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Research Progress of Stimuli-Sensitive Polymer Carriers for Anti-Tumor Drug Delivery

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Abstract

Stimuli-sensitive polymer nanocarriers have attracted much attention from researchers because of their good application prospects in drug delivery and intelligent controlled release of drugs. They consist of pH sensitive polymer carriers, redox sensitive polymer carriers, hypoxic sensitive polymeric carriers, light sensitive polymeric carriers and ultrasonically sensitive polymeric carriers. This article reviews the research progress of different stimuli-sensitive polymer carriers and multiple stimuli-responsive polymer carriers, and encourages future researchers to design and synthesize novel stimuli-responsive polymer carriers for more efficient drug delivery and intelligent controlled release.

Keywords

Stimulating Sensitive Polymer Nanocarriers, pH Sensitive, Redox Sensitive, Hypoxic Sensitive, Light Sensitive, Ultrasonic Sensitive, Multiple Stimuli Response

用于抗肿瘤药物递送的刺激敏感型聚合物载体的研究进展

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摘　要

刺激敏感型聚合物纳米载体由于在药物递送和药物的智能控释方面具有良好的应用前景，受到了广大研究人员的广泛关注。其种类包括响应内源刺激的pH敏感聚合物载体、氧化还原敏感聚合物载体和低氧敏感聚合物载体，响应外源刺激的光敏感聚合物载体和超声波敏感聚合物载体。本文主要综述不同刺激敏感型聚合物载体和多重刺激响应聚合物载体的研究进展，激励未来的研究人员设计和合成新型刺激响应聚合物载体，以便实现更加高效的药物递送和智能控释的效果。

关键词

刺激敏感型聚合物纳米载体，pH敏感，氧化还原敏感，低氧敏感，光敏感，超声波敏感，多重刺激响应

1. 引言

刺激敏感型聚合物载体是指可以响应外部环境的刺激，在外部环境刺激的条件下发生解体，进而快速释放药物的聚合物载体。由于其具有智能控释化疗药物的能力，它不仅可以在肿瘤组织加速释放药物，达到杀灭肿瘤的效果，同时在正常组织释放药物速率缓慢，从而降低药物的毒副作用，所以受到了越来越多研究人员的广泛关注[1] [2] [3] [4] [5]。目前研究的较多的刺激敏感型聚合物载体主要分为响应内源刺激的聚合物载体和响应外源刺激的聚合物载体。其中，内源刺激主要是指不同于正常组织的肿瘤组织的微环境的刺激，如低的 pH 和缺氧等刺激。而外源刺激主要是指外加的条件的刺激，如光照和超声波的刺激[5] (图 1)。当聚合物载体受到这些刺激时，它就会发生解体，从而快速释放药物，达到智能控释药物的效果。本文主要综述可以响应不同条件刺激和同时响应多种条件刺激的聚合物载体的研究成果，并对其未来的研究方向进行展望。

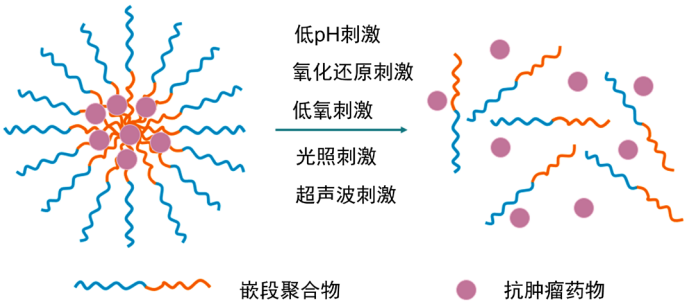

Figure 1. Schematic diagram of polymer carrier releasing drug in response to various internal and external conditions
图 1. 聚合物载体响应各种内外条件刺激释放药物的示意图

2. 响应内源刺激释放药物的聚合物载体

响应内源刺激加速释放药物的聚合物载体包括 pH 敏感型聚合物纳米载体、氧化还原敏感型聚合物载体和低氧敏感型聚合物载体，下面将分别介绍这几类刺激敏感型聚合物载体的研究进展。

