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Biogenic magnetic nanoparticles in human organs and tissues

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1. Introduction

Biogenic magnetic nanoparticles (BMN) are the subject of intense research since 1975 when they were first discovered in magnetotactic bacteria (MTB) which show taxis in the direction of the geomagnetic field (Blakemore, 1975; Frankel et al., 1979). Since then, BMN were found in several organisms that belong to all three domains: prokaryotes, archaea and eukaryotes.

BMN were experimentally found in algae and protozoa (Lins de Barros et al., 1981), worms (Cranfield et al., 2014), clams (Lowenstam, 1962), snails (Suzuki et al., 2006), ants, butterflies (Ferreira de Oliveira et al., 2010; Wajnberg et al., 2010; Acosta-Avalos et al., 1999), honey bees (Chin-Yuan et al., 2007), termites (Maher, 1998), lobsters (Lohmann et al., 2008), tritons (Brassart et al., 1999), fish (Kirschvink, 1989; Diebel et al., 2000; Eder et al., 2012; Moore and Riley, 2009), sea turtles (Irwin and Lohmann, 2005), birds (Falkenberg et al., 2010; Cadiou and McNaughton, 2010; Edelman et al., 2015), bats (Holland et al., 2008), dolphins, whales (Zoeger, 1981) and human (Kirschvink et al., 1992; Quintana et al., 2004; Collingwood et al., 2008; Brem et al., 2006; Grassi-Schultheiss et al., 1997; Kirschvink, 1981; Schultheiss-Grassi and Dobson, 1999; Kobayashi et al., 1997).

BMN were experimentally found in such human organs and tissues as heart, liver, spleen (Grassi-Schultheiss et al., 1997), adrenal glands (Kirschvink, 1981), ethmoid bone (Baker et al., 1983) and brain (Kirschvink et al., 1992; Collingwood et al., 2008; Brem et al., 2006; Kobayashi et al., 1997). It were also found in pathologically changed tissues during neurodegenerative diseases (Hautot et al., 2003), cancer (Kobayashi et al., 1997), atherosclerosis (Alexeeva et al., 2014). Moreover, BMN concentration is higher in the zone of inflammation during neurodegenerative disease (Moos and Morgan, 2004; Bartzokis and Tishler, 2000) and cancer (Brem et al., 2006; Kobayashi et al., 1997) than in the same tissues in a norm.

Nowadays considerable attention is paid to the research of magnetic nanocomposites and magnetic vectors (liposomal, bacterial, viral). These materials can be used for the magnetically targeted drug delivery to specific organs (Upadhyay, 2014). However, there are some difficulties with its practical implementation:

- BMN are located on cell membranes in several normal and abnormal human organs and tissues (Kirschvink et al., 1992; Collingwood et al., 2008; Brem et al., 2006; Grassi-Schultheiss

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et al., 1997; Kirschvink, 1981; Kobayashi et al., 1997; Baker et al., Hautot et al., 2003). This may cause toxic and allergic effects and even corking of vessels during uncontrolled accumulation of magnetic drugs in such organs and tissues (Dong-Hyun Kim et al., 2010) because of their magnetic dipole-dipole interaction with BMN on cell membranes (Gorobets et al., 2013a, b, Gorobets et al., 2014a, b, c). These forces are much greater than those that held magnetic carrier using an external static magnetic field in target organs under certain conditions (Gorobets et al., 2013a, b). Besides magnetic dipole-dipole interaction forces can exceed the strength of specific interactions such as antigen-antibody between magnetic carriers and BMN in cells (Gorobets et al., 2013a, b).
- Modern methods of magnetic vector producing (liposomal, bacterial, cell) don't practically ensure homogeneity of the magnetic properties and lack of clustering that even increases the probability of corking of vessels with the presence of BMN in cells.

In view of the above, the development of BMN detection methods in human tissues and organs, the study of their properties, localization in cells, the calculation of interaction forces between BMN and magnetic carriers (artificial and natural origin) (Upadhyay, 2014) are extremely important tasks.

The main objective of this work is the prediction and detection of human organs and tissues, characterized by BMN biomineralization process.

