Spermidine-Functionalized Injectable Hydrogel Reduces Inflammation and Enhances Healing of Acute and Diabetic Wounds In Situ

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Abstract The inflammatory response is a key factor affecting tissue regeneration. Inspired by the immunomodulatory role of spermidine, an injectable double network hydrogel functionalized with spermidine (DN-SPD) is developed, where the first and second networks are formed by dynamic imine bonds and non-dynamic photo-crosslinked bonds respectively. The single network hydrogel before photo-crosslinking exhibits excellent injectability and thus can be printed and photo-crosslinked in situ to form double network hydrogels. DN-SPD hydrogel has demonstrated desirable mechanical properties and tissue adhesion. More importantly, an "operando" comparison of hydrogels loaded with spermidine or diethylenetriamine (DETA), a sham molecule resembling spermidine, has shown similar physical properties, but quite different biological functions. Specifically, the outcomes of 3 sets of in vivo animal experiments demonstrate that DN-SPD hydrogel can not only reduce inflammation caused by implanted exogenous biomaterials and reactive oxygen species but also promote the polarization of macrophages toward regenerative M2 phenotype, in comparison with DN-DETA hydrogel. Moreover, the immunoregulation by spermidine can also translate into faster and more natural healing of both acute wounds and diabetic wounds. Hence, the local administration of spermidine affords a simple but elegant approach to attenuate foreign body reactions induced by exogenous biomaterials to treat chronic refractory wounds.

Spermidine-functionalized hydrogel can mitigate aseptic inflammation induced by exogenous biomaterials and direct more natural healings of acute and diabetic wounds. The aspiration is to mitigate foreign body response by the local administration of spermidine in biomaterials, which may be a game changer for medical implants and even for organ transplantation. image

Keywords **Author Keywords:** biomaterials; hydrogel; spermidine; inflammation; wound healing
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The inflammatory response is a key factor affecting tissue regeneration. Inspired by the immunomodulatory role of spermidine, an injectable double network hydrogel functionalized with spermidine (DN-SPD) is developed, where the first and second networks are formed by dynamic imine bonds and non-dynamic photo-crosslinked bonds respectively. The single network hydrogel before photo-crosslinking exhibits excellent injectability and thus can be printed and photo-crosslinked in situ to form double network hydrogels. DN-SPD hydrogel has demonstrated desirable mechanical properties and tissue adhesion. More importantly, an "operando" comparison of hydrogels loaded with spermidine or diethylenetriamine (DETA), a sham molecule resembling spermidine, has shown similar physical properties, but quite different biological functions. Specifically, the outcomes of 3 sets of in vivo animal experiments demonstrate that DN-SPD hydrogel can not only reduce inflammation caused by implanted exogenous biomaterials and reactive oxygen species but also promote the polarization of macrophages toward regenerative M2 phenotype, in comparison with DN-DETA hydrogel. Moreover, the immunoregulation by spermidine can also translate into faster and more natural healing of both acute wounds and diabetic wounds. Hence, the local administration of spermidine affords a simple but elegant approach to attenuate foreign body reactions induced by exogenous biomaterials to treat chronic refractory wounds.

1. Introduction

Biomaterials are playing an increasingly important role in tissue engineering and implantable medical devices.[1] However, exogenous biomaterials may trigger a series of cellular and molecular events in the host immune system, leading to inflammatory responses and even rejection of medical devices.[2] Indeed, inflammation has been widely recognized as a key factor affecting regeneration.[3] Hence, anti-inflammatory agents, such as dexamethasone and heparin, have been used to endow immunomodulatory functions to implanted biomaterials.[4] Yet, the application of these drugs often leads to adverse reactions and high costs.[5]

Spermidine (SPD) is a natural polyamine originally identified in semen. Recently, it has been reported that the level of SPD is significantly lower in the semen of infertile men; thus, it has been speculated that SPD can regulate the female immune system to protect sperms, as "foreigners" in the woman's body, to facilitate fertilization.[6] Consistent with this hypothesis, animal experiments have shown that SPD can improve the

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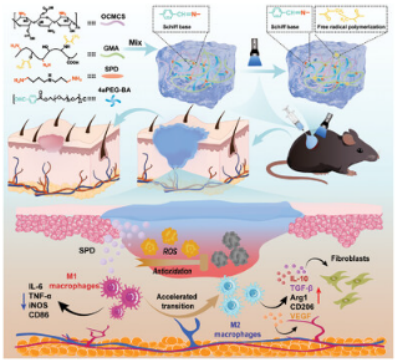

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