2.1. pH 敏感型聚合物纳米载体

pH 敏感型聚合物载体是指可以响应 pH 的变化，当 pH 变化到一定值后，能发生解体，释放药物的载药体系。由于肿瘤组织和细胞内溶酶体的 pH 值(分别为 6.75 和 5.5)低于血液的 pH 值(7.23)，所以 pH 敏感型聚合物纳米载体成为了抗肿瘤药物载体研究的热点[6] [7] [8] [9]。一般 pH 敏感型纳米载体的结构中会含有一些 pH 敏感的化学键，如肼键，缩醛键，苯甲酸亚胺键和腙键等，这些化学键对酸敏感，当 pH 下降时，他们会发生断裂，从而使聚合物载体发生解体，释放药物[10] [11] [12]。Li 研究组做了大量的 pH 敏感载药胶束的工作，他们使用苯甲酸亚胺键将 DOX 连接到聚合物胶束的结构上构建了 pH 敏感的药物释放体系[13] (图 2)。苯甲酰亚胺键是独特的酸敏共价键，它在中性和碱性 pH 环境下相当稳定，但是在弱的酸性条件下，如肿瘤组织液和细胞内溶酶体中就会发生断裂。体外研究显示 pH 敏感的载药胶束可以有效地进入癌细胞，然后通过响应溶酶体低的 pH 值快速释放 DOX 以发挥抗癌活性。之后的研究者通过在聚合物胶束上连接靶向基团等手段赋予了载药体系更多的功能。

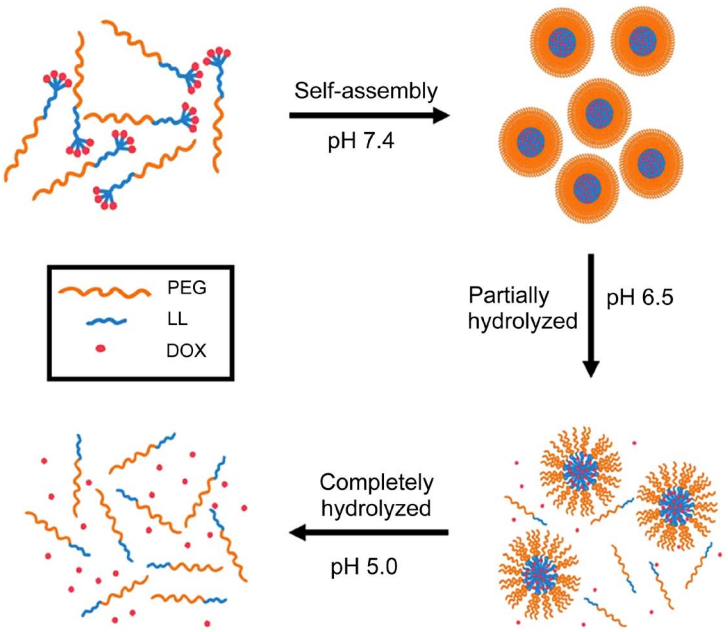

Figure 2. Schematic diagram of polymer micelle self-assembly and pH-sensitive drug release
图 2. 聚合物胶束自组装和 pH 敏感药物释放示意图[13]

2.2. 氧化还原敏感型聚合物载体

氧化还原敏感型聚合物载体是可以响应外部氧化还原环境变化的载体，它的结构中通常含有二硫键或巯基，它们可以在氧化或还原的环境中相互转换[14]。由于细胞内富含谷胱甘肽(GSH)，它是一种分子量较低的天然还原剂，而细胞外的 GSH 浓度不到细胞内的百分之一，所以细胞内被认为是处于还原的环境而细胞外是氧化环境[15] [16]。所以含有二硫键或巯基的氧化还原敏感型聚合物载体也受到了越来越多研究者的关注[17] [18] [19] [20] [21]。当载体处于细胞外时，结构中含有大量的二硫键，可以对载体进行捆绑作用，防止药物泄漏，而当载体进入细胞内后，二硫键断裂，转变为巯基，促进药物释放。Shuai 课题组使用含有二硫键的聚合物载体与 siRNA 复合，制备成了具有还原敏感性的纳米聚合物载体[22] (图 3)。该载体进入细胞内以后，受到细胞内还原剂 GSH 的影响，二硫键迅速断裂，从而促进了基因药物的释放。该聚合物胶束具有细胞内快速释放药物的优点，是一种非常有应用前景的载体材料。

