論文 / 著書情報
Article / Book Information

題目(和文)	
Title(English)	Design of coiled-coil based biomaterials for therapeutic applications
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出典(和文)	学位:博士(学術), 学位授与機関:東京工業大学, 報告番号:甲第9343号, 授与年月日:2013年9月25日, 学位の種別:課程博士, 審査員:小畠　英理,十川　久美子,山口　雄輝,有坂　文雄,小倉　俊一郎
Citation(English)	Degree:Doctor (Academic), Conferring organization: Tokyo Institute of Technology, Report number:甲第9343号, Conferred date:2013/9/25, Degree Type:Course doctor, Examiner:,,,,
学位種別(和文)	博士論文
Category(English)	Doctoral Thesis
種別(和文)	論文要旨
Type(English)	Summary

（博士課程）
Doctoral Program

論 文 要 旨

THESIS SUMMARY

専攻： Department of	生命情報	専攻	申請学位（専攻分野）： Academic Degree Requested	博士 Doctor of	(Philosophy)
学籍番号： Student ID Number			指導教員（主）： Academic Advisor(main)	Prof. Eiry Kobatake	
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要旨（英文800語程度）
Thesis Summary（approx.800 English Words ）

Angiogenesis has often been associated to tissue regeneration and tumorigenesis. In wound repair process, angiogenesis is controlled by both angiogenic growth factors and extracellular matrix. In tumorigenesis, vascularization inhibition is regulated by drug delivery system and growth factor receptors detection.

Recently researchers have turned their focus to protein-mediated growth factors and drug delivery by developing various biodegradable systems such as hydrogels and nanoparticles. Elastin-like polypeptides showed outstanding extracellular matrix properties. Its ability to form various platforms such as gels and nanoparticles demonstrates its flexibility in tissue engineering application and drug delivery system.

An appropriate method to bind elastin-like polypeptides and growth factors using advanced protein engineering techniques has the potential to enhance cell proliferation and differentiation for tissue regeneration and repair along with successful drug delivery and release. In this study a new method has been developed to bind non-covalently an elastin-like polypeptide (in a hydrogel or nanoparticle form) to single-chain vascular endothelial growth factor ($scVEGF_{121}$) through a coiled-coil structure formed by two α-helice strands: helixA and helixB in order to promote or to inhibit angiogenesis.

This work aims at developing two different growth factor carriers involving elastin-like peptides using helixA and helixB for two distinctive purposes:

- For tissue engineering, where the construction of coiled-coil structure is used to maintain co-immobilized growth factors' activity on extracellular matrix for the promotion of angiogenesis.
- For drug delivery, where the design of coiled-coil interaction between a growth factor and a thermo-responsive nanoparticle is made for delivering paclitaxel drug to cancer cells.

In the second chapter, our protein engineering approach aimed at co-immobilizing three growth factors via a coiled-coil structure on a collagen scaffold containing our engineered ECM protein to enhance tubular network formation. We demonstrated that the coiled-coil compound formation maintained a steady activity accumulation of both growth factors fusion protein and extracellular matrix fusion protein. This formation also stimulated the growth-promoting activity of HUVECs, improved cell survival, controlled the release of growth factors and promoted capillary-like formation.

We successfully developed a different way to co-immobilize growth factors on matrix using a

non-covalent binding through a coiled-coil structure. The cell proliferation was not inhibited and it promoted angiogenesis. This design of matrix-growth factor delivery system may lead to new advances in tissue engineering and regenerative medicine field.

In the third chapter, the design of an elastin-like polypeptide fused with a α-helix peptide (helixB) in order to favor a heterodimer formation when combined to another α-helix peptide (helixA) fused with a growth factor as constructed previously has been developed. The ELP fused with polyaspartic acid sequence and α-helix peptide at its C-terminal induced the formation of nanoparticles. The unfolding and folding state of the nanoparticles appear to respond under temperature change. Moreover, encapsulation of small molecules and drugs seems to occur during the phase transition temperature. In addition to those attributes, HA-scVEGF121 or HA-EGF constructed previously, was combined to the nanoparticles in order to form a non-covalent bonding around the phase transition temperature for targeted drug delivery.

We succeeded in developing a new approach for a targeted drug delivery and controlled release using ELP thermo-responsive nanoparticles non-covalently bound to growth factor. Nanoparticles have effectively delivered paclitaxel and induced cell death and detachment. This new strategy established a promising biomaterial for drug delivery.

This work focused on angiogenesis in health (tissue engineering) and disease (drug delivery). Therefore, this study would be valuable in broadways from extracellular matrix scaffolds to bio-grafts and from cell-sheets to nanoparticles.