Potential role of Anitschkow cells in cardiovascular disease in human and veterinary medicine: A review of the literature

Anitschkow cells: potential role in the development of vascular degeneration. A review of the literature

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Summary

Anitschkow cells (AC) are a peculiar type of stromal cells observed in myocardium, cardiac valves and coronary vessels wall whose origin, characterization and role remain controversial. In human heart they represent an histological hallmark of Aschoff nodules in rheumatic fever, but they have also been observed in other myocardial pathologies. Firstly

they have been considered a myocyte-derived cells but light microscopy, immunohistochemical and ultrastructural studies pointed out that a macrophagic/histiocytic origin cannot be excluded. Many authors also reported extracardiac AC or an Anitschkow nuclear pattern, thus suggesting that these cells may represent a chromatin pattern rather than a specific cell type. In veterinary medicine AC were described in myocarditis, myocardial necrosis and endocardiosis of several species. Recently, the authors of the present paper observed AC in intramural coronary arteries of different animals (including cattle and fish) affected by arteriosclerotic processes. Immunohistochemical and ultrastructural studies performed on cattle permit us to hypothesize that AC may arise from smooth muscle cells of the arterial tunica media as an adaptive reaction to adverse chemical or mechanical stimuli. The authors hypothesize that the stress related to the intensive livestock farming could represent a mechano-transduction promoting factor of arteriosclerotic changes allowing the development of Anitschkow chromatin pattern. Further studies both in human and veterinary medicine are needed to confirm the origin and role of these peculiar cells.

Keywords: adaptive reaction, Anitschkow cells, cattle, heart, human.

Introduction

Anitschkow cells (AC) are a peculiar, large mononuclear cells in which the nuclear chromatin is present in an undulating wavy ribbon with slender processes radiating from the nucleus, showing a typical "caterpillar" appearance in the longitudinal section and an

"owl-eyed" appearance in the cross one. The AC origin, characterization and role remain controversial and still debated, despite being studied from more than 100 years. Several hypotheses have been formulated, since they may arise from degenerated smooth or striated muscle cells, macrophages or fibroblasts, pericytes or endotelial cells, reticuloendothelial cells, cardiac mesenchyme or cardiac lymphatic cells (Radsdale, 1973). The most reliable hypotheses suggest that AC may have either cardiac muscle origin as an expression of attempted regeneration of damaged myocytes (Anitschkow, 1913; Murphy et al., 1966) or inflammatory origin from the macrophage-histiocyte population (Robinson et al., 2016).

The AC were firstly observed in myocardium of human patients (von Oppel, 1901; Wagner, 1990); in veterinary medicine they have rarely been reported in normal and degenerated mitral valves and myocardium of pigs, horses, dogs and cattle (Robinson et al., 2016).

Aim of this paper was to summarize the basic morphological and immunophenotypical characteristics of AC and to describe the state of the art in human and veterinary medicine.

Anitschkow cells in human medicine

The presence of AC in heart granulation tissue was originally reported by Von Oppel (1901) during a microscopic study on experimental foreign bodies effects on the myocardium. Von Oppel (1901) considered that AC arised from altered striated muscle fibers suggesting that they may represent an expression of attempted regeneration of damaged myocyte.

A few years later, in 1904 Aschoff observed the AC in the human myocardium and cardiac valves of patients affected by rheumatic fever, an acquired human heart disease that is considered the major cause of cardiovascular death during the first five decades of life (Haffejce, 1992). Since then, AC are a well-known histological hallmark of Aschoff nodules, which are aggregates of inflammatory cells near fibrinoid necrosis characterized by AC, multinucleated giant cells and macrophages (Stollerman, 1975). As a result, Aschoff (1904) suggested a macrophagic origin of AC in chronic inflammatory processes.

In 1913, Anitsckhow described the same cells in a report of his experimental studies on granulation tissue formation in the myocardium produced by the introduction of several foreign substances. According to Von Oppel (1901), also Anitschkow (1913) concluded that AC derived from altered muscle fibers.

On the contrary, Erlich and Lapan (1939) described these cells as capable of storing injected materials and subsequently classified them as histiocytic cells or cells belonging to the reticulo-endothelial system.

In the following years AC were observed for the first time in extracardiac human tissues such as muscle layer of the stomach, mucosa of the bronchi, atherosclerotic arteries (Zak, 1947), conjunctiva (Marner, 1980; Kobayaski, 1992) and oral neoplasms (Mohanta et al., 2016).

At ultrastractural level, Pienaar and Price (1967) in experimentally-induced granulomas in rat hearts hypothesized that AC may originate from both pericytes and endothelial cells of the terminal vascular bed in the myocardium, subsequently evolving into fibroblast at the end of the healing process. The same authors also considered a fibroblastic origin on the basis of the nuclear morphology but this hypothesis seemed less probable since the number of fibroblasts increased as the lesion progressed in age and AC became less prominent.

In 1970, Wagner and Siew observed that AC could develop from the undifferentiated mesenchymal cell, representing an intermediate phase in the development of a macrophage or fibroblast in response to undefined stress factors.

