

Homogeneous Heparan Sulfate Glycopeptides: Synthetic and Functional Studies

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Contact information of lead PI Country

USA

Title of project or programme

Homogeneous Heparan Sulfate Glycopeptides: Synthetic and Functional Studies

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NIH (NIA)

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01/03/2005

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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Glycopeptides, Heparan Sulfate Proteoglycan, Heparitin Sulfate, Polysaccharides, Amyloid

Research Abstract

? DESCRIPTION (provided by applicant): Heparan sulfate proteoglycans (HSPGs) play important roles in many biological events including amyloid plaque formation, viral infection,

inflammation, and cancer development. HSPGs isolated from nature exist as a highly heterogeneous mixture due to the variable structures of the heparan sulfate side chains. Heparan sulfates are traditionally believed to dictate the functions of HSPGs. Recent studies have gained increasing evidence suggesting that both the glycan chains and the core peptides/proteins can be critical. Therefore, to thoroughly understand their functions, it is important to have access to HSPGs bearing homogeneous glycans. However, to date, no general synthetic methodologies are available to prepare this type of structures. In order to overcome this obstacle, in this application, novel methodologies will be developed to synthesize these highly challenging molecules, which will then be used to understand how HSPGs interact with amyloid β . There are four aims in this application. In aim 1, a chemical synthesis strategy will be established towards HSPG glycopeptides bearing one heparan sulfate chain. Suitable protective group and glycosylation chemistry has been developed demonstrating the feasibility of chemically synthesizing HSPG glycopeptides with one glycan chain. In aim 2, a divergent approach will be established to modify HSPG glycopeptides with heparan sulfate biosynthetic enzymes. Promising preliminary results have been obtained suggesting enzymatic synthesis can be well integrated with chemical synthesis to enable the preparation of glycopeptides with diverse glycan structures from a common intermediate. In aim 3, through a combination of chemical and enzymatic methods, HSPG glycopeptides bearing multiple glycan chains and extended peptide backbone will be produced. This will lead to glycopeptides approaching the full complexities of HSPGs. In aim 4, using the synthetic heparan sulfate/HSPG glycopeptides, the structural features critical for their interactions with amyloid β , the pathological hallmark of Alzheimer's disease, will be identified. The proposed studies will provide the unprecedented access to HSPGs containing homogeneous heparan sulfate glycans, which will lead to exciting opportunities for studies of their fascinating biological properties.

Lay Summary

PUBLIC HEALTH RELEVANCE: Heparan sulfate proteoglycans are important for many biological processes. The overall goals of this project are to develop novel methods to synthesize structurally well-defined heparan sulfate glycopeptides. The availability of these complex structures can greatly expedite the understanding of their functions in the biological systems as exemplified by the study on how heparan sulfate glycopeptides interact with amyloid β , a hallmark of Alzheimer's disease.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:

Alzheimer's disease & other dementias

Years:

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Database Categories:

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