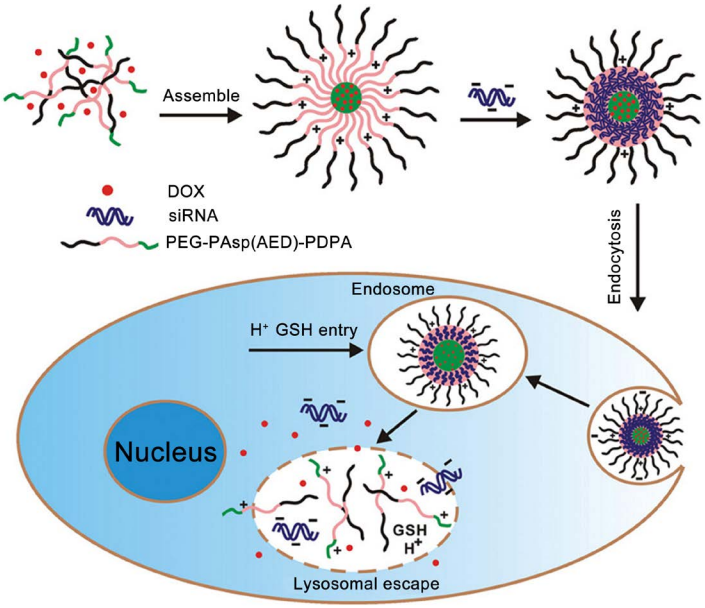

Figure 3. Schematic diagram of polymer nanocarrier and intracellular drug release
图 3. 聚合物纳米载体的制备和细胞内还原敏感释放药物的示意图[22]

2.3. 低氧敏感聚合物纳米载体

我们知道，肿瘤组织由于生长旺盛，而血液供应相对不足，与正常组相比，其内部往往处于一种缺氧状态。低氧敏感纳米载体因为可以响应缺氧的环境，在缺氧的环境中解体，进而快速释放药物，近年来受到了研究人员的广泛关注[23] [24] [25]。一般低氧敏感聚合物纳米载体中都含有硝基、醌基或偶氮键等低氧敏感基团[26]。Park 等人合成了羧甲基葡聚糖接枝 2-硝基咪唑衍生物的低氧敏感聚合物[27]。由于含有亲水的羧甲基葡聚糖和疏水的 2-硝基咪唑衍生物，该聚合物在常氧的条件下，可以自组装成纳米胶束负载化疗药物。而进入缺氧的肿瘤细胞时，在还原酶的催化下疏水的硝基咪唑转变成了亲水的氨基咪唑，胶束因为疏水嵌段的缺失发生解体(图 4)。细胞毒性实验表明载药胶束对缺氧细胞毒性高于常氧细胞。体内生物分布研究表明载药胶束可以在缺氧肿瘤组织中选择性地积累。除了用来做低氧敏感药物载体，这些低氧敏感的化学基团还可以用作氧气探针。Hanaoka 等人设计了含有偶氮键的缺氧敏感性荧光探针，他将罗丹明荧光剂与偶氮键结合，利用偶氮键的超快速构相变化将光能转换成动能，来抑制罗丹明发光，当探针进入缺氧的肿瘤部位时，偶氮键发生断裂，罗丹明恢复发光。根据发光的强弱，可以检测出氧气浓度的高低。通过对罗丹明结构的调整，他们有望制备出一系列检测不同氧气浓度水平的缺氧敏感探针[28]。

3. 响应外源刺激释放药物的聚合物载体

响应外源刺激加速释放药物的聚合物载体包括光敏感型聚合物纳米载体和超声波敏感型聚合物载体等，下面将分别介绍这两类刺激敏感型聚合物载体的研究进展。

3.1. 光敏感型聚合物纳米载体

光敏感型聚合物载体是指可以响应不同条件光照的刺激而发生解体的聚合物载体，它的结构中通常含有光敏感的组份，这些组份在光照刺激下，会发生光致异构化，光二聚化或光裂解等变化，从而使载体结构遭到破坏进而释放药物。通过选择和设计光敏组份，聚合物纳米载体可以响应从红外波段到紫外波段的光的刺激，而红外光由于具有组织穿透性好，生物破坏性弱的优点，受到研究人员的广泛研究[29]

[30]。Zhao 等人将聚合物载体上连接上光敏基团，当其暴露于不同波长的光时，载体的亲疏水平衡遭到破坏，从而可以用于智能控释药物。还有研究人员将可光裂解的基团引入到疏水侧链和主链之间或疏水和亲水链段之间，通过光照使亲疏水嵌段断裂来破坏胶束结构，从而构建光敏型聚合物载体[31] (图 5)。

