins associated to DNA/DNA marks like methyl groups. Binding DNA is usually reserved to having affinity to the phosphate backbone or the sugar or the nucleotides) To regulate endogenous gene expression by DNA-binding polyamides, the molecules require effective nuclear localization. The work that has been done previously in employing confocal microscopy to study uptake of fluorophore-labeled polyamides has demonstrated the difficulty of predicting the nuclear uptake of a given polyamide. The data suggests that dye identity influences the uptake sufficiently such that a dye-conjugate cannot be used as a proxy for unlabeled analogs (quantum-dots).

Polyamides capable of nuclear localization unaided by fluorescent dyes are desired due to size and other limitations of fluorophores. Recently, a polyamide-fluorescein conjugate targeted to the hypoxia response element (HRE) was found to inhibit vascular endothelial growth factor (VEGF) expression in cultured HeLa cells. Currently, the study uses inhibition of VEGF expression as a biological read-out for effective nuclear localization of HRE-targeted polyamides. A new study synthesized a focused library of non-fluorescent, HRE-targeted polyamides in which the C-terminus 'tail' has been randomly changed in order to find members that bind HRE with affinities comparable or superior to that of the fluorescein-labeled analog.

Most library members demonstrate modest or no biological activity, even though two non-fluorescent polyamides reported have shown activity rivalling that of the previously reported fluorescein-labeled polyamide. The study also shows evidence that promoter occupancy by HIF-1, the transcription factor that binds the HRE, is inhibited by HRE-targeted polyamides (Dervan, Doss et al. 2005).

DNA Binding Polyamides and the Importance of DNA Recognition in their use as Gene-Specific and Antiviral Agents

A long history for the bioorganic and biomedical use of N-meth-

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*Correspondence: EMAN Research and Testing Laboratory, Department of Pharmacology, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia.
E-mail: sara.creed89@yahoo.com

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Author Affiliation:
EMAN Research and Testing Laboratory, Department of Pharmacology, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia

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yl-pyrrole-derived polyamides (PAs) which are the higher homologs (the most conserved) of natural products such as distamycin A and netropsin. This work has been pursued by many groups, with the Dervan and Sugiyama groups responsible for many breakthroughs. They studied PAs since the late 1990s, in this program, they reported methods to control the cellular uptake of polyamides in cancer cell lines and in other cells likely to have overexpression of multidrug resistance efflux pumps. The study went on to discover antiviral polyamides that are active against HPV31, where SAR showed that a minimum binding size of about 10 bp of DNA was necessary for activity.

Subsequently they discovered polyamides that are active against two additional high-risk HPVs, HPV16 and 18, a subset of which showed broad spectrum activity against HPV16. For example, molecules with the same cognate DNA recognition properties varied from active to inactive against HPVs. They describe the dramatic consequences of β-alanine positioning even in relatively small, 8-ring polyamides; these results contrast sharply with prior reports.

Polyamides (PAs) that recognize and bind the minor groove of DNA have been studied by a number of groups, including those of Dervan, Sugiyama, Lee, Laemmli, Kodadek and others. Following this extensive work, a set of binding rules was developed primarily by the Dervan group to allow prediction and control of polyamide-DNA interactions in the minor groove. They have been engaged in several collaborative N-methylpyrrole/ N-methylimidazole (Py/Im) polyamide projects over the years. One project involved the design of polyamides to repress cyclooxygenase-2 (COX-2) gene expression by targeting the binding site of the ETS (E26 transformation specific) transcription control superfamily member Ets-1 in the COX-2 promoter, followed by study of the detailed thermodynamics of interactions between active PAs and their Ets-1 target. (Koeller, Harris et al. 2014).

Highly Efficient Synthesis of DNA-Binding Polyamides

Two advances in the synthesis of hairpin pyrrole-imidazole polyamides (PAs) are described. First, the application of a convergent synthetic strategy is shown, involving the Boc-based solid phase synthesis of a C-terminal fragment and the solution phase synthesis of the N-terminal fragment. Second a new hybrid resin is developed that allows for the preparation of hairpin PAs lacking a C-terminal β-alanine tail. Both methods are compatible with a range of coupling reagents and provide a simple , modular route to prepare PA libraries in high yield and crude purity. (Fallows, Singh et al. 2014).

Antiangiogenic oligomers

The present invention relates to the use of certain anionic polyamide and polyurea oligomers for inhibiting angiogenesis, and for their use in treating diseases associated with angiogenesis. These oligomers have a number average molecular weight (Mn) less than 10,000, comprise recurring units coupled by carbonyl-linking moieties and have a predominantly linear geometry such that regular spacing between anionic groups exists in an aqueous medium. The oligomers also have a preferably linear backbone and are in their salt form, preferably with a pharmaceutically acceptable salt.

Angiogenesis has become an attractive target for drug therapy due to its key role in tumor growth. An extensive array of compounds is currently in pre-clinical development, with many now entering the clinic and/or achieving FDA approval. Several regulatory and signalling molecules governing angiogenesis are of interest, including growth factors (e.g. VEGF, PDGF, FGF, EGF), receptor tyrosine kinases, transcription factors such as HIF, as well as molecules involved in MAPK and PI3K signalling. Pharmacologic agents have been identified that target these pathways, yet for some agents (notably thalidomide), an understanding of the specific mechanisms of anti-tumor action has proved elusive.

Vascular endothelial growth factor (VEGF) and its receptors have been implicated as key factors in tumor angiogenesis that are up-regulated during hypoxia. Studies evaluated the effects of small DNA-binding molecules on hypoxia-inducible transcription of VEGF. A synthetic pyrrole-imidazole polyamide designed to bind the hypoxia response element (HRE) was found to disrupt hypoxia-inducible factor (HIF)-binding to HRE. In cultured HeLa cells, this resulted in a reduction of VEGF mRNA and secreted protein levels. The observed effects were polyamide-specific and dose-dependent. Analysis of genome-wide effects of the HRE-specific polyamide revealed that a number of hypoxia-inducible genes were downregulated. Pathway-based regulation of hypoxia-inducible gene expression with DNA-binding small molecules may represent a new approach for targeting angiogenesis. (Olenyuk, Zhang et al. 2004).

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Author Contribution

Sarah F. made substantial contributions to the conception of the review.

Competing financial interests

The author(s) declare no competing financial interests.

References

Dervan, P. B., et al. (2005). "Programmable DNA binding oligomers for control of transcription." Current Medicinal Chemistry-Anti-Cancer Agents, 5(4), 373-387.

Fallows, A. J., et al. (2014). "Highly efficient synthesis of DNA-binding polyamides using a convergent fragment-based approach." Organic letters, 16(17), 4654-4657.

Koeller, K. J., et al. (2014). "DNA binding polyamides and the importance of DNA recognition in their use as gene-specific and antiviral agents." Medicinal chemistry, 4, 338.

Olenyuk, B. Z., et al. (2004). "Inhibition of vascular endothelial growth factor with a sequence-specific hypoxia response element antagonist." Proceedings of the National Academy of Sciences of the United States of America, 101(48), 16768-16773.