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生物医用钛植入体表面微纳结构与生物活性离子对生物相容性影响研究综述*

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摘要：生物医用钛植入体的表面微观形貌及化学组成作为影响植入体生物相容性的重要因素，决定了植入的稳定性和使用寿命，得到广泛研究，对钛植入体的表面改性研究现状进行系统梳理变得极为重要。针对钛植入体表面微纳米复合结构的构建及添加典型生物活性离子的研究现状进行综述，以及二者的结合对促进细胞黏附、增殖、分化和促进动物体内成骨的协同效应，简述微纳米复合结构对细胞行为的内在调控机制。结果表明，钛植入体表面的微纳米复合结构及生物活性离子对细胞的行为均表现出积极作用，兼具二者的植入体能够更好地促进细胞的黏附、增殖及分化，植入动物体内后更有利于植入体与周围组织的骨性整合。最后，根据当前生物医用钛植入体表面改性研究中存在的抗菌性能较差、对细胞的影响机制不明确等问题，提出植入体在表面改性领域的研究趋势。提出了钛植入体表面改性领域微纳结构构建和生物活性离子添加的研究现状和未来的发展方向，填补了钛植入体表面改性领域目前缺少综述文章来引领的空白，可为未来钛植入体的表面改性的发展提供借鉴。

关键词：钛植入体；表面改性；微纳米复合结构；生物活性离子；协同作用；生物相容性
中图分类号：TG146；R318

Review on the Influence of Surface Micro-nano Structure and Bioactive Ions of Biomedical Titanium Implants on Biocompatibility

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Abstract: As an important factor affecting the biocompatibility of implant, the surface micromorphology and chemical composition of the biomedical titanium implant determine the stability and service life of the implant, and have been widely studied. It is extremely important to systematically review the research status of surface modification of titanium implants. This paper reviews the research status of the construction of micro-nano structure on the surface of titanium implants and the addition of typical bioactive ions, and the synergistic effects of the combination of the two on promoting cell adhesion, proliferation, differentiation and promoting osteogenesis in animals. Besides, this paper briefly describes the internal regulation mechanism of micro-nano structure on cell behavior. The review indicates that the micro-nano structure and bioactive ions on the surface of titanium implants have a positive effect on the

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behavior of cells, and implants with both can better promote cell adhesion, proliferation and differentiation. It is more conducive to the osseointegration of the implant and the surrounding tissue after in *vivo*. Finally, according to the problems of poor antibacterial performance and unclear effect on cells in the current research on surface modification of biomedical titanium implants, the research trend in the field of surface modification is proposed. The research status and future development direction of micro-nano structure construction and bioactive ions addition in the field of titanium implant surface modification are proposed, This paper fills the gap in the surface modification of titanium implant and provides a reference for the future development of titanium implant surface modification.

Keywords: titanium implant; surface modification; micro-nano structure; bioactive ions; synergistic effect; biocompatibility

0　前言

钛及其合金具有良好的力学性能、耐腐蚀性和生物相容性，广泛应用于骨骼和牙齿等硬组织的替换领域[1-3]。然而，钛植入体具有生物惰性，难以与周围组织发生良好的骨结合，在植入体内后，容易产生松动甚至脱落以及周围组织炎症等问题[4-6]。因此，对钛植入体进行表面改性，提高其与周围组织的结合强度、结合稳定性和使用寿命，已成为钛植入体领域研究的热点问题。

现有研究表明，表面微观形貌和表面化学组成是影响植入体与周围细胞和组织结合的重要因素[7-8]，针对二者的改性研究，得到了学者们的广泛关注[9-11]。当前，钛植入体的表面改性主要分为表面形貌改性和表面化学成分改性。在表面形貌改性领域，人们已通过喷砂酸蚀、阳极氧化、微弧氧化、碱热处理等方法在植入体表面构建出微米级或纳米级形貌，以增强其表面的生物活性。研究发现，植入体表面的微米级（表面单元和尺寸为 1～100 μm）结构有利于成骨细胞的迁移和生长，增加植入体与周围骨组织的嵌合[12]，而纳米级（表面单元和尺寸为 1～100 nm）结构则有利于细胞的黏附和成骨相关基因的表达[13-14]。在表面化学成分改性领域，众多研究者通过等离子体注入[15]、水热处理[16]、离子置换[17-18]等方式，在植入体表面添加了各种生物活性离子，其中，水热处理和离子置换常结合使用，通过离子置换，将溶液中有助于成骨的生物活性离子与植入体表面的离子发生交换，从而将离子添加到表面。离子置换多发生在碱热反应后，当对钛植入体进行碱热反应后表面会生成钛酸钠纳米层，再将碱热处理后的钛植入体置于其他阳离子浓度较高的溶液中时，阳离子会将钠离子置换出来达到添加生物活性离子的目的。体内外试验结果表明，成骨细胞的迁移、生长等活动及新骨的形成受到多种生物活性离子的影响，在材料表面添加生物活性离子能够影响细胞的行为，增强细胞内某些信号通路的表达，从而加速植入体周围组织的骨生长和骨整合[19]。

植入体的表面微观形貌从尺寸上讲，主要分为微米级形貌和纳米级形貌[20]。然而，单一的微米级形貌和纳米级形貌对细胞行为的促进作用表现出一定的局限性，因此，越来越多的研究聚焦在对促进细胞行为具有协同效应的微纳米复合结构上。同时，为进一步提高植入体的生物活性，在构建微纳米复合结构的基础上，进一步在其表面添加生物活性离子逐渐成为当前的研究热点[21-22]。本文对钛植入体表面微纳米复合结构的构建和生物活性离子的添加及其对生物相容性的影响的研究现状进行了概述，并针对当前研究存在的问题，提出了未来钛植入体表面改性的研究展望。

1　微纳米复合结构制备及其生物相容性

天然骨组织由密质骨和松质骨组成，其表面包含微米、亚微米和纳米等多级结构[23-24]，从仿生学的观点来看，植入体表面的微纳米复合结构有助于周围骨组织与植入体形成较好的骨结合。

微米结构（1～100 μm）表面分为不规则微米结构表面和规则微米结构表面。不规则微米结构表面主要通过磨削[25]、酸蚀[26]、喷丸[27]、喷砂[28]等方法获得。规则微米结构表面可以通过光刻[29]、掩膜曝光电化学微加工[30]和微细铣削[31]等方法获得。表面的微图形对细胞的增殖、分化和骨整合均有着积极作用[32]。

纳米结构（1～100 nm）包括纳米花、纳米线、纳米管等纳米结构表面，钛表面获得纳米结构的方法主要包括阳极氧化法[33]、溶胶-凝胶法[34]、碱热处理法[35]、电化学沉积法[36]等，通过控制反应条件可在表面获得不同纳米结构。植入体表面的纳米结构可以通过影响 RGD 肽的构象来改善植入体与蛋白的相互作用，从而增强细胞在具有纳米结构的植入体表面的黏附[37]。

微纳米复合结构能够发挥微米级结构和纳米级结构的协同作用，通过在具有微米级结构的基底上

制备纳米级结构，细胞内碱性磷酸酶的活性和成骨相关基因的表达均得到增强[38]。目前，人们在构建规则微米结构和不规则微米结构的基础上，通过各种方法的排列组合在微米级表面叠加纳米管、纳米花、纳米线等纳米级结构，获得了规则微纳米复合结构和不规则微纳米复合结构，同时，微纳米复合结构的形貌大多呈现出纳米级形貌的特征。表面润湿性试验结果表明，微米级表面的润湿性根据 Wenzel 模型[39]，液滴会渗透进表面的微结构中，造成接触角降低，然而根据 Cassie-Baxter 模型[40]，当将液滴滴在表面时，会在水滴下形成空气垫，造成接触角增大，表面在叠加纳米级结构形成微纳米复合结构后，空气垫的作用大大减小，表面的亲水性则会进一步增强。体内外试验结果表明，相比于单一的微米级结构和纳米级结构，微纳米复合结构有效促进了细胞的黏附、增殖和分化及动物体内新骨的形成。