Genetic regulation of BMN synthesis is studied experimentally in details only in MTB for which there is a strict genetic control of properties and BMN structural organization (Richter et al., 2007; Abreu et al., 2011). Most proteins that are involved in BMN biomineralization inside MTB are encoded in magnetosome islands (in mamGFDC, mms and mamAB operons) (Ullrich et al., 2005) and is a manifestation of magnetosome island (MI) gene expression (Richter et al., 2007; Schubbe et al., 2006). MI MTB proteins can be divided into two functional classes: proteins essential for the BMN biomineralization process - MamA, MamB, MamM, MamE, MamO and regulatory proteins responsible for the formation of magnetosome chain - MamJ, MamK, formation of membrane vesicles - MamQ, MamI, MamL, the number and size of BMN in the chain - MamF, MamD, MamT, MamP, MamR, MamS) (Richter et al., 2007; Abreu et al., 2011).

The general mechanism of BMN biomineralization genetic regulation in both prokaryotes and eukaryotes (including humans) demonstrated a clear homology between the proteins essential for BMN biomineralization. The only one regulatory MTB protein MamK has a homologous human protein responsible for the formation of BMN chains among all the MI regulatory proteins (Gorobets et al., 2014a, b, c). The presence of homologous proteins is consistent with the phenotypic expression of BMN in both MTB and humans. Lack of homologues in the human proteome for other MI MTB regulatory proteins is also consistent with experimental data (Kirschvink et al., 1992; Kobayashi et al., 1997) about lack of control over the size, shape and number of BMN and lack of magnetosome vesicles around BMN in human cells.

There is a clear correlation between extracellular levels of oxygen and magnetite quantity in MTB *Magnetospirillum gryphiswaldense* (Schubbe et al., 2006). Biomineralization of magnetite in these bacteria is possible at the levels of oxygen below the threshold of 2 kPa (2%). The largest number of BMN in magnetosomes was found at 25 Pa (0.025%). The oxygen levels higher than 2 kPa completely inhibit the formation of BMN (Schubbe et al., 2006). In addition, BMN biomineralization depends on the availability of iron in the growth medium. Magnetite crystals synthesis in the cell is accompanied by accumulation of endogenous iron, so BMN biomineralization is impossible among the iron deficiency in the growth medium.

It is known that the oxygen level in the human blood is about 2–4% (Brunton et al., 2011) that corresponding to microaerobic growth conditions of MTB. Therefore, in this paper, the expression levels of protein homologs essential for BMN biomineralization in human organs and tissues with the corresponding MI MTB proteins are comparing at different levels of oxygen.

2. Materials and methods

Homologs were found by means of pairwise and multiple alignment of amino acid sequences methods using BLAST program of National Center for Biotechnology Information (NCBI). Table 1 provides a list of human proteins homologous to MI proteins of

Table 1
MTB proteins, human homologs and functions.

MTB protein	MTB protein functions	Human homologous protein	Human homologous protein functions
mamA	Contains TPR domen, that takes part in protein-protein interactions, chaperone functionality, cell cycle, transcription and protein transporting	Pex-5	Pex-5 required for the assembly of functional peroxisomes. It is involved in the peroxisomal import of proteins.
mamB	Transporter of cations Co^{2+}, Zn^{2+}, Cd^{2+}.	Slc30a9 Slc39a4 Slc39a3	Transporter of cations Zn^{2+}.
mamM	Transporter of cations Co^{2+}, Zn^{2+}, Cd^{2+}.	Slc30a9 Slc39a4	Transporter of cations Zn^{2+}.

Table 2
Classification of BMN localization and properties.

MTB protein	Extracellular amorphous BMN	Extracellular crystalline BMN	Intracellular amorphous BMN	Intracellular crystalline BMN
MamA		+		+
MamB	+	+	+	+
MamM	+	+	+	+
MamO			+	+
MamE			+	+
MamK			+	+

Sign + in the table indicated the presence of MI MTB homologues in BMN producers proteome with relevant amorphous or crystalline structure and extra- or intracellular localization.

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