In a 1987 study about the pediatric non-rheumatic human hearts, Favara and Moores observed the AC pattern in different mesenchymal cells (striated muscle cells, histiocytes, Schwann cells) of both interstitial tissue and valves. In immunohistochemical investigations, AC revealed myoglobin and desmin positivity (striated muscle markers) but also S100 (Schwann cells marker), lisozyme and alpha-1-antichymotrypsin (histiocyte markers) positivity confirmed that it is difficult to classify AC as cells belonging to a single cytological type.

In 1992 Beranek supported a myocitic origin, suggesting that the degenerated myofibers lose most of their myofibrils and start to be perceived as fibroblast-like cells by light microscopy. Nevertheless, the remaining myofibrils, now invisible, continue to exercise their force and impose their periodicity on nuclear chromatin originating lateral chromatin projections from the central bar that is the most striking feature of Anitschkow nuclei.

To conclude the most reliable hypotheses suggest that AC may have either cardiac muscle origin as an expression of regeneration of damaged myocytes (Von Oppel, 1901; Anitschkow, 1913; Erlich and Lapan, 1939; Beranek, 1992) or inflammatory origin from the

macrophage-histiocyte population (Aschoff, 1904; Piennar and Price, 1967; Wagner and Siew, 1970; Wagner, 1990).

As the AC were observed in many tissues, in 1999 Stehbens and Zuccollo suggested that the term AC probably indicates a cellular immaturity rather than any specific cell type. They argued that the term "Anitschow cell", which is widely used to designate cells with unique nuclear features, erringly connoted a single cell type. Indeed, the identification of AC in cardiac and extracardiac tissue revealed that different type of cells in yet undefined conditions showed AC nuclear pattern. The failure of AC to react with a single specific antibody reflect a lack of cytologic differentiation of AC cells, suggesting that it could be inappropriate to speak of AC but it could be better to consider an Anitschkow chromatin pattern of the nucleus (Zak, 1947; Stehbens and Zuccollo, 1999).

Anitschkow cells in veterinary medicine

In veterinary medicine, apart from the heart and aorta of rabbit experimentally submitted to adverse administration of horse serum and sulfadiazene (Hopps and Wissler, 1946), AC were described in myocarditis, myocardial necrosis and heart valves of several species such as dogs (Robinson et Robinson; 2016), pigs (Gagna et al., 1998), horses (Guarda et al., 1999) and cattle (Guarda, 1985; Nordstoga and Aleksandersen, 1988; Guarda et al., 2013; Ellulu et al., 2016). Recently, the authors of the present article, observed AC in intramural coronary arteries of different species of freshwater hatchery-bred fish, including trout and sturgeon (Capucchio, 2018).

In aortic and mitral valves of horses older than 5 years, AC were abundant in areas of myxoid degeneration or in the surrounding fibrous tissue. Similarly, they were observed in mitral valves of regularly slaughtered pigs affected by myxoid degeneration, fibrosis and valvulitis (Guarda et al., 1999). In calves inoculated with corticosteroid, AC were detected in the areas of myocardial necrosis and tunica media of the intramural coronary arteries (Guarda, 1985).

Biasato et al. (2018) firstly observed AC in the arteriosclerotic coronary arteries of regularly slaughtered veal calves and beef cattle raised in intensive livestock farming. AC were abundant in the tunica media and rarely observed in the adventitia of the intramural coronary arteries affected by both degenerative and hyperplastic changes (Fig. 1). No relationship with the presence of inflammatory perivascular reactions was observed. The severity of AC infiltration did not revealed differences between stenotic and non-stenotic vessels, thus suggesting no influence of AC on the temporal evolution of the

arteriosclerotic changes. No differences between the number of AC and the myocardial districts (interventricular septum, papillary muscles, ventricular free walls and atria) were also detected.

In immunohistochemical investigations performed on coronary arteries of regularly slaughtered veal calves, AC revealed diffuse vimentin (Fig. 2A), desmin (Fig. 2B) and actin (Fig. 2C) positivity. On the contrary, these cells did not express cytocheratin (Fig. 2D), CD31 (Fig. 2E) and Iba1 (Fig. 2F) (Biasato et al., 2017) . These immunohistochemical findings suggest that AC may represent modified muscle cells, because of their expression of muscle specific antigens (desmin and actin). A potential origin from macrophages or vascular endothelial cells appears to be unlikely since the morphological and immunological results do not support this hypothesis.

The presence of contractile elements in AC cytoplasm at ultrastructural examination suggests that they may represent modified muscle cells probably originating from the tunica media of the coronary arteries (Biasato et al., 2018). This finding seems to confirm the muscular origin of AC in coronary vessels wall previously hypothesized, also suggesting the smooth muscle cells of the arteries as potential progenitors instead of the cardiomyocytes.