为进一步精确调控细胞行为，众多学者对微纳米复合结构调控细胞行为的分子机制进行了深入探究[41-42]。Wnt / β-catenin、Hedgehog-Gli1、YAP / TAZ 作为影响细胞行为的典型信号通路，得到了越来越多的关注[43-44]。Wnt 信号通路在细胞成骨分化中发挥着重要作用，参与干细胞的分化调控和细胞对机械信号的响应[45]。研究表明，植入体表面的微纳米复合结构可以影响整合素介导信号的途径，调控 Wnt / β-catenin 信号通路的调节因子，激活 β-catenin 信号，从而 β-catenin 信号入核调控成骨相关基因的表达，促进细胞的成骨分化[46-47]，但对于 Wnt / β-catenin 信号通路对促进细胞成骨分化的具体实施途径仍然存在争议[48]。Hedgehog-Gli1 信号通路可以调控细胞向成骨方向分化并参与新骨的形成[49]。LIN 等[50]将 MG63 成骨细胞接种到具有微纳米复合结构的钛表面，发现微纳米复合结构有效促进了细胞内 Hedgehog 家族蛋白 Shh（Sonic hedgehog）、细胞膜受体蛋白 Smo（Smoothened）以及下游蛋白 Gli1 的表达，并通过促进 Runx2、ALP、OCN 及 BMP-2 等相关基因的表达来促进细胞的成骨分化。YAP / TAZ 作为细胞内重要的机械响应分子，参与基底硬度、剪切应力等机械因素对细胞行为的调控，并对细胞的分化有着重要作用[51]。在微纳米复合结构对细胞分化的调控过程中，细胞通过感受基底的机械特性，获取基底的位置、内在机械力的方向、强度等信息，并通过 YAP 和 YZP 的调控作用，实现对细胞骨架的调控，进而促进细胞的成骨分化[52]。LIU 等[53]通过酸蚀和阳极氧化，在钛植入体表面构建了微纳米复合结构，结果显示，微纳米复合结构通过提高蛋白 AMOT130 的水平，增强了成骨基因的表达和 YAP 对细胞核的定位，进而将细胞骨架和细胞核之间的机械连接信息更好地传递至细胞核，促进了干细胞的成骨分化，调节过程如图 1 所示。然而，对于微纳米复合结构对细胞行为的具体调控方式和影响机理仍然不明确，需要进行更多更深入的研究。

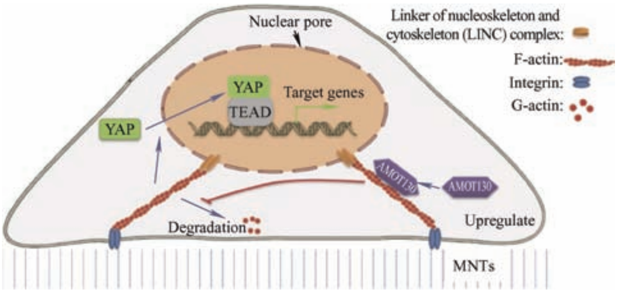


图 1　AMOT130 介导骨髓间充质干细胞对微纳米复合结构应答的分子机制示意图[51]

Fig. 1　Schematic of molecular mechanism by which AMOT130 mediates BMSC response to micro-nano structure cues[51]

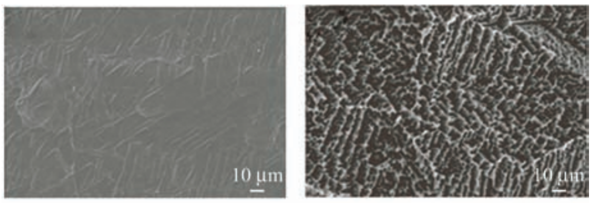
1.1　喷砂酸蚀+碱热处理

喷砂是一种以压缩空气为动力，将氧化铝、二氧化硅等小颗粒喷到材料表面以在材料表面获得微米级凹坑的方法。喷砂之后表面通常会有残余颗粒和碎屑，且表面凹坑形状不规则，有较多的棱角等，后续的酸蚀处理可以将残余的颗粒去除并使表面变得更加平整光顺，使表面应力不均一的情况得到改善，同时在表面构建微米级和亚微米级形貌[54]。碱热处理是指将钛或钛合金放在一定温度特定浓度的强碱溶液中，OH^-与钛发生反应，在钛表面生成纳米级多孔结构的方法[55]，改性后的表面能够有效诱导羟基磷灰石的形成，两种方法结合后有效提高了植入体的生物相容性。

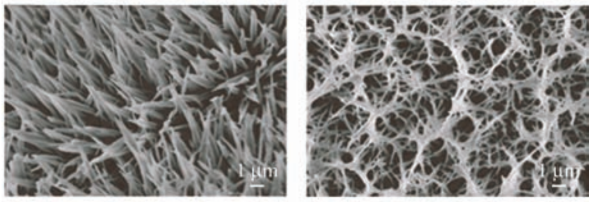
WANG 等[56]通过喷砂酸蚀和碱热处理，在钛合金样品表面制备了微纳米复合结构，抛光组表现出较为平坦的表面，经过喷砂酸蚀处理后，表面形成了微米级和亚微米级的凹坑，具有光滑表面的样品经过碱热处理后，形成了精细多孔的表面，产生了纳米级大小的凹坑，喷砂酸蚀后的样品碱热处理后，表面形成了微纳米复合织构表面形貌。

为进一步研究微纳米复合结构对体内外生物相容性的影响，进行了一系列体内外生物相容性试验。ZHUANG 等[57]通过喷砂酸蚀在表面构建了微米级和亚微米级结构，之后分别通过高温和低温碱热处理，在纯钛表面叠加了纳米针和纳米网结构，表面形貌如图 2 所示。体内外试验结果表明，喷砂酸蚀和碱热处

理构建的微纳米复合结构有效促进了细胞的黏附、增殖及分化，并增加了骨与植入体之间的接触面积和骨结合力，提高了植入体的稳定性（如图 3 所示，其中，Ti-control 为抛光钛表面，SLA 为喷砂酸蚀后的微米结构表面，SB-AH1 为喷砂酸蚀+高温碱热处理后的微纳米复合结构表面，SB-AH2 为喷砂酸蚀+低温碱热处理后的微纳米复合结构表面）。



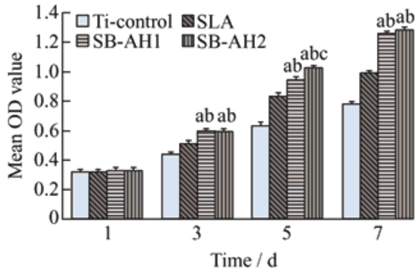
(a) Polished titanium　　(b) Titanium after sandblasting and acid etching



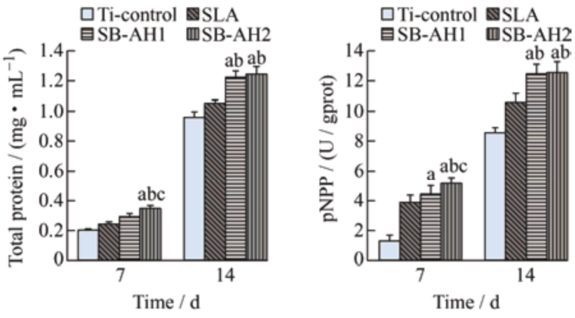
(c) Titanium after high temperature alkali heat treatment　　(d) Titanium after low temperature alkali heat treatment

