MINI-REVIEW

Mycoplasma genitalium and Cancer: A Brief Review

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Abstract

Approximately, 15-20% of all cancers worldwide are caused by infectious agents. Understanding the role of infectious agents on cancer development might be useful for developing new approaches to its prevention. *Mycoplasma genitalium* is a clinically important sexually transmitted pathogen that has been associated with several human diseases. There have been a few studies suggestive of probable roles of *Mycoplasma genitalium* in cancer development, including prostate and ovarian cancers and lymphomas, but the role of this microorganism like other *Mycoplasma* species in neoplasia is still conjectural. Considering the prevalence of *Mycoplasma genitalium* infections and also the emergence of resistant strains, *Mycoplasma genitalium* needs more attention in the infectious agent cancer-causing research area.

Keywords: *Mycoplasma* - cancer - infectious etiology - infection

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Introduction

Approximately, 15-20% of all cancers worldwide are caused by infectious agents (Parkin, 2006; de Martel and Franceschi, 2009). Different bacterial (Vogelmann and Amieva, 2007), viral (Bergonzini et al., 2010) and parasitical (Khurana et al., 2005) agents have been shown might be involved in cancer development. *Mycoplasma*s are the smallest microorganisms which are capable to self replication. They found in animals and humans also are distinguishable from other bacteria by their small size and genome also total lack of cell wall (Razin et al., 1998).

Among them, *Mycoplasma genitalium* is a clinically important sexually transmitted pathogen that since its discovery by isolation from urethral specimens of two men with non-gonococcal urethritis in 1981 (Tully et al., 1981), has been associated with several human diseases such as non-gonococcal urethritis (Tully et al., 1983; Jensen et al., 1993; Totten et al., 2001) and chronic persistent prostatitis in men (Krieger and Riley, 2004, Mändar et al., 2005), also urethritis, cervicitis (Falk et al., 2005), endometritis (Cohen et al., 2002), salpingitis (Cohen et al., 2005), tubal factor infertility (Clausen et al., 2001) and Pelvic Inflammatory Disease (PID) (Simms et al., 2003) in women. Furthermore *M genitalium* has been isolated from synovial (Tully et al., 1995), respiratory system (Baseman et al., 1988) and rectal (Soni et al., 2010) specimens. After early indicative reports to presence of *Mycoplasma* species or antibody against them in leukemic patients in 1960s (Fallon et al., 1965; Grace et al., 1965; Hayflick and Koprowski, 1965; Murphy et al., 1965; 1967; Barile, 1967; Murphy et al., 1967; 1970), many attempts have been performed to find linkage between these microorganisms and cancer.

Cancer Associations

Several *in vitro* evidences have demonstrated the potential of *Mycoplasma* species to malignant transformation and chromosomal instability of long term *Mycoplasma*-infected cell cultures (Paton et al., 1965; MacPherson and Russell, 1966; Tsai et al., 1995; Shaw-Huey et al., 1999; Zhang et al., 1999; 2004; 2006a; 2006b). Also some epidemiological studies, based on detection of *Mycoplasma* strains in cancer samples or evaluation of antibody status against these microorganisms in cancer patients, have been documented (Erturhan et al., 2013). *M. hyorhinis* (Ji et al., 2002), *M. penetrans* (Zhu et al., 2007; Yan et al., 2009), *M. hominis* (Barykova et al., 2011) and *M. salivarium* (Baracaldo et al., 2012) are the most detected species from cancer patients. In contrast, there are a few studies which are suggestive the absence of any association between *Mycoplasma* and cancer (Ebbesen and Lind, 1969; Zhang et al., 1998; Chanudet et al., 2007). To find association between *M genitalium* and cancer, there are some reports based on detection of *Mycoplasma* species DNA in cancer samples using PCR and universal primers which are capable to detect several *Mycoplasma* species genome, including *M genitalium* (Huang et al., 2001; Pehlivan et al., 2005; Jun et al., 2008), but in comparison to other species, the numbers of studies that have targeted just *M genitalium*-detection in cancer patients also studies for understanding this microorganism's role in cancer development are few. Idahl

