Titanium Modulates Immune System and Bone Metabolism

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Introduction

The concept of titanium implants being inert when in contact with the bone has been challenged^{1,2} and the hypothesis of an immune interaction between titanium and host bone tissue has been proposed², following the concept of foreign body reaction to biomaterials³. The authors believe this concept is important to understand the processes leading to osseointegration and the development of peri-implantitis, which may depend of an intimate relationship between the immune system and bone cells.

A pilot study was designed with the aim to study the immune system during bone healing in the absence and presence of a titanium implant⁴.

Material and Methods

Six New Zealand white rabbits had an osteotomy performed on the distal portion of the femur on both sides: on one side a sham site was left to heal without an implant (Sh) and on the other side a titanium implant was placed (Ti). Three rabbits were sacrificed at 10 days and three rabbits at 28 days (within and after the inflammatory period of approximately 14 days³, respectively). On each time point implants were removed and bone was collected from the periphery of both Sh and Ti sites and processed using quantitative-polymerase chain reaction (qPCR) for gene expression analysis. A panel of three reference genes was used and specific study markers were chosen (table 1).

Biological Marker	Primer
Neutrophil	NCF-1
Macrophage	CD68, CD11b, CD14, ARG1
Macrophage fusion	IL-4, IL-13, M-CSF
Bone resorption	OPG, RANKL, TRAP, CathK, PPAR-gamma
Complement	Activation: C3, C3aR1, C5, C5aR1 Inhibition: CD46, CD55, CD59
T-lymphocytes	CD3, CD4, CD8
B-lymphocytes	CD19
Reference genes	GAPDH, ACT-beta, LDHA

Table 1. List of markers organized per biological group

Results

At 10 days (table 2), there were not many significant differences between Sh and Ti, which was expected given that during the first two weeks there is an inflammatory response related to the healing process in response to the trauma caused by the osteotomy- although ARG1 (M2-macrophage marker) already presents a significant up-regulation in Ti samples when compared to Sh.

Up-regulated Significant	p-Value	Regulation
ARG1	0,0111	X2
Down-regulated Significant	p-Value	Regulation
IL-13	0,0339	x4

Table 2. 10 days, Ti compared to Sh

However, at 28 days (table 3), innate immunity markers ARG1, CD11b, NCF1 and C5aR1 are significantly up-regulated, while bone resorption markers OPG, RANKL, Cathepsin K and TRAP are significantly down-regulated on Ti samples when compared to Sh.

Up-regulated Significant	p-Value	Regulation
CD11b	0,000093	13x
ARG1	0,0157	2x
C5aR1	0,0302	2x
NCF-1	0,0064	3x
Down-regulated Significant	p-Value	Regulation
RANKL	0,0005	X3
OPG	0,0065	X5
TRAP	0,0055	X4
CATH K	0,0029	X2

Table 3. 28 days, Ti compared to Sh

Figure 1. 28 days. Sh- Sham. Ti- Titanium. OS- osteotomy site. B- new bone. Hematoxylin-Eosin staining.

Conclusion

This pilot study, within its limitations, indicates that titanium implants are not inert when in contact with bone.

The immune system seems to be activated and bone resorption mechanisms seem to be suppressed around Ti after 28 days.

More studies are needed with longer time points to understand if the immunological presence persists through time.

References

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