图 2　各组试件表面的 SEM 图[57]

Fig. 2　SEM images of each specimen surface[57]



(a) Cell proliferation



(b) Total protein values in cell　　(c) ALP activity of in cell

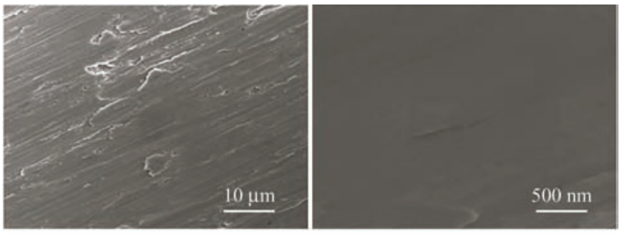
图 3　细胞增殖、胞内蛋白和 ALP 活性[57]

Fig. 3　Cell proliferation, intracellular proteins and ALP activity[57]

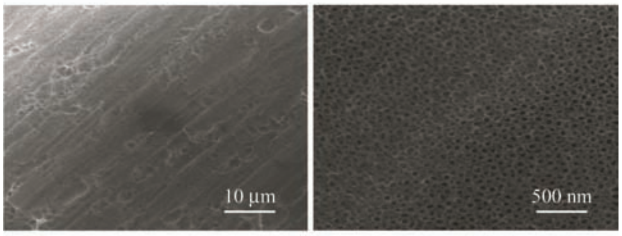
1.2　酸蚀+阳极氧化

阳极氧化是在基于氟化物的电解液中，将钛作为阳极并施加恒定电压，在钛表面生成二氧化钛纳米管的过程，与其他方法相比，该方法效率较高且纳米管长度和管径可控[58]，其中，氧化过程中的电流、溶液的温度和 pH 值均会影响最终纳米管的形貌[59-61]。

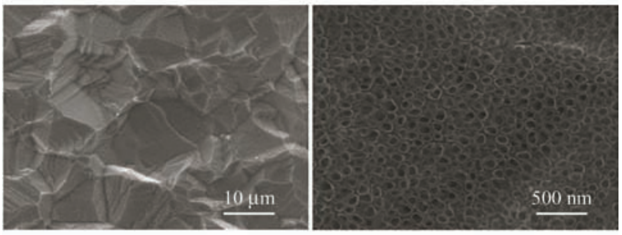
CHEN 等[62]通过酸蚀和阳极氧化，在钛植入体表面构建了微纳米复合结构，表面形貌如图 4 所示，细胞试验结果表明，相比于未经过处理的钛，具有微纳米复合结构的钛基底有效促进了间充质干细胞的成骨分化。HAO 等[63]通过酸蚀，在植入体表面构建了峰-谷状的凹槽，而后，阳极氧化在植入体表面构建了直径约 70 nm 的有序排列的纳米管阵列。体内外生物相容性试验结果表明，改性后的表面有利于小鼠成骨细胞 MC3T3 的增殖分化和成骨相关基因的表达，植入小鼠体内后，改性后的植入体与周围骨组织的结合强度明显增强，组织学染色结果如图 5 所示，改性后的表面有效促进了新骨的形成。



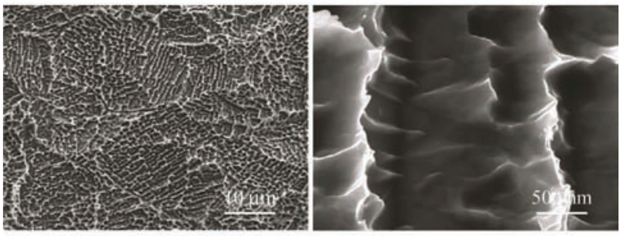
(a) Polished titanium



(b) Titanium after anodic oxidation



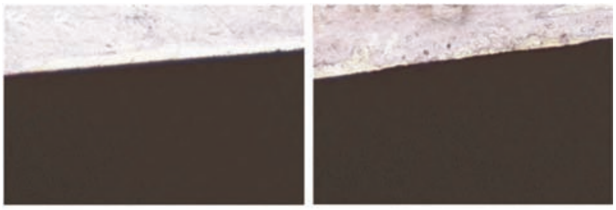
(c) Titanium after acid etching and anodic oxidation



(d) Titanium after acid etching

图 4　不同样品表面形貌[62]

Fig. 4　Surface morphology of different samples[62]



(a) Polished titanium

(b) Titanium after acid etching and anodic oxidation

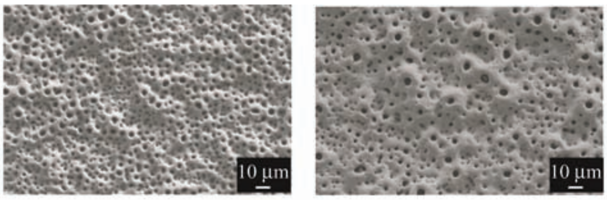
图 5 植入 5 周后的组织学切片染色[63]

Fig. 5 Staining of histological sections 5 weeks after implantation [63]

1.3 喷砂酸蚀+微弧氧化

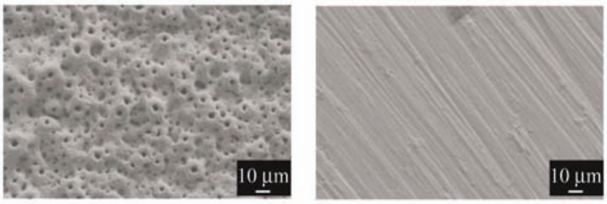
喷砂酸蚀可以在植入体表面构建不规则的微米级和亚微米级凹坑，而微弧氧化可以在表面构建纳米级形貌。微弧氧化又称等离子体电解氧化，是一种在钛、铝、镁等表面制备多孔陶瓷涂层的技术，通过调整微弧氧化过程中的参数（电压、电流、电解液浓度和工作时间等）可以改变氧化层的厚度、表面的微观结构和粗糙度等[64-65]。

HE 等[66]将钛植入体进行喷砂处理后，在含有醋酸和醋酸钠的电解液中进行微弧氧化，相比于抛光钛，改性后的植入体的表面粗糙度和润湿性均得到显著提升，体内外试验结果表明，处理后的植入体有效促进了细胞的增殖分化和动物体内新骨的形成。DENG 等[67]对纯钛植入体进行喷砂酸蚀，而后在含有醋酸钙和磷酸钙的电解质溶液中进行微弧氧化，扫描电镜结果如图 6 所示，结果显示，经过处理，表面产生了 30～40 μm 的不规则峰-谷状结构和微弧氧化产生的微孔，细胞试验结果表明，经过喷砂酸蚀和微弧氧化的钛植入体具有增强的生物相容性，细胞内 ALP 含量和总蛋白含量均显著提升。



(a) Titanium after sandblasting-acid etching and micro-arc oxidation

(b) Titanium after micro-arc oxidation



(c) Titanium after micro-arc oxidation and hydrothermal teatment

(d) Titanium after polishing

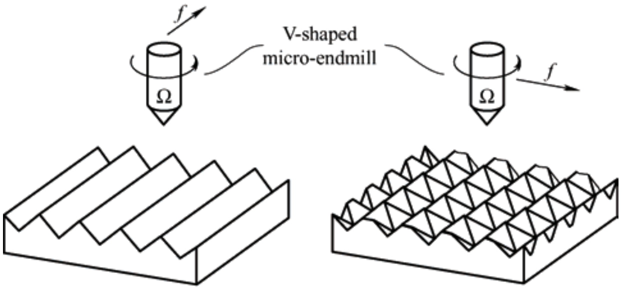
图 6 各组样品的表面形貌[67]