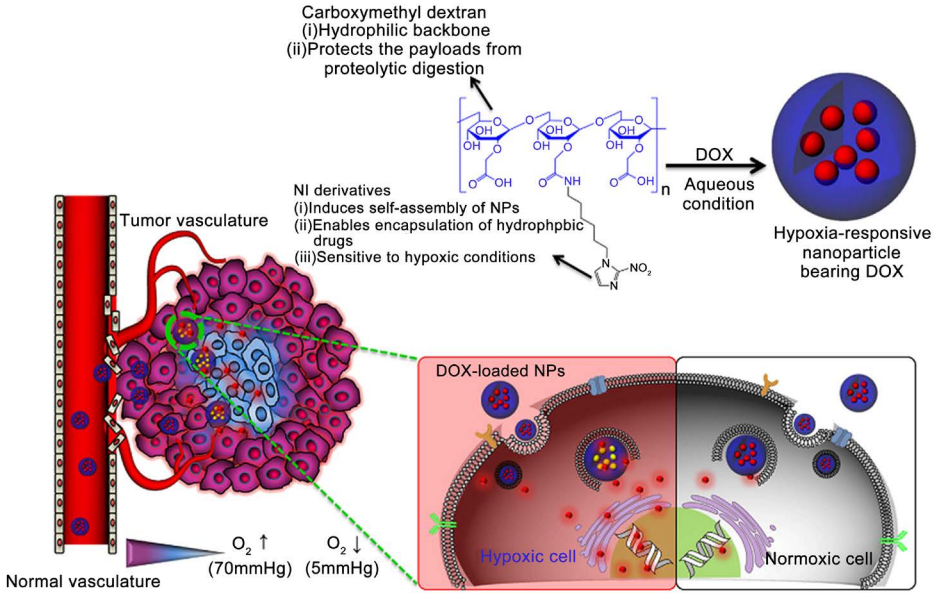

Figure 4. Schematic diagram of passive targeting of drug-loaded micelles and release of hypoxic sensitive drugs
图 4. 载药胶束体内被动靶向以及低氧敏感药物释放示意图[27]

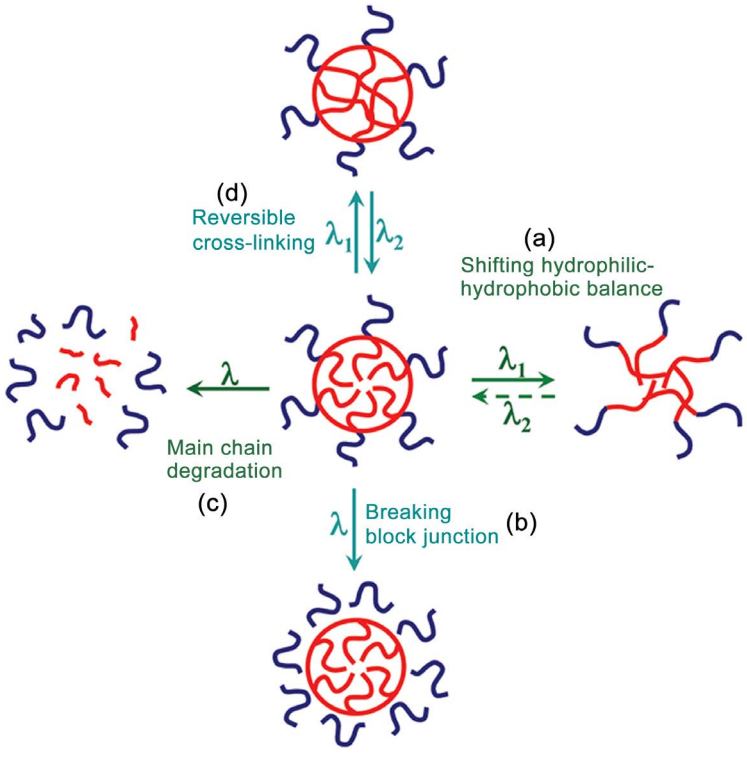

Figure 5. Schematic illustration of various types of light-responsive block copolymer micelles (a)~(d)
图 5. 各种类型的光响应性嵌段共聚物胶束(a)~(d)的示意图[31]

