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Review

Inflammatory phenotype of the nurse cell harboring *Trichinella* spp.

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ABSTRACT

The nurse cell (NC), formed from muscle cells upon infection with the parasitic nematode *Trichinella* spp. constitutes a confined habitat for muscle larvae of encapsulating species. Signaling pathway-directed analysis of microarray data allowed identification of the stage of NC cell cycle arrest as being of G1-like type, accompanied by cellular senescence. In accord with the specificity of senescent cellular systems, up-regulation of pro-inflammatory molecules was also found within the NC preparations. Potential immune-related activities associated with NCs as inferred from the aforementioned analysis, are reviewed herein. Transcriptional data suggest that the NC which harbors the larvae may exhibit the following immune-related functions: (i) production of complement components, (ii) antigen presentation and phagocytosis, (iii) pro-inflammatory cytokine secretion, (iv) oxidative stress generation and (v) eicosanoid synthesis.

Contents

1. Introduction

The nurse cell (NC) is a cellular niche for *Trichinella* spp. muscle larvae. It is formed within 20 days post-infection (dpi), as a fusion between degenerating parasite-invaded myotubes and mis-differentiated muscle satellite cells. A NC–parasite complex is stably maintained within a collagen capsule throughout the life span of the host though calcification can and does occur over time (Despommier, 1998). Hypertrophy accompanied by 4N DNA content was found to characterize NC (Jasmer, 1993). Inasmuch as the NC cyclin transcription profile was found to target the cell cycle G1 phase, NC growth arrest was postulated to be G1-like (Dabrowska et al., 2008). Such a phenomenon is known to occur due to mitotic slippage when a cell enters the G1 phase without prior chromatid separation, and is consistent with the NC origin from muscle cells which are incapable of carrying out karyokinesis due to

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the loss of centrioles (Jasmer, 1993). Functional analysis of the NC transcriptome also permitted identification of transcripts that correspond to cellular senescence, a metabolically active period of growth arrest underpinned by DNA damage. Cellular senescence is proposed to occur due to hypermitogenic stimulation exerted in an autocrine manner, counterbalanced by up-regulation of inhibitors of cyclin dependent kinases (CDKs) (Blagosklonny, 2003). Although DNA fragmentation in NC nuclei had already been reported (Wu et al., 2005), a scrutinized study of DNA damage in this cellular system is still needed. The putative autocrine hypermitogenic stimulation axes of NC were identified as epidermal growth factor (EGF) family members stimulating EGF receptor, fibroblast growth factors FGF10, 12 and 18 acting upon FGF receptors 1 and 2, as well as platelet-derived growth factors PDGFA and PDGFD stimulating PDGF receptor A (Dabrowska et al., 2008).

A gain in NC proliferative activity has long been proposed as essential to NC phenotype specificity based on well-established correlations between proliferation and inhibition of muscle gene transcription (Jasmer, 1995). The CDK inhibitors $p15^{INK4b}$, $p16^{INK4a}$ and $p57^{Kip2}$ were found up-regulated in NC. Senescence-associated β-galactosidase activity, a key marker of senescence, was detected in NC (not shown) and correlated with up-regulation of the corresponding gene (Dabrowska et al., 2008). Hypermitogenic growth arrest accompanied by senescence is characterized by cellular expansion indicative of hypertrophy, and high secretory activity known as senescence-associated secretory phenotype (SASP). It has been demonstrated elsewhere that a prominent role of SASP is induction of inflammation (Kuilman et al., 2010). This was also inferred in characterizing NC based on up-regulation of interferon IFN-γ, interleukins IL-1α, IL-1β and IL-11, as well as tumor necrosis factor TNF-α, genes. Nurse cells were also found to express complement factors and major histocompatibility (MHC) class II molecules (Dabrowska et al., 2008).

The above transcriptomic studies of *Trichinella* NC were performed with the use of Ingenuity Pathways Analysis (IPA) software, employed for competitive expression microarray data analysis (Dabrowska et al., 2008). Murine C2C12 myoblasts and myotubes served as referral cellular systems for NCs isolated from mice infected with *Trichinella spiralis*, 5–12 months p.i., when possible contamination of NCs with immune infiltrating cells was estimated at the level of RNA preparation, not to exceed 10% (Jasmer, 1990, 1993). Scientific interpretations and conclusions derived from the experimental model employed, i.e. comparison of NC transcriptome to the transcriptome of C2C12 cells cultured and differentiated in vitro, are constrained and must be considered tentative given the possibility for contamination of isolated NC with infiltrating immune-related cells. Furthermore, the analyses are based upon transcriptional changes and may not necessarily reflect changes occurring at the level of translation and/or post-translational processing. Nonetheless, identified molecules scored as pathways-eligible were found expressed at high levels in NC. These data provided general insights into the specificity of NC functionality.

While the emphasis of previously published studies was based on regulation of cell cycle and the identification of the most prevalent signaling circuits operating in NC, the present review deals with immunologically relevant functions identified in the NC preparations. GenBank accession numbers and expression value parameters for the molecules identified and not included in the previous study (Dabrowska et al., 2008) are listed in Supplementary Table 1. It is proposed that the immune-related functions executed by NC as determined from expression profiles of specific molecules, may result in the recognition of the NC by the host immune system as functionally relevant or self-derived and thus assure its existence throughout the host life span.

2. NC synthesizes C1, C2, C3 and CFB factors of the complement system

Complement factors are primarily synthesized by cells of the monocyte/macrophage lineage. The NC is found to synthesize C1QA, C1QB, C1QC and C2 factors of the classical complement activation pathway, factor CFB of the alternative activation pathway, and factor C3 which participates in both pathways (Dabrowska et al., 2008). The molecules C1q and C3a, the latter of which is formed after cleavage of C3 factor, are known as extracellular *p*athogen-*r*ecognition *r*eceptors (PRRs) for pathogen-associated molecular patterns (PAMPs). Although the functional significance of complement signaling in the vicinity of NC remains unknown, the apparent protection of NC against complement may be attributed to (i) the serpin peptidase inhibitor SERPING1 (C1 inhibitor), and/or (ii) complement membrane attack complex inhibitor, CD59. Both these molecules are up-regulated in NC (Dabrowska et al., 2008).

3. NC is capable of antigen presentation

Apart from MHC class II molecules (Dabrowska et al., 2008), MHC class I molecules HLAA and HLAC are also upregulated in NC, indicating their capability to present antigen to $CD4^+$ and $CD8^+$ lymphocytes, a function normally performed by antigen presenting cells (APCs). In accord with antigen processing and peptide editing in the context of MHC class II and class I molecules, genes encoding lysosomal cathepsins and CD74, as well as proteasomal peptidases and the TAP-binding protein, are up-regulated in NC, respectively (Dabrowska et al., 2008). The APCs, i.e. dendritic cells and macrophages, associated with the innate immune response display endocytic functions. Genes involved in caveolin- and clathrin-mediated endocytosis (caveolin CAV1 and clathrins CLTA and CLTB), as well as phagosome structural molecules (FYB, LCP2, RAC2, VAV1, and WAS), were also found up-regulated in NC.

4. NC expresses molecules executing dendritic cell (DC) functional maturation

Nurse cells presented gene expression patterns specific for both DC maturation induction and antigen presentation