Fig. 6 Surface morphology of different samples[67]

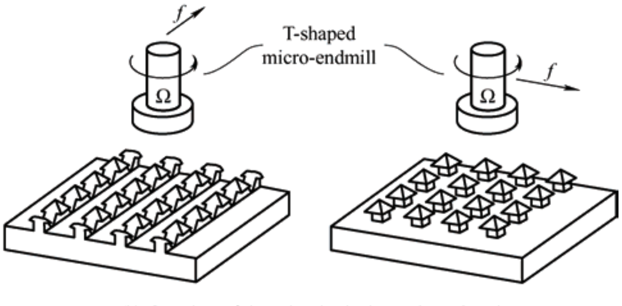
1.4 微细铣削+阳极氧化

随着精密和超精密加工技术的发展，微细铣削因具有极高的加工精度和表面质量，广泛应用于植入体的表面改性。微细铣削是指通过微细铣削机床在植入体表面加工出特定图案的方法，微细铣削过程中，切削深度很小，因此可以直接加工出微米级沟槽。该方法的最大特点是可以加工自由曲面和规则微图形，且参数可控[68]。

FILIZ 等[69]使用两种微铣刀，通过微细铣削在生物相容性材料表面构建了不同尺寸、包含角度和杆高的微倒钩阵列，并研究了微铣削条件对微铣削力、表面粗糙度和毛刺形成的影响，加工过程如图 7 所示。在植入体表面加工出的微沟槽、微倒钩等微米尺度结构可以增加植入体的表面积，增强与人体的组织嵌合，有效降低了植入体脱落和松动的风险[70]。



(a) Creation of the micropyramids by V-shaped tool



(b) Creation of the microbarbs by T-shaped tool

图 7 构建微倒钩的工艺步骤[69]

Fig. 7 Process steps for the creation of microbarbs[69]

WAN 等[71]首先使用微细铣刀在钛合金表面加工出深度为 40 μm、间距为 150 μm 的微槽，阳极氧化后，微细铣削产生的毛刺被去除，并生成了有序排列的直径为 70 nm 左右的纳米管阵列。表面润湿性结果显示，光滑表面、微米级表面、

微纳米复合结构表面的接触角分别为 67.3°、114.8°、60.3°，阳极氧化显著增强了微细铣削后的表面润湿性。

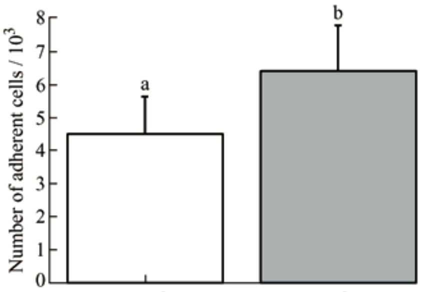
2　生物活性离子的添加及其生物相容性

为进一步提高钛植入体的生物活性和与周围组织的生物相容性，在植入体表面添加生物活性离子得到了越来越多学者的关注[72-74]，其中，钙[75]、锌[76]、镁[77]、锶[78]作为组成人体骨骼的重要元素，在促进成骨细胞的黏附、增殖、分化和新骨的形成中起着极大的促进作用，添加各种生物活性离子后，原表面的物理特性基本不发生变化，而表面物相和元素组成会发生变化造成化学特性的变化。

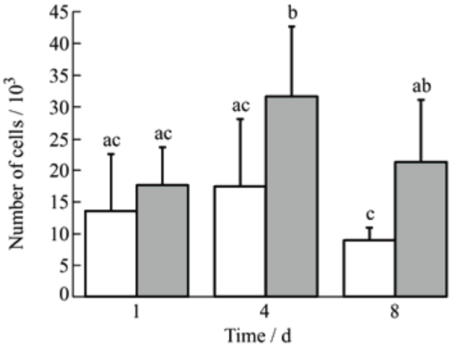
2.1　钙离子

钙作为骨骼的重要组成元素，在骨再生中起着十分重要的作用，钙离子参与了骨从形成到修复的整个生命周期[79-81]，介导血小板的激活和临时基质的生成，能够结合富含酸性的蛋白质，并为骨矿核的形成创造过饱和条件。植入体表面注入钙离子可以使磷灰石薄膜与钛基底之间形成强键，加速植入体表面磷酸钙的沉积，使细胞和其他生物矿化分子优先与植入体发生静电结合[82-84]，同时，钙是羟基磷灰石的重要组成部分，参与骨的矿化，从而促进植入体和天然骨的骨整合。研究表明，在表面钙离子浓度较高时，α5β1 整合素水平显著上调，整合素与基质黏附以及细胞活化密切相关，其通过与纤维连接蛋白的结合介导细胞与底物的黏附，这一过程也会产生细胞内的信号，导致细胞增殖的增加[85]。

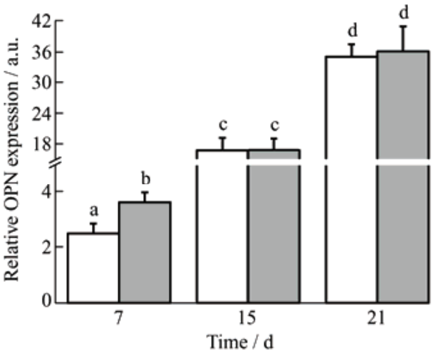
SUNARSO 等[86]将纯钛分别用 NaH_2PO_4 和 $CaCl_2$ 溶液处理，制备了钙和磷酸盐改性的钛，相比于抛光钛，改性后的钛的表面润湿性得到很大提升，细胞试验结果显示，钙离子改性后的钛有效促进了细胞的黏附、增殖和分化。ANITUA 等[87]通过将钛植入体在 $CaCl_2$ 溶液中进行超声处理，将钙离子添加到样品表面，细胞试验结果如图 8 所示。结果表明，成骨细胞在添加钙离子的植入体表面的黏附和增殖明显高于对照组，植入绵羊胫骨后，Micro-CT 和组织切片染色结果表明（图 9），添加钙离子的植入体的骨体积、骨表面、骨体积密度、骨表面密度和骨种植接触均优于对照组。



(a) Cell adhesion on the substrates measured at 3 h (*n*=7)



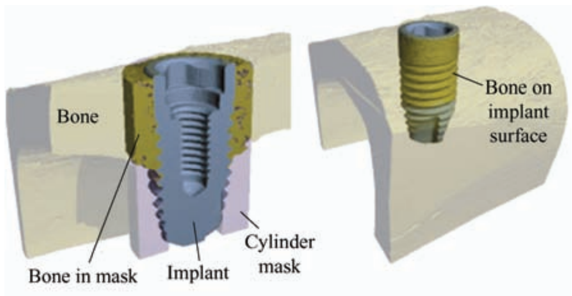
(b) Cell proliferation at 1，4 and 8 d (*n*=7)



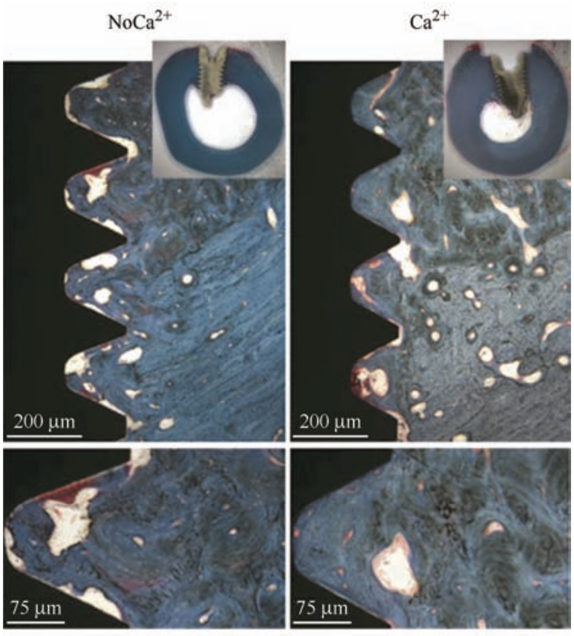
(c) Osteopontin synthesis at 7，15 and 21 d (*n*=5)