3.2. 超声波敏感型聚合物纳米载体

超声波敏感型聚合物纳米载体是指可以响应超声波的刺激而发生解体加速释放药物的聚合物载体，他通常是通过在聚合物载体中引入可以响应超声波刺激的微泡得到的。由于微泡在超声波的刺激下会迅速坍塌，而这种坍塌产生的能量可以增强药物向肿瘤组织深部渗透的能力，所以受到了越来越多研究人员的关注[32] [33]。Wang 等人通过异构组装策略将装载基因药物的聚合物胶束和脂质体微泡结合，制备出超声波敏感的纳米聚合物载体，研究其在药物递送到肿瘤部位后响应间歇性低频超声波额能力。结果表明，超声波响应的纳米载体可以有效地穿透到肿瘤的深部位置[34]。

4. 响应多重刺激释放药物的聚合物纳米载体

随着刺激响应聚合物研究的不断深入，响应多重刺激而更加快速释放药物的聚合物载体也被开发了出来。研究人员结合不同刺激敏感聚合物的特点，开发出了如 pH 和氧化还原双重敏感聚合物载体、温度和 pH 双重敏感聚合物载体以及温度和氧化还原双重敏感聚合物载体[35]-[41]。由于 pH 和氧化还原双重敏感载体在抗肿瘤药物的智能控释方面研究的更加深入，本章主要介绍 pH 和氧化还原双重敏感聚合物载体。由于肿瘤细胞存在着低 pH 和还原性的特点，同时响应 pH 和氧化还原环境的双重敏感聚合物载体受到了深入的研究。Shuai 课题组使用含有巯基和聚乙烯亚胺(PEI)的阳离子聚合物载体与 siRNA 复合，通过在氧化环境下形成二硫键将药物捆绑起来，制备成了体内长循环时间的稳定的聚合物载体[42] (图 6)。该载体进入 pH 较低的肿瘤组织部位时，载体中的 PEI 首先响应 pH 变化，使载体的表面电位从负电位反转正电位，从而促进载体进入肿瘤细胞。而当载体进入肿瘤细胞以后，受到细胞内还原剂 GSH 的影响，二硫键迅速断裂成巯基，捆绑作用消失，从而促进了基因药物的释放。该聚合物胶束具有体内稳定性强和细胞内快速释放药物等优点，是一种非常有应用前景的载体材料。

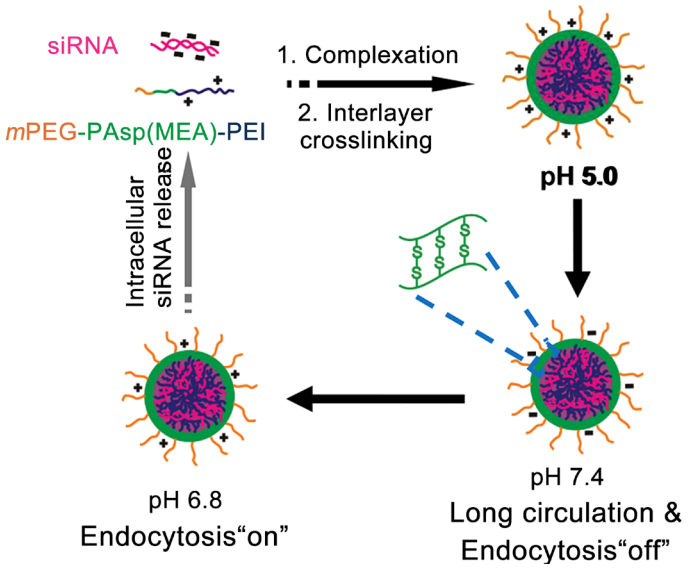

Figure 6. Schematic diagram of polymer nanocarrier loaded gene drug and the dually sensitized release of siRNA inside cell
图 6. 双重响应聚合物纳米载体负载基因药物及胞内药物释放示意图[42]

5. 结论与展望

多年来，研究人员一直都在探索合成更加安全高效的刺激敏感型聚合物载体，以提高抗肿瘤药物的治疗效果，并且降低其毒副作用。本文主要介绍了不同刺激响应聚合物载体的研究现状，以及多重刺激

响应聚合物载体的研究进展。虽然刺激响应聚合物载体取得了很大的进展，但是，还存在着很多的问题影响其在临床上的进一步应用，如它们生物相容性、生物体内的可降解性和稳定性依然有限。因此，开发出生物相容性和可降解性优异，体内稳定性高以及响应刺激灵敏性更强的聚合物载体将成为未来刺激敏感型聚合物载体材料的研究重点。

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