Baseballs, tennis balls, livestock farm manure, the IDH1 mutation, endothelial cell proliferation and hypoxic pseudopalisading (granulomatous) necrosis: Mycobacterium avium subspecies paratuberculosis and the epidemiology, cellular metabolism and histology of diffuse gliomas, including glioblastoma

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Abstract
An increased rate of diffuse gliomas, including glioblastoma, has been noted in livestock farmers in Western countries. Some researchers have suggested that a zoonotic virus or bacteria present in the livestock animal’s feces or manure may be a possible etiologic factor. Mycobacterium avium subspecies paratuberculosis (MAP), the cause of a chronic enteropathy in domestic livestock and a probable zoonosis, is heavily excreted in an infected animal’s feces or manure, contaminating soil and ground on the animal’s farm. Once excreted in an animal’s feces, MAP lasts indefinitely in a dormant but viable form, and easily spreads outside farms to the surrounding environment. MAP’s presence throughout the soil in countries where MAP infection of domestic livestock is extensive and long-standing may explain the increased rates of glioblastoma in tennis and baseball players who handle balls coated with MAP-contaminated dirt. MAP infection is consistent with glioblastoma’s two defining histopathologic characteristics: endothelial cell proliferation and pseudopalisading necrosis. MAP is a non-tuberculous or atypical mycobacterium, which can cause hypoxic necrotizing granulomas, granulomas that resemble areas of pseudopalisading necrosis. There are known bacterial causes of endothelial cell proliferation. Almost unique amongst intracellular bacteria, MAP’s variant isocitrate dehydrogenase 1 (IDH1) enzyme, a type 2-oxoglutarate ferredoxin oxidoreductase, can use a host cell’s cytosolic α-ketoglutarate in its own Krebs or tricarboxylic acid cycle. MAP’s ability to use a host cell’s α-ketoglutarate may explain the survival advantage of the cytosolic IDH1 enzyme mutation for patients with diffuse gliomas including glioblastoma, astrocytoma, and oligodendroglioma, a mutation that results in a reduced supply of cytosolic α-ketoglutarate. MAP may therefore be one possible infectious cause of glioblastoma and the other histologic categories of diffuse glioma.

Keywords: Diffuse gliomas infectious etiology, Endothelial cell proliferation, Mycobacterium avium subspecies paratuberculosis, Necrotizing atypical mycobacterial granulomas, Transdifferentiation.

Introduction: Suspected infectious causes of glioma
Infectious agents have been suggested as possible causes of nervous system tumors of several histopathologic types (Altieri et al., 2006; Alibek et al., 2013). Given their neurotropism, viruses have been the focus of investigation into possible infectious causes of brain cancers (Kofman et al., 2011), including the human herpes viruses cytomegalovirus (Pandey, 2011; Dzurzynski et al., 2012; Wick and Platten, 2014; Holdhoff et al., 2017) and Epstein–Barr virus (Akhtar et al., 2018). The parasite Toxoplasma gondii is a proposed non-viral infectious cause of brain cancer (Schuman et al., 1967; Thirugnanam et al., 2013). Two case reports relate the bacteria Borrelia burgdorferi to glioblastoma (Colpak et al., 2014; MacDonald, 2018).

Zoonoses on ruminant animal farms and the epidemiology of glioblastoma and other diffuse gliomas
There is a long noted increased rate of gliomas, including glioblastoma, in rural residents of Western countries who live in areas where domestic livestock farms are located (Brooks, 1972; Wingren and Axelsson, 1992; Howell et al., 1995; Hansson and Ferguson, 2011). Farm residents (Choi et al., 1970) and farm workers (Musisco et al., 1982; Blair et al., 1985; Khuder et al., 1991) farmers, have an increased risk for brain cancers, with a predominance of diffuse gliomas including astrocytoma and glioblastoma in one study (Choi et al., 1970). Pesticides have been extensively investigated as the possible reason for the increased rate of gliomas in rural and farm residents and workers but the research has been unable to confirm an association between pesticides and diffuse gliomas (Samanic et al., 2008; Yin et al., 2012). Investigators have occasionally suggested that it is not pesticides but a zoonotic microorganism, an animal virus or bacteria that may be responsible for the...
increased rate of gliomas in rural and farm residents and workers (Carozza et al., 2008; Efrid et al., 2014). Zoonotic microorganisms are excreted in an infected animal’s feces or manure and contaminate the ground the animal is defecating on (Manning and Collins, 2001). Rural residents who live near animal farms, live on animal farms or work on animal farms can become infected with a zoonosis by inhaling, ingesting, or directly contacting or handling pathogen-contaminated manure or manure-contaminated soil, dirt, and dust (The Center for Food Security and Public Health, 2017). Increased rates of glioblastoma in tennis players (Imbriano, 2012) and baseball pitchers (Martinez, 2016; Gartland, 2017), catchers, infield position players, and umpires (Franklin, 2011; Imbriano, 2012), including glioblastoma clusters of American professional baseball players from the Philadelphia Phillies, New York Yankees, and Kansas City Royals (Avril, 2013; Longman, 2017) suggest that the same zoonotic microorganism excreted in an infected domestic ruminant’s manure, contaminating the soil of rural environments, may also be present in the baseline soil of baseball fields and in tennis grass and clay courts.