图 8　人胎儿成骨细胞 hFOB 1:19 的细胞行为[87]

Fig. 8　Human Fetal Osteoblast hFOB 1:19 cell behavior[87]



(a) Representative Micro-CT sceans



(b) Histological sections at 12 weeks after implantation

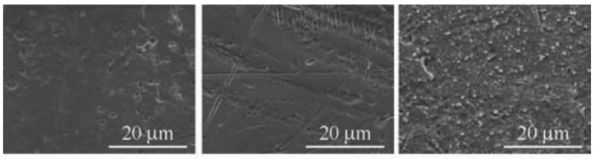
图 9 Micro-CT 和组织学切片结果[87]

Fig. 9 Micro-CT and histological section results[87]

2.2 锌离子

锌是人体内重要的微量元素，参与人体内的蛋白质代谢、细胞膜稳定和生长发育，并能促进成骨细胞的骨形成和矿化，加速破骨细胞的凋亡，同时，锌缺乏与胎儿在生长过程中的骨骼异常和生长迟缓密切相关[88-90]。研究表明，锌离子作为一种生物活性离子，能够有效调节成骨细胞的活性和行为，以提高钛植入体与周围组织的骨整合能力，在细胞微环境中，锌可以阻止破骨细胞的吸收过程并刺激成骨细胞的造骨过程。同时，锌离子是碱性磷酸酶的辅基，能促进细胞内 ALP 和胶原蛋白的表达，促进新骨形成，锌的缺乏会降低 ALP 的活性，进而引起骨钙化[91-92]。另外，锌离子表现出较好的抗菌活性，能够有效降低植入体的感染风险[93-95]。

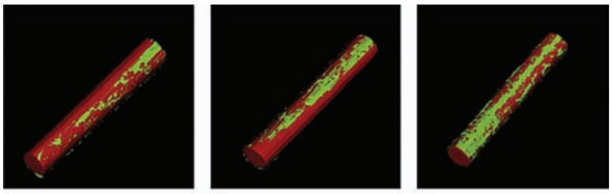
FANG 等[96]采用等离子体浸没离子注入技术对抛光后的钛表面进行修饰，通过改变注入时间产生含不同锌离子浓度的表面，XPS 分析结果表明，随着注入时间的延长，锌离子的浓度逐渐增加。抗菌试验结果表明，随着锌离子浓度的增加，植入体表面对细菌生长的抑制作用逐渐增强，锌离子浓度的增加有效促进了细胞的黏附、增殖和分化。WANG 等[97]将含锌离子的聚多巴胺涂层添加到钛植入体表面，并将改性后的植入体植入到大鼠股骨内。各组样品的表面形貌如图 10 所示，相比于未改性的钛，添加锌离子后的植入体表面覆盖了一层聚集的颗粒。Micro-CT 结果表明（图 11），相比于未经过处理的钛植入体，含锌离子的聚多巴胺涂层有效促进了植入体周围骨的矿化，骨结合性能得到了明显提高。



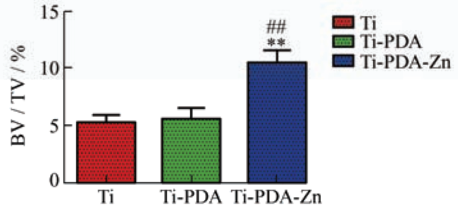
(a) Ti (b) Ti-PDA (c) Ti-PDA-Zn

图 10 各组样品的表面形貌[97]

Fig. 10 Surface morphology of each sample[97]



(a) Ti (b) Ti-PDA (c) Ti-PDA-Zn



(d) Bone volume fraction (BV / TV) of the three groups

图 11 种植 4 周后 Ti、Ti-PDA、Ti-PDA-Zn 周围骨整合情况及三组骨体积分数（n= 4）[97]

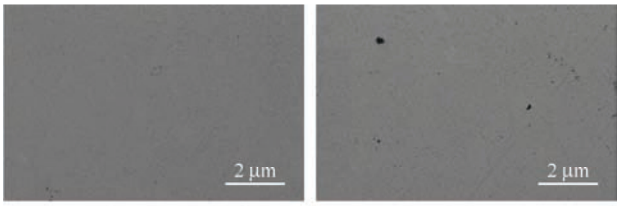
Fig. 11 Osseointegration around Ti, Ti-PDA, Ti-PDA-Zn 4 weeks after implantation, and Bone volume fraction in three groups (n= 4)[97]

2.3 镁离子

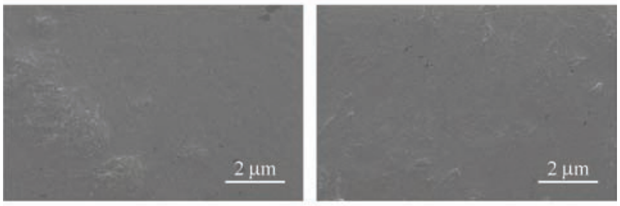
镁离子是人体内含量极其丰富的离子，富集在骨骼和牙齿中，高镁摄入量已被证明可以有效防止骨质疏松患者骨密度的降低[98]。镁离子可以通过激活成骨细胞、促进细胞内 BMP-2 的分泌来促进新骨的形成，并诱导破骨细胞的凋亡[99-100]，ZHANG 等研究结果表明，镁离子可促进由降钙素基因相关肽（CGRP）介导的成骨分化[101]，同时，镁已被证明具有较好的抗菌性能，能够有效阻止细菌的附着和生物膜的形成[102]。

LI 等[103]通过脉冲偏置电弧离子镀在多孔钛合金植入体表面成功添加了镁涂层，SEM 结果表明，涂层由尺寸约为 1 μm 的均匀镁晶粒组成，涂层厚度约为 5 μm，细胞增殖结果表明，相比于未经过处理的样品，添加镁涂层后的钛合金有效促进了细胞的增殖，免疫荧光染色结果显示，镁包覆的多孔钛合金植入体的钙化沉积明显高于未经过处理的钛合金，Micro-CT 及组织切片染色结果表明，沉积镁涂层的多孔钛合金的 BV / TV 值及新生骨组织的生成量明显高于原生组。ZHU 等[104]通过等离子体浸没

离子注入技术将镁固定在钛基底上，SEM 结果如图 12 所示，等离子体浸没离子注入处理未改变植入体原有的表面形貌，但亲水性得到改善。对细胞的活力、黏附、增殖、迁移和分化进行了分析，细胞活力分析结果如图 13 所示，染色结果表明，添加镁离子后，细胞行为均得到明显增强。蛋白质印迹结果表明，镁离子可以通过激活 PIK3 来诱导碱性磷酸酶的磷酸化，从而促进细胞的成骨分化。



(a) Pure titanium　　(b) 60 min-30 Mg-PIII



(c) 90 min-30 Mg-PIII　　(d) 120 min-30 Mg-PIII

图 12　等离子体沉积前后试件的表面形貌[104]

Fig. 12　Surface morphology of the sample before and after Mg-PIII treatments [104]