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et al. (2011) have perfumed two works. First, using ELISA, they evaluated the presence of anti-*M genitalium* antibody in ovarian cancer patients. Their results were suggestive the possibility of association between *M genitalium* and ovarian cancer (Idahl et al., 2011), but in another study, they could not detect *M genitalium* DNA from ovarian cancer specimens by Real time PCR (Idahl et al., 2010). Biernat-Sudolska and colleagues, to show an association between presence of urogenital *mycoplasmas* and Human Papiloma Virus (HPV) infections (as an infection which strongly associate with cervical carcinogenesis), assessed the presences of this microorganisms by PCR using specific primers in cervical smears of women diagnosed with abnormal cervical cytology of various grades. Their statistical analysis demonstrated that the risk of HPV infection while already infected with any of the four analyzed species of *Mycoplasmataceae* (*Ureaplasma urealyticum, Ureaplasma parvum, Mycoplasma hominis, and Mycoplasma genitalium*) increased two-fold. With concomitant of *U urealyticum* infection, the risk of HPV infection was 4.7-fold greater than in the absence *U urealyticum* infection. Their investigation also in women with cervical cancer group showed a significant increase in the detection rate of *U urealyticum* in comparison to women with normal cytology but they did not detect infections with the *Mycoplasma* species (*M hominis*, *M genitalium*) in women with cervical cancer, although such infections were observed in other groups (ASCUS: atypical squamous cells of undetermined significance; LSIL: lowgrade squamous epithelial lesions; HSIL: high grade squamous epithelial lesions, and control–normal cytology groups). Thus, they suggested that *M hominis*, *M genitalium* infections do not play any major role in cervical carcinoma development (Biernat-Sudolska et al., 2011). At least there are two studies related to the *M genitalium* effects on apoptosis, in one of them, the data did not show any significant effect on apoptosis in *M genitalium*-infected 32D (a murine myeloid cell) cell line (Zhang and Lo, 2007). In contrast, the other one indicated *M genitalium* can inhibit apoptosis in 32D cell line (Feng et al., 1999). Overall, it seems, the well documented *in vivo* and *in vitro* study has performed by Namiki et al. (2009) which their data demonstrated that infection the BPH-1 (Benign prostatic hyperplasia) cell by *M genitalium* for 19 weeks, induces increasing migration/invasion, the acquisition of anchorage-independent growth, karyotypic entropy and formation of xenograft tumors in immune-compromised mice (Namiki et al., 2009).

It is clear, the epidemiological evidences to definitive explanation of *M genitalium* potential to cancer development are not enough and its possible mechanisms also are unclear. One of the major reasons for little studies in this area might be fastidious nature of *M genitalium* to culture that limited direct detection and required researchers to develop other methods. Nucleic acid amplification-based methods have widely used for detection of *M genitalium* in urogenital specimens (de Barbeyrac et al., 1993; Jurstrand et al., 2005; Edberg et al., 2008; Ouzounova-Raykova et al., 2011; Twin et al., 2011), so it seems, this techniques and ELISA which has used to show antibody status against *M genitalium* in patient sera (Baseman et al., 2004; Svenstrup et al., 2006) could be useful tools in epidemiological studies. Immunohistochemistry (IHC) has been used to detection of *Mycoplasma* species in clinical tissue samples (Adegboye et al., 1995; Moorkamp et al., 2010; Yang et al., 2010a; 2010b) but, this method has not developed for *M genitalium*, although polyclonal and monoclonal antibodies (as main tools for Immunohistochemistry and other immunoassays methods) against major antigens of *M genitalium* have been produced (Svenstrup et al., 2002; Burgos et al., 2006; Zarei et al., 2011). In situ hybridization (Saglie et al., 1988; Heiskanen-Kosma et al., 1992; McCully and Brock, 1992; Kwon and Chae, 1999; Yanget al., 2010) also is another method which has used to detection of *Mycoplasma* spices, therefore this methods also could be develop to show the presence of *M genitalium* genome in cancer samples.

Conclusion

Understanding the role of infectious agents on cancer development might be useful for developing new approaches to cancer prevention. The role of *M genitalium* like other *Mycoplasma* species in cancer is still conjectural. To improve our understanding about the initial or co-factorial probable roles of this microorganism in cancer, more epidemiological studies based on *M genitalium*-detection in cancer patient in comparison to control groups also more *in vitro* and *in vivo* studies for understanding its mechanisms to malignant transformation should be sought. By considering the prevalence of *M genitalium* infections (Jones et al., 2009) also emerging the resistance strains (Bradshaw et al., 2008; Jensen et al., 2008), *M genitalium* needs more attention in infectious agent cancer-causing research area.

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