**Mycobacterium avium subspecies paratuberculosis: the zoonosis responsible for some cases of diffuse gliomas, including glioblastoma?**

*Mycobacterium avium* subspecies *paratuberculosis* (MAP) is a zoonotic microorganism present in domestic livestock feces or manure that may be responsible for the increased rate of diffuse gliomas, including glioblastoma, in domestic livestock farmers, rural residents living near domestic livestock farms and herds, and baseball and tennis players playing on fields and grass and clay courts far from domestic livestock farms (Pierce, 2017). MAP causes a chronic intestinal disease in domestic ruminants known as Johne’s disease (Tiwari et al., 2006). MAP is a long suspected cause of Crohn’s disease (Uzoigwe et al., 2007; Kuenstner et al., 2017), but has also been implicated in a wide range of autoimmune diseases (Zhang et al., 2017, 2018) as well as the neurologic disorders Parkinson’s disease (Dow, 2014; Arru et al., 2016) and multiple sclerosis (Sechi and Dow, 2015). A recent study describes MAP antibodies in sera from patients with neuromyelitis optica disorder (Slavin et al., 2018). A significant segment of the medical community considers MAP to be a zoonosis (Davis, 2015; Davis et al., 2017; Kuenstner et al., 2017, 2018). Like other zoonoses (Corbel, 2006), MAP may cause a range of diseases in its human host but MAP does not cause in its animal hosts.

**MAP in feces or manure and soil and dirt**

MAP is heavily excreted in an infected animal’s feces or manure (McKenna et al., 2006). MAP lasts indefinitely in the environment once excreted, and is diffusely distributed throughout the soil in countries where MAP infection of domestic livestock is longstanding (Rhodes et al., 2013).

**How to catch MAP and other non-tuberculous or atypical mycobacteria**

MAP is a type of non-tuberculous or atypical mycobacterium. Non-tuberculous mycobacteria are environmental mycobacteria, bacteria which are present in soil, dirt, and dust (O’Brien, 1989; Falkinham, 2009; Nishiuchi et al., 2017). Other non-tuberculous mycobacteria can be contracted by direct contact with or inhalation of the mycobacterium in dirt or dust. Children who contract non-tuberculous mycobacteria frequently get infected by putting soil or dirt into their mouths (Krantz et al., 2016). Baseball pitchers often lick their fingers between pitches after holding balls coated with possibly MAP-contaminated dirt. Baseball catchers crouch in the possibly MAP-contaminated dirt above home base, have dirt thrown into their faces by players running on or sliding into home base, and repeatedly catch and handle balls coated with possibly MAP-contaminated dirt. Baseball infield players are positioned on possibly MAP-contaminated baseline dirt. Tennis players constantly handle tennis balls coated with possibly MAP-contaminated grass, dirt, and clay. Farmers who do not wash their hands after applying pesticides, and probably don’t wash their hands after other farm work, have an increased risk of glioma (Ruder et al., 2009).

**Areas of pseudopalisading necrosis in glioblastoma: are they hypoxic necrotizing mycobacterial granulomas?**

MAP may be responsible for the two pathognomonic histologic features of glioblastoma: endothelial cell proliferation and pseudopalisading necrosis. Areas of pseudopalisading necrosis in glioblastomas (Pathpedia, 2018) resemble necrotizing granulomas, which are characterized by a “pseudopalisading” lymphoproliferative reaction (Shah et al., 2017). Both tuberculous and non-tuberculous mycobacteria as well as fungi are the major causes of necrotizing granulomas (Shah et al., 2017). Necrotizing granulomas come in several shapes. If the location of the granuloma is cutaneous and the lymphoproliferative reaction has a more definite palisading shape, the necrotizing granuloma is described as a palisading granuloma. If the necrosis is in a wavy, curvilinear pattern, it is described as a serpentine granuloma. Non-tuberculous mycobacteria are known causes of palisading (Bartralot et al., 2000) and serpentine (University of Medicine and Dentistry of New Jersey, 2018) granulomas. Areas of pseudopalisading necrosis in glioblastoma most closely resemble the palisading and serpentine granulomas caused by non-tuberculous mycobacteria. Necrosis is not a feature of MAP infection of dairy and beef cattle, but is a feature of MAP infection of goats, sheep, and water buffaloes (Williams et al., 1983; Kurade et al., 2004; Sivakumar et al., 2005). Granulomas caused by *Mycobacteria* including *Mycobacterium tuberculosis* and non-tuberculous or atypical mycobacteria including *M. avium complex* species (of which MAP is a subspecies) are a result of...
MAP may have a predilection for the human brain. The normal temperature of a dairy cow, the original and natural animal host of MAP, is 101.5°F. The human brain is the warmest part of the human body, although its “intense heat production” is rapidly cleared by cerebral blood flow, so only a small thermal gradient exists between the brain and the rest of the human body (Wang et al., 2014). MAP may prefer the slightly higher temperature of the human brain compared to the rest of the human body.