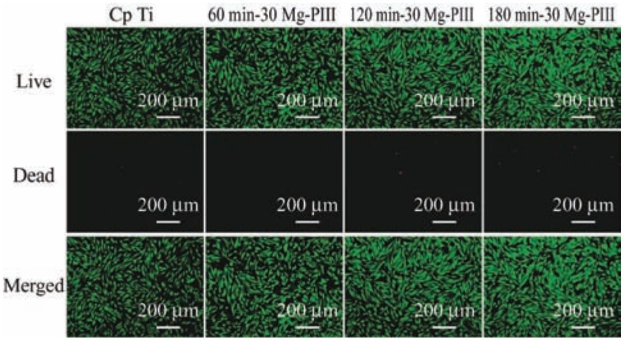


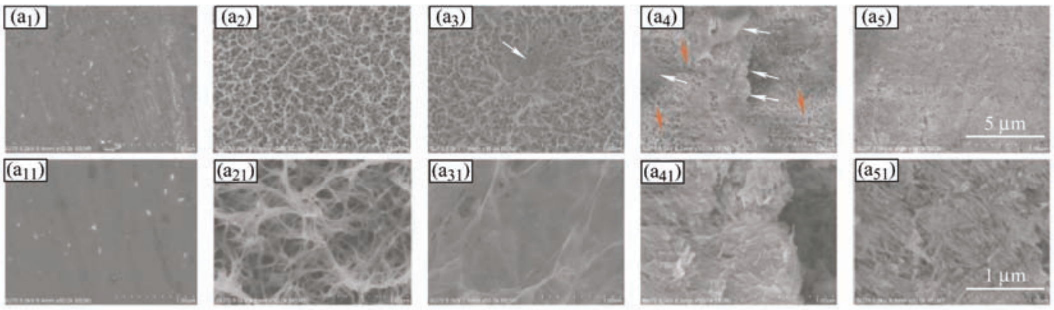
图 13　细胞活力分析（绿色代表活细胞，红色代表死细胞）[104]

Fig. 13　Cell viability assay, indicating live cells (green) and dead ones (red)[104]

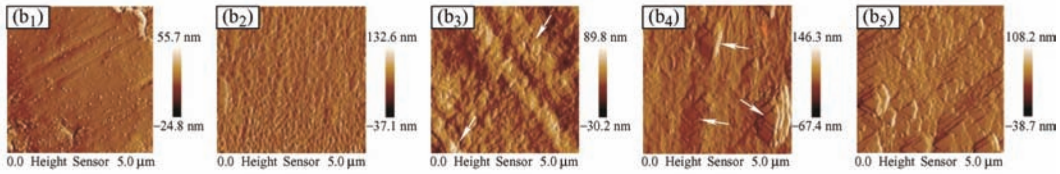
2.4　锶离子

锶主要存在于骨组织中，是人体内一种重要的微量元素，具有与钙几乎相同的生物性能[105]，研究表明，锶离子可以刺激成骨细胞中的钙敏感受体（CaSR），从而促进 OPG（骨保护素）的形成[106]，同时，锶离子可以刺激成骨细胞的增殖并抑制破骨细胞的生成和骨吸收[107-108]。另外，锶可以在成骨细胞中增加 OPG 的产生和降低 RANKL（kB 受体活化因子配体）的表达[109-110]，RANKL-RANK 相互作用对许多破骨细胞分化和功能至关重要，包括破骨细胞前体分化为成熟的破骨细胞[111]，并附着在骨表面[112]以及骨吸收的激活[111, 113-114]，OPG 是一种通过作为 RANKL 的诱导受体抑制 RANKL 诱导的破骨细胞发生的蛋白。因此，成骨前细胞和成骨细胞中 OPG / RANKL 的比值是决定破骨细胞发生和骨吸收的重要因素。由于锶离子在骨再生和骨重建中具有双重作用，很多研究将锶离子加入到生物材料的表面，以促进植入体与周围组织的骨整合[115-117]。

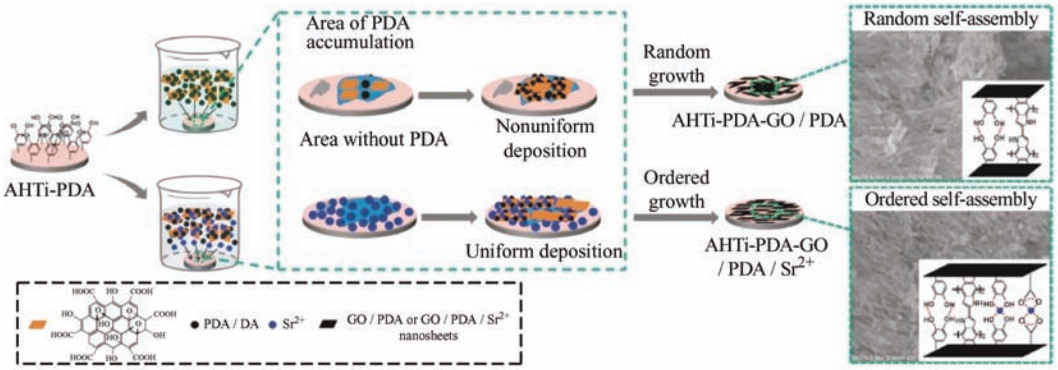
XING 等[118]通过选择性激光熔化、微弧氧化和空气等离子体处理技术在钛合金植入体表面制备了掺锶的磷酸钙涂层。SEM 结果显示，锶离子的引入没有改变涂层 b_5 的形貌，电化学腐蚀试验结果表明，Sr-CaP 涂层有效提高了植入体的耐腐蚀性。改性后的植入体表面润湿性得到了明显改善。体外试验结果表明，添加了锶离子的钛植入体有效促进了细胞的增殖和成骨分化。XU 等[119]通过原位自组装，在钛表面成功制备了氧化石墨烯 / 聚多巴胺 / 锶离子纳米复合涂层（图 14），EDS 分析结果显示，锶元素均匀的沉积在样品表面；体外细胞试验结果表明，添加了锶离子的复合涂层有效促进了细胞的黏附、增殖和迁移，并增强了成骨相关基因的表达和细胞外基质的矿化。



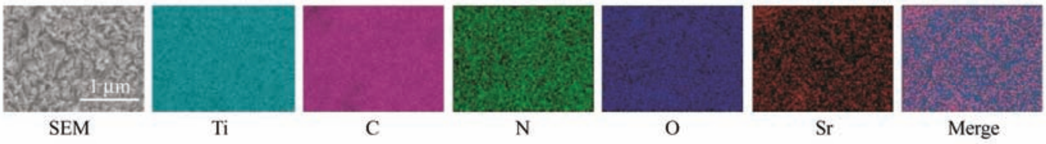
(a) Surface morphology. (a_1)，(a_{11}) polished titanium；(a_2)，(a_{21}) alkali heat treatment；(a_3)，(a_{31}) PDA-alkali heat treatment；(a_4)，(a_{41}) PDA-GO-alkali heat treatment；(a_5)，(a_{51}) PDA-GO-Sr^{2+} -alkali heat treatment



(b) AFM images of samples. (b_1) polished titanium; (b_2) alkali heat treatment; (b_3) PDA-alkali heat treatment; (b_4) PDA-GO-alkali heat treatment; (b_5) PDA-GO-Sr^{2+} -alkali heat treatment



