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Cellulose Nanocrystals as a Versatile Platform for Regulation of Myeloid Cell Immunogenicity

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Extended Abstract

Phosphonates possess a great potential for the therapy of bone tumours due to their inhibitory potential for osteoclasts. The delivery of phosphonates via cellulose nanocrystals (CNCs) seems a promising approach for their increased efficacy in target tissues. However, the immunological effects of these conjugates have not been investigated thoroughly.

Here we modified used wood-based native (n)CNC, oxidized (ox-CNC) and phosphonate (3-AminoPropylphosphonic Acid (ApA))-conjugated CNC to test their physicochemical properties and immunomodulatory potential. Modification of CNC increased their elasticity module and hardness, which resulted in their reduced internalization by phagocytic cells. The non-toxic doses of native and modified CNC displayed different immunomodulatory properties in models of human peripheral blood mononuclear cells (PBMCs) and monocyte-derived dendritic cells (moDCs). Namely, nCNC displayed a tolerogenic potential upon internalization by MoDCs, as judged by their capacity to up-regulate IDO-1, PDL1, ILT3 and IL-27 expression, and potentiate their capacity to induce FoxP3+ regulatory T cells when present during the differentiation of monocytes into MoDCs. These properties make nCNC promising in the treatment of chronic inflammatory diseases such as autoimmunity and transplantation.

In contrast, ApA-CNC induced oxidative stress and autophagy in MoDCs and up-regulated maturation markers on MoDCs, including CD83, CD86, NLRP3, IL-1β and IL-12 production. Consequently, ApA-CNC-treated MoDCs displayed an increased allostimulatory potential and Th1/CTL polarizing activity in co-cultures with T cells. We found that the stimulatory effects of ApA-CNC on MoDCs were mediated via GABA-B receptor and down-regulation of cAMP levels in MoDCs, as the blockage of the receptor diminished the effects of ApA-CNC. Moreover, the Th1 polarizing and allostimulatory capacity of MoDCs differentiated with ApA-CNC were preserved upon LPS and IFN-γ treatment, which correlated with late expression of R2 subunit of GABA-B receptor during MoDCs differentiation.

Therefore, the delivery of ApA via CNC induces potent DC-mediated Th1 polarization which could be harnessed for development new treatment of bone malignancies.

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