Is there any evidence of MAP causing vascular endothelial cell hyperplasia?

A study of remote (non-gastrointestinal) MAP lesions in infected goats described MAP organisms being present in the endothelial cells of the intermediate sinuses of lymph nodes, and of causing increased glomerular tufting “due to the proliferation of vascular endothelium” (Sato et al., 1968). A tiny literature suggests that endothelial cell proliferation is the precursor of granuloma formation in bovine MAP infection (Liang et al., 2016). There are other known bacterial causes of endothelial cell proliferation, including Mycobacterium lepromatosis (Han et al., 2008) and species of Bartonella (Berrick et al., 2011).

MAP and the cellular metabolism of diffuse gliomas: the isocitrate dehydrogenase 1 (IDH1) mutation

In the World Health Organization (WHO)’s new (2016) central nervous system tumor classification system (Komori, 2017), diffuse glioma histology, categorized as glioblastoma, astrocytoma, oligodendroglioma, and oligoastrocytoma, has been almost completely superseded by the presence or absence of the isocitrate dehydrogenase 1 (IDH1) mutation (Tateishi et al., 2017). According to WHO’s new classification, the only characteristic that ‘matters’ in a diffuse glioma, the most important characteristic in terms of patient survival, is whether or not the diffuse glioma has the IDH1 mutation (Lee, 2018). Patients whose glioblastomas have mutations, primarily the R132H mutation, in the IDH1 enzyme gene have an improved survival rate compared to patients with the wild-type or ‘normal’ IDH1 gene. How might the wild-type, normal IDH1 enzyme ‘help’ MAP proliferate or persist in an infected brain, and how might the mutant IDH1 enzyme ‘hurt’ MAP, suppressing MAP’s replication or persistence in an infected brain?

The normal or wild-type IDH1 enzyme catalyzes the conversion of isocitrate to α-ketoglutarate, and vice versa, in the cytoplasm of a eukaryotic cell. α-Ketoglutarate produced by wild-type or normal IDH1 is in the cytosol, and it can either translocate into a mitochondrion and participate in the tricarboxylic acid cycle (TCA) cycle, or it can remain in the cytosol and, via IDH1, undergo reductive carboxylation back into isocitrate, eventually resulting in the acetyl-coenzyme A necessary for lipid synthesis (Maus and Peters, 2017).
Intracellular bacteria usually lack the next enzyme in the TCA cycle, α-ketoglutarate dehydrogenase, needed to convert α-ketoglutarate to succinate (Munoz-Elias and McKinnery, 2006). MAP has a unique type of α-ketoglutarate dehydrogenase, called type 2-oxoglutarate (another name for α-ketoglutarate) ferredoxin oxidoreductase, which can convert α-ketoglutarate to succinyl-coenzyme A (Weigoldt, 2012; Weigoldt et al., 2013) in MAP’s version of the TCA cycle. Wild-type or normal IDH1, therefore, is helpful to MAP, it ‘gives’ MAP the α-ketoglutarate it needs for its own variant TCA cycle. The mutant IDH1 enzyme has a reduced ability to convert isocitrate to α-ketoglutarate, and the little α-ketoglutarate that is produced is converted to 2-hydroxyglutarate, resulting in a deficiency of α-ketoglutarate. The lack of α-ketoglutarate in an IDH1-deficient MAP-infected host cell may result in MAP going into a dormant, non-replicating mode. The dormancy of MAP resulting from host α-ketoglutarate deficiency may be responsible for the improved survival rate in diffuse glioma patients with the IDH1 mutation. The fact that the IDH1 mutation occurs in the majority of what the 2016 WHO classification now just calls astrocytomas and oligodendrogliomas and correlates with their improved survival rate suggests that MAP may be involved in the pathogenesis of all diffuse gliomas, not just glioblastoma.

Challenges to the identification of MAP in glioblastoma and other diffuse gliomas
Several obstacles exist in identifying MAP organisms in human tissue. In the United States, laboratories handling animal tissue, that have commercial automated systems for culturing, histopathologic, and immunohistochemical identification of MAP in tissue, are not permitted to process human tissue. Identification of acid fast organisms using traditional acid fast stains require prolonged light microscopic examination at high (oil immersion) magnification (Shah et al., 2017). Researchers have noted that MAP organisms are often not found within the histologic lesions of infected animals (Brady et al., 2008).

Conclusion: diffuse gliomas, including glioblastoma, as possible MAP-associated brain lesions
There are epidemiologic, cellular metabolic, and histologic suggestions of a possible etiologic relationship between MAP and diffuse gliomas, including glioblastoma. A specific bacterial cause of some cases of diffuse glioma would have implications for their prevention by vaccination (Abdellrazeq et al., 2018) and potential response to antimicrobial treatments (Wu et al., 2016; RedHill Biopharma, 2017).

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Conflict of interest
The author declares that there is no conflict of interest.

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