(c) Schematic diagram of the reaction process



(d) EDS distribution analysis diagram of each element

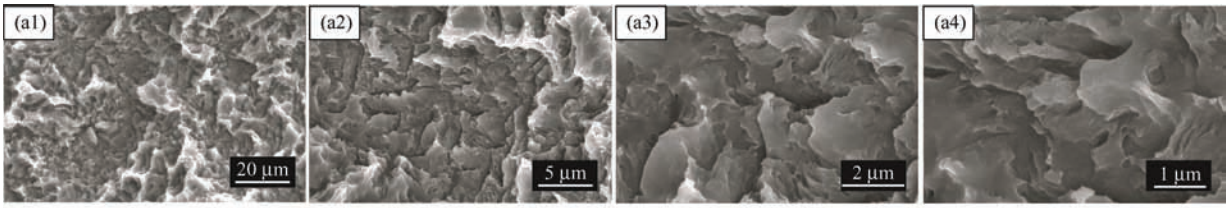
图 14 样品表面表征[119]

Fig. 14 Sample surface characterization [119]

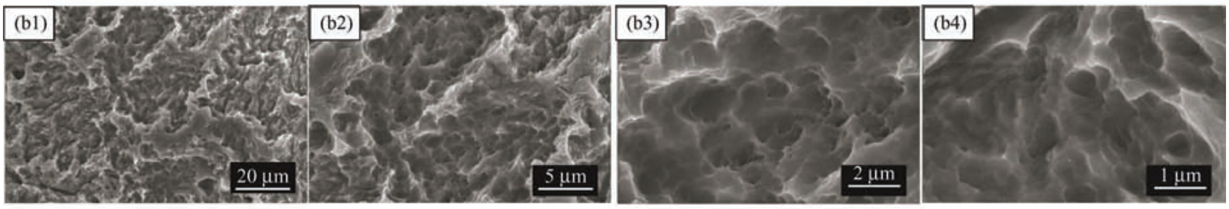
3 微纳米复合结构及生物活性离子对提高生物相容性的协同作用

为进一步提高钛植入体的生物活性和成骨性能，当前研究不局限于单一的表面形貌改性和化学成分改性，更多则是将二者结合，通过物理或化学的方法将生物活性离子添加到具有微纳米复合结构的钛植入体表面。钙、锌、镁、锶作为骨骼重要的组成元素，得到了广泛研究[120-122]。

ZHANG 等[123]通过对纯钛进行喷砂酸蚀，产生了层次化的微结构钛表面，之后在植酸和饱和氢氧化钙混合溶液中进行水热处理，通过化学转化沉积，成功制备了兼具微纳米复合结构和植酸钙涂层的钛植入体，表面形貌如图 15 所示，喷砂酸蚀后，Ti-SLA



(a1)-(a4) Titanium surface after sandblasting and acid etching



(b1)-(b4) Titanium surface atfer sandblasting, acid etching and hydrothermal treatment

图 15 两种表面在不同放大倍数下的 SEM 图[123]

Fig. 15 SEM images of two surfaces at different magnifications[123]

表面出现了微米级的凹坑，水热处理后，Ti-PACH 表面形貌未发生明显变化。表面润湿性试验结果表明（图 16），水热处理后的表面接触角明显小于喷砂酸蚀后的表面接触角，表现出较好的亲水性，体内外试验结果表明，添加了钙离子的微纳米复合结构能够有效促进细胞的增殖、分化和动物体内新骨组织的生成。

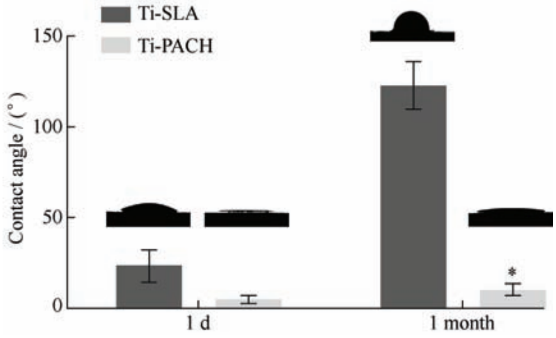


图 16　新制备的样品及在干燥、阴凉、密封的环境中贮存一个月后的表面接触角[123]

Fig. 16　Surface contact angle of freshly prepared samples and stored in a dry, cool and sealed environment for one month[123]

SHAO 等[124]通过对抛光钛进行喷砂酸蚀，制备了具有微米级和亚微米级结构的表面，之后在 NaOH 溶液中进行碱热处理，获得了具有微纳米复合结构的钛表面，在 $ZnSO_4$ 溶液中通过水热处理进行离子置换后，锌离子将表面生成的钛酸钠纳米层中的钠离子成功置换，在植入体表面沉积了锌离子，试验过程如图 17 所示，其中，SEM 结果表明，水热处理后，喷砂酸蚀和碱热处理构建的微纳米复合结构未发生明显变化。表面润湿性结果表明，水热处理后的表面具有较好的亲水性。XPS 结果显示，经过水热处理，表面成功添加了锌离子，离子释放试验结果表明，在初始阶段锌离子大量释放，随后一直保持在较高的水平。体外试验结果表明，相比于具有单一的微米级结构和微纳米复合结构的表面，添加了锌离子的表面有效促进了细胞的增殖分化和成骨相关基因的表达，并表现出良好的抗菌性。

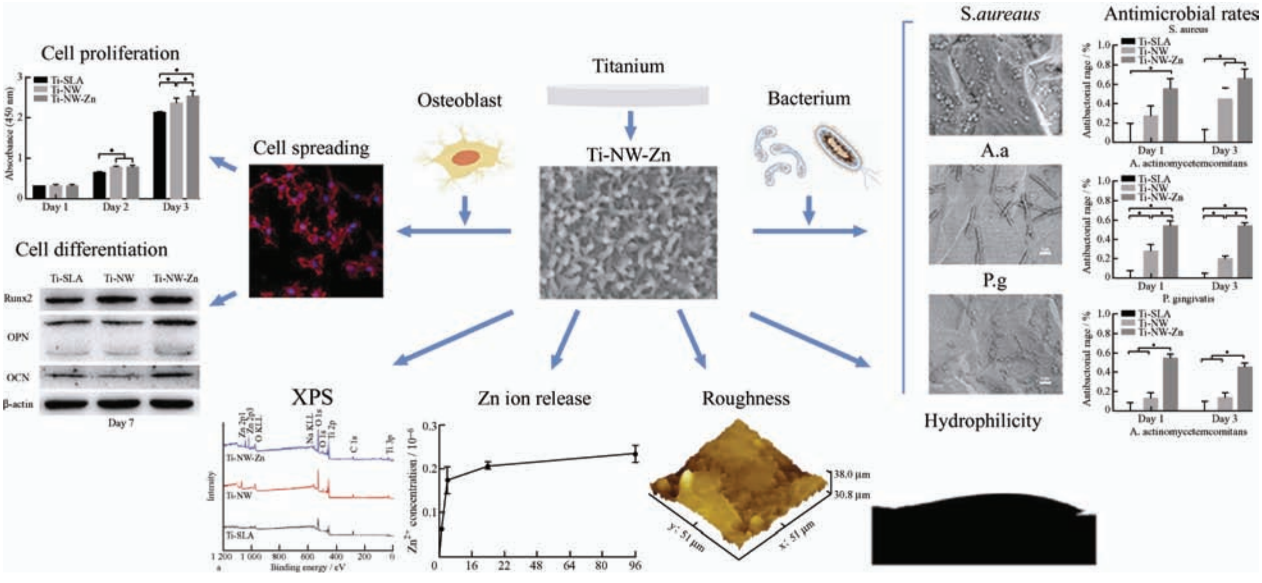
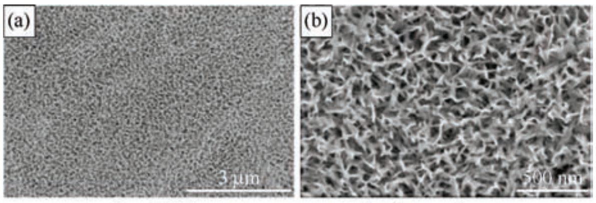


