Biocompatibility of Metallic Zinc for Bioabsorbable Stents

Roger J. Guillory[1], Patrick K. Bowen[2], Jaroslaw Drelich[2], Jeremy Goldman[1]

[1]Department of Biomedical Engineering, and [2]Department of Materials Science and Engineering, Michigan Technological University, Houghton, MI 49931, USA

Statement of Purpose

A new degradable biomaterial is needed for the next generation of arterial stents that will degrade and resorb between 6 and 9 months after implantation. Our group recently introduced metallic zinc as a promising candidate material for bioabsorbable vascular stents, due to its near-ideal corrosion rate and ease of conventional alloying approaches to improve mechanical strength.[1] However, the biocompatibility of metallic zinc and the products produced by corrosion in the artery are largely unknown. A thorough characterization of cellular and tissue response to the material over time is critical to gauge the compatibility of pure zinc for stents, and to guide rational material modifications to improve performance.
Here, we have conducted a year-long *in vivo* study of two zinc materials whose main difference is their manifest *in vivo* corrosion rates and uniformity. We investigated important aspects of biocompatibility, including inflammation, dysplasia, cytotoxicity and foreign body response. The body of work collected allows us to conclude on the feasibility of a zinc material to serve for bio-absorbable vascular stent constructs.

Methods

Two zinc wires of varied purity were implanted into rat arteries. Wires of 99.99+% zinc (Zn1) were purchased from Goodfellow Corporation, and special high grade (SHG, ~99.7%) (Zn2) ingots were processed into wire form by rolling, cutting, and electropolishing. A series of wires for each material were implanted in the arterial wall of the abdominal rat aorta. Twelve rats were implanted with Zn1 and explanted monthly, concurrently with 4 rats that were implanted with Zn2, with extractions made at 1.5, 3, 4.5, and 6 months. At endpoints, the artery was collected along with the wire, snap frozen in liquid nitrogen, and cross-sectioned transversely with a cryotome at 10 μm thickness. The tissue/wire cross sections underwent staining by either Masson's Trichrome (MT), Hematoxylin and Eosin (H+E), or Macrophage F4/80 Fluorescent staining (MP).

Results

H+E staining revealed no obvious signs of cell cytotoxicity or necrosis in the arterial adventitia or at the tissue/implant interface for either the Zn1 or Zn2 implants. H+E images demonstrated extensive degradation of Zn2 material with a thick corrosion layer occupied by cell infiltrates, with evidence of neo-tissue synthesis. Minimal degradation was observed on the surface of the Zn1 material, with a thin and compact corrosion layer that was relatively lacking in cell infiltration. MT as well as H+E showed early onset and progression over time of fibrous encapsulation of Zn1, beginning as early as one month post-implantation, whereas tissue regeneration and cell/tissue integration predominated for the Zn2 material. The MP fluorescence staining showed extensive macrophage accumulation around both the Zn1 and Zn2 surfaces, however macrophages surrounding Zn1 had adopted an elongated shape consistent with fibrous encapsulation, whereas macrophages surrounding Zn2 had not become elongated. H+E images revealed severe chronic inflammation and foreign body rejection for the slowly degrading Zn1 material, whereas mild/moderate inflammation was detected for the rapidly corroding Zn2 implanted wires. H+E and MT stains depicted morphological tissue regeneration and a migrating tissue/implant interface for Zn2 wires. The same techniques revealed a static tissue/implant interface for the Zn1 wires, as well as intense fibrous and collagenous deposits around the material. H+E also suggested that degradation of Zn1 began to slow after 5-6 months.

Conclusions

- Neither the Zn1 nor Zn2 wires exhibited any signs of cytotoxicity on surrounding cells and tissue.
- The corrosion progression of the 99.99+% purity Zn1 was slower than that of the SHG Zn2 wire.
- Fibrous encapsulation of the Zn1 wires may have contributed to its slow corrosion rate at later time points, but may have been a consequence of the relatively inert foreign material at earlier times.
- Fibrous encapsulation implies that Zn1 may not be amenable to macrophage-mediated phagocytosis.
- The presence of extensive cell infiltration and tissue regeneration at the Zn2 implant surface indicates good biocompatibility and an ability of the local tissue to eliminate the products of corrosion.
- Early fibrous encapsulation of an implanted bio-absorbable material may inhibit implant degradation, which could lead to failure of the device to fully degrade.
- Zinc materials continue to hold promise as candidates for bio-absorbable stent materials due to their low to non-existent cytotoxicity along with biocompatibile corrosion products and susceptibility to macrophage-mediated corrosion.
- There may be a threshold value of initial corrosion rate and corrosion product particulate size that regulates macrophage-mediated phagocytosis of the material.

Reference

1) Bowen, P.K., Drelich, J., Goldman, J., Zinc Exhibits Ideal Physiological Corrosion Behavior for Bioabsorbable Stents, *Adv. Mater*. **25**(2013)2577-82.