Independently of their origin, the authors of the present article consider AC development in animals as an adaptive reaction to adverse stimuli. Therefore, according to Stehbens and Zuccollo (1999), they suggest to refer to an AC nuclear pattern instead of an AC type. The almost exclusive detection of these cells in the tunica media of the coronary walls affected by hyperplastic/degenerative changes without alterations of the tunica intima allows hypothesizing their potential involvement in the pathogenesis of intramural coronary arteriosclerosis. This finding also suggests that in cattle AC do not appear to be related to the coronary atherosclerotic process whose major initiators are vascular mediators resulting in endothelial dysfunction (tunica intima), as reported in human medicine (Yahagi et al., 2015). Furthermore, the absence of relationship between AC and inflammatory perivascular reactions in association with the immunohistochemical negativity to macrophage markers (Iba1) suggest that in cattle AC may be an adaptive cell reaction independent of vascular inflammatory processes (Biasato et al., 2017).

The identification of the etiopathogenetic factors involved in the development of AC in cardiac tissue or coronary vessel wall affected by arteriosclerosis in veterinary medicine remain a dilemma. In humans, coronary artery disease (especially atherosclerosis) can depend on age, gender, family history (Mack and Gopal, 2014) tobacco use, alcohol

consumption, physical inactivity and obesity (Bergh et al., 2015). As seen for psychosocial stress in humans, adverse socio-environmental factors have been reported to be a major stimulus to the development of intramural coronary degeneration (in the form of arteriosclerosis) in young swine (Ratcliffe, 1969), chicken (Ratcliffe and Snyder, 1967), mice (Henry et al., 1971), elephants (Sikes, 1968) and monkey (Ratcliffe, 1974). Behavioral responses (competitive interactions) in social situations could be the reasons behind this phenomenon. Indeed, difference in apparent susceptibility to cardiovascular disease that are usually attributed to sex or genetic influence may, therefore, reflect inherent and strictly species-specific behavior patterns (Ratcliffe, 1969). Therefore, a potential influence of intensive livestock farming in the development of coronary arteriosclerosis cannot be excluded. Traditional housing methods of beef cattle fattening system are characterized by restricted space, lack of movement, overfeeding and hormonal treatment to increase the muscle mass and could represent an important stress factor potentially associated with the development of intramural coronary arteriosclerosis including the AC adaptive reaction from smooth muscle cells.

The role of these cells in animal myocarditis, cardiac necrosis and heart valves remains to be elucidated, even if an reaction of cardiomyocytes to stressing stimuli seems to be the most accredited hypothesis.

Conclusion

AC represent peculiar mononuclear cells mostly detected in the myocardium and in coronary vessel walls. In human heart, AC represent a histological hallmark of Aschoff nodules in rheumatic fever, but their origin and role remain to identify. The AC were firstly considered myocyte-derived cells by light microscopy (Anitschkow, 1913), but immunoistochemical and ultrastructural studies pointed out that a macrophagic origin cannot be excluded (Aschoff, 1904). However, many authors reported a lack of reaction with specific antibodies, thus suggesting that AC may represent a chromatin pattern rather than a specific cell type as they are present in different cardiac and extra cardiac tissues (Stehbens and Zuccollo, 1999). In veterinary medicine, immunoistochemical and ultrastructural studies performed on cattle permit to hypothesize that AC may arise from smooth muscle cells of the arterial tunica media as an adaptive reaction to adverse stimuli (Biasato et al., 2018). However, the AC role in the development of arteriosclerosis in veterinary medicine still remains a dilemma.

Further studies in both human and veterinary medicine are necessary to confirm the origin and role of these peculiar cells.

Conflict of Interest

The authors declared no potential conflict of interests with respect to the research, authorship and/or publication of this article.

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Figure legends

Figure 1. Histological characterization of the Anitschkow cells. A) Anitschkow cells in the tunica media of a small intramural coronary artery characterized by degenerative changes of the tunica media (change of orientation of smooth muscle cells, vacuolar degeneration of their cytoplasm, multifocal rarefaction of the tunica). Haematoxylin & Eosin stain, bar = 50 µm. B) Anitschkow cells in the tunica media of a small intramural coronary artery characterized by degenerative changes of the tunica media and intimal hyperplasia. Haematoxylin & Eosin stain, bar = 50 µm. C) Anitschkow cells in the tunica media of a small intramural coronary artery characterized by severe degenerative/proliferative changes of the vessel wall with lumen narrowing. Haematoxylin & Eosin stain, bar = 50 µm. D) Detail of the Anitschkow cells in the tunica media of a small intramural coronary artery. The cells appear as large mononuclear cells in which the nuclear chromatin was present in an undulating wavy ribbon with slender processes radiating from it. Haematoxylin & Eosin stain, bar = 10 µm.

Figure 2. Immunohistochemical characterization of the Anitschkow cells. Diffuse vimentin (A), desmin (B) and actin (C) positivity in the tunica media of the small intramural coronary artery showed in Figure 1A. The cells do not express cytocheratin (D), CD31 (E) and Iba1 (F). Immunohistochemical reactions for vimentin, cytocheratin, CD31, desmin, actin, Iba1 counterstained with haematoxylin stain. Bar = 50µm.