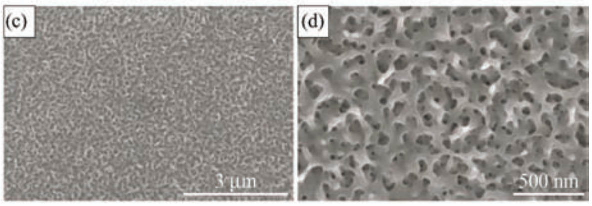
图 17　钛植入体表面喷砂酸蚀-碱热处理-水热处理试验过程示意图[124]

Fig. 17　Schematic diagram of the experimental process of sandblasting, acid etching and alkali heat treatment-hydrothermal treatment on the surface of titanium implants[124]

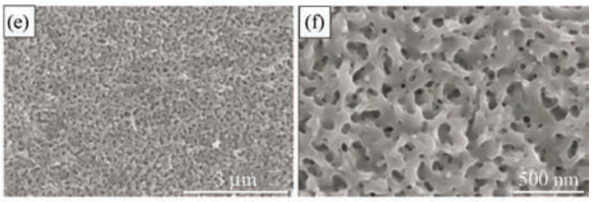
WANG 等[125]将纯钛在草酸中进行酸洗，之后在 H_2O_2 和 NaOH 溶液中进行水热处理，在钛植入体表面构建了微纳米复合结构，并通过盐酸对表面进行质子化，而后采用过滤阴极电弧等离子体源将镁注入具有微纳米复合结构的钛表面。SEM 结果显示（图 18），与碱性 H_2O_2 反应后，具有微米级结构的基底表面生成了均匀的纳米尖端结构，经过等离子体注入后，纳米尖端形貌发生了变化。EDS 分析结果表明，镁元素均匀分布在样品表面。体外细胞试验结果表明，兼具镁和微纳米复合结构的钛表面有效促进了 rBMMSCs 的增殖和成骨分化。



(a)，(b) Micro-nano structured titanium surfaces



(c), (d) Micro-nano structured titanium surfaces followed by magnesium ion implantation for 30 min



(e), (f) Micro-nano structured titanium surfaces followed by magnesium ion implantation for 60 min

图 18 不同倍数下三种样品的表面形貌[125]

Fig. 18 Surface morphology of three samples at different magnifications[125]

WANG 等[126]将抛光钛进行碱热处理后，成功在表面构建出微纳米复合结构，之后，通过磁控溅射将锶离子沉积在钛表面，获得了叠加生物活性离子的微纳米复合结构表面。SEM 图像和 AFM 图像如图 19 所示，抛光组表面可以观察到明显的划痕，经过碱热处理，表面呈现海绵网状结构，而沉积锶离子后，海绵结构的纳米线变厚，表面发现了大量的纳米颗粒，随着溅射时间的延长，纳米层的厚度逐渐增加。EDS 分析结果表明，随着磁控溅射时间的延长，锶元素的含量逐渐升高。细胞试验结果表明，细胞在添加了锶离子后的植入体表面的增殖分化能力明显增强，Micro-CT 和组织切片染色结果显示，加入锶离子后的植入体更有效地促进了新骨的形成。

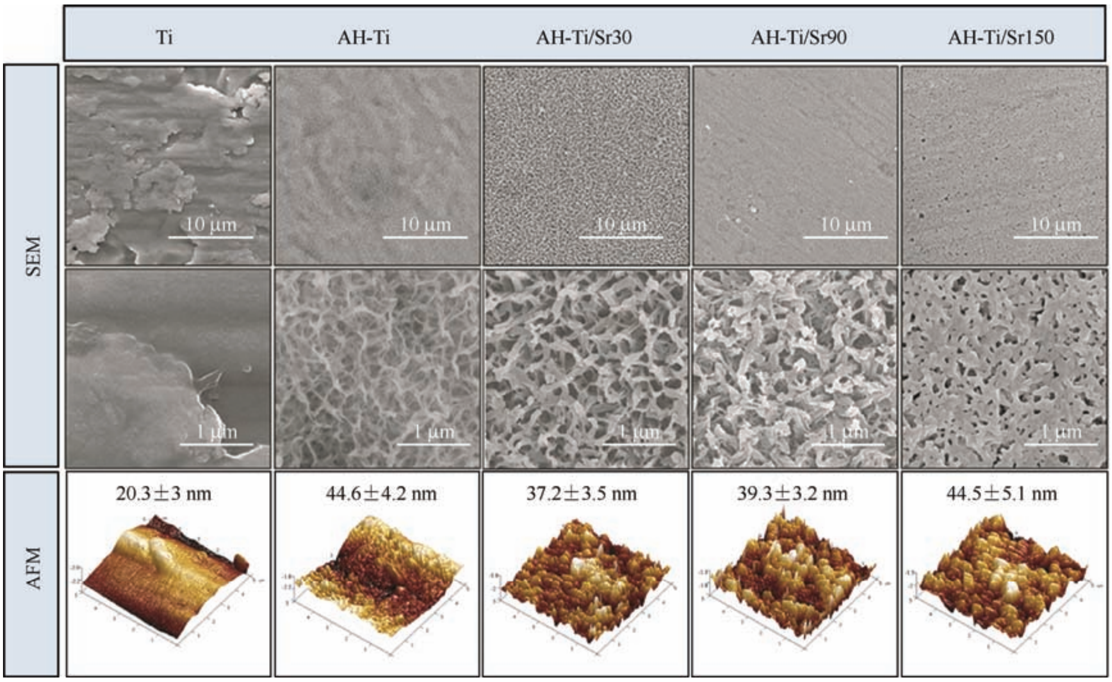


图 19 不同样品的 SEM 图像和 AFM 图像[126]

Fig. 19 SEM images and AFM images of different samples[126]

4 结论与展望

综述了钛植入体表面微观形貌和化学组成对生物相容性的影响，得出的主要结论如下：

（1）植入体表面的理化特性对生物相容性有着十分重要的影响。其中，植入体表面的微纳米复合结构相较于单一的微米级结构和纳米级结构，更有利于细胞的黏附、增殖和分化以及动物体内新骨的形成。

（2）通过等离子体注入、水热处理、离子置换等方式添加钙、锌、镁、锶等生物活性离子后，相比于未经过处理的钛，植入体的生物相容性得到明显增强。

（3）在构建微纳米复合结构的基础上，加入生物活性离子后，二者可以发挥协同作用，进一步增强植入体的成骨性能。

目前，多采用物理、化学或生物化学的方式在钛植入体表面构建微纳米复合结构并添加生物活性离子，但存在一定的局限性，对未来钛植入体表面

改性的研究展望如下：

（1）在构建微纳米复合结构和添加生物活性离子等生物活性物质的基础上，未来可深入对其细胞行为内在影响机制和信号通路激活方式的研究，为植入体表面改性研究构建理论基础。

（2）目前关于细胞对植入体表面微纳结构和生物活性离子的反应的研究较多，由于体内的生理环境较复杂，未来可深入到动物体内植入试验，研究其对促进成骨的内在影响机制。

（3）目前对于巨噬细胞极化对促进成骨的作用机制尚未明确，未来可通过调控巨噬细胞的极化方向减轻医用材料植入体内后的炎症反应，并探索炎症反应影响成骨的内在机理。

（4）当前对于促进细胞行为的最佳微纳米复合结构的形式、尺寸及各种离子的最佳浓度范围尚未明确，需进一步研究。

（5）细菌感染是当前植入手术失败的重要原因之一，未来可通过载药、载抗菌离子等方式进行抗菌表面的设计制造。

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