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Modulation of inflammation by tomatoes and lycopene in the context of cardiometabolic diseases..

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Abstract: Tomato, tomato products as well as lycopene consumption are overall acknowledged to exert anti-inflammatory effects. This has been reported in numerous *in vitro*, animal and clinical studies, on various tissue and cell types, including adipose tissue and adipocytes, and in several physiopathological contexts, such as cardiovascular diseases, type-2 diabetes, obesity or metabolic syndrome. These anti-inflammatory effects are partly related to tomato and lycopene impact on inflammatory signaling pathways.

The goal of this review is to summarize the current knowledge on this topic and to identify gaps that remain to be filled and data that still need to be reinforced in order to definitely demonstrate the interest of tomato or lycopene consumption to blunt the inflammation associated with cardiometabolic diseases.

Abbreviations:

AKT: protein kinase B

BCO1: beta-carotene oxygenase 1

BCO2: beta-carotene oxygenase 2,

CCL2: chemokine (C-C motif) ligand 2

CCL5: chemokine (C-C motif) ligand 5

CRP: C-reactive protein

CVD: cardiovascular disease

CXCL: chemokine (C-X-C motif) ligand

ERK: extracellular signal-regulated kinase

HF/HChol: high fat / high cholesterol

HMGB1: high mobility group box 1

HUVEC: human umbilical vein endothelial cell

ICAM : intercellular adhesion molecules

I- κ B : inhibitor of nuclear factor kappa B

IL: interleukin

JNK: c-Jun N-terminal kinase

LDL: low density lipoprotein

LPS: lipopolysaccharide

MCP-1: monocyte chemoattractant protein 1

MMP9: matrix metalloproteinase 9 (MMP9)

NF- κ B: nuclear factor kappa B

NHANES III: third national health and nutrition examination survey

NRF2: nuclear factor (erythroid-derived 2)-like 2

PBMC: peripheral blood mononuclear cell

PGC-1 α : peroxisome proliferator-activated receptor gamma coactivator 1- α

PI3K: phosphatidylinositol-3-kinase

PPAR: peroxisome proliferator-activated receptor

RANTES: regulated on activation, normal T cell expressed and secreted

RAR: retinoic acid receptor

SAA: serum amyloid A

SIRT1: Sirtuin 1

THP-1: Tohoku hospital pediatrics-1

TNF α : tumor necrosis factor α

TP: tomato powder

VCAM: vascular cell adhesion molecule

YALTA: young adults longitudinal trends in antioxidants

Introduction

Lycopene is a lipophilic pigment which is responsible for the red color of various fruits, such as tomato, water melon, guava or grapefruit. It belongs to the carotenoid family, and more specifically to the carotene class, but it is not a precursor of retinol (vitamin A). In Western diets, tomatoes and tomato products represent the major sources of lycopene (Rao, Ray, and Rao 2006).

Whereas all-trans lycopene is the main dietary form (Richelle et al. 2012), lycopene can be found in human blood and tissues under the all-*trans* form and as *cis*-isomers and the conformation of the molecule could modulate its activity. It is unclear whether the change in its conformation results from chemical and/or enzymatic processes but it has been observed that the percentage of *cis* isoforms increased following the absorption of all-*trans* lycopene (Richelle et al. 2010) (Moran et al. 2015) and represented around a third of the total lycopene (Ross et al. 2011). The ratio between *trans* and *cis* isomers seems to vary depending on the tissues investigated: in humans, it is close to 1 in plasma and to 2 in the human liver (Khachik et al. 2002).

Beside native lycopene, several metabolites have been described in various tissues and biological fluids. Indeed, Khachik *et al.* have identified a metabolite of lycopene named 2,6-cyclolycopene-1,5 diol that is present in human plasma, liver and milk (Khachik et al. 1998, Khachik et al. 2002). Studies have identified circulating and tissue lycopene metabolites (aldehydes) produced by the shortening of the isoprenoid chain of the molecule: apo-6', apo-8' and apo-12'-lycopenals have been found in the liver of rodents fed with lycopene (Gajic et al. 2006) or tomato products (Tan et al. 2014, Martin-Pozuelo et al. 2015). These compounds have also been identified in human plasma following the consumption of tomato juice, together with apo-10' and apo-14'-lycopenals (Kopeck et al. 2010). However, it was not possible to find out whether they were produced endogenously from lycopene since they were also present in the tomato products.

The identification of the genetic sequences of two isoforms of carotenoid oxygenases (beta-carotene oxygenase 1 and 2, BCO1 and BCO2) in mammals has allowed the synthesis of the corresponding

recombinant proteins. Studies have been undertaken to characterize their ability to cleave lycopene *in vitro*. BCO1 activity is located in the cytoplasm and is in charge of the first step of synthesis of retinoids (i.e. retinal) from provitamin A carotenoids (Redmond et al. 2001). Redmond *et al.* have reported a weak activity of recombinant mouse BCO1 towards lycopene (Redmond et al. 2001) but more recently, dela Sena *et al.* found that recombinant human BCO1 is able to cleave lycopene at position 15,15' almost as efficiently as beta-carotene (dela Sena et al. 2013). BCO2 activity is restricted to mitochondrial membrane, where it prevents non provitamin A carotenoid accumulation, which can impair the respiratory chain (Amengual et al. 2011, Palczewski et al. 2014, Raghuvanshi et al. 2015). BCO2 seems to play an important role in lycopene metabolism since *Bco2*^{-/-} mice fed with tomato/lycopene enriched diets accumulate more lycopene in their liver than their wild type or *Bco1*^{-/-} littermates (Ford et al. 2010, Ford, Elsen, and Erdman 2013, Tan et al. 2014), suggesting a higher absorption and/or a decreased degradation of lycopene. BCO2 affinity seems to vary across species: recombinant ferret BCO2 displayed activity only towards 5-*cis* and 13-*cis* lycopene isoforms, but not towards the all-*trans* isoform (Hu et al. 2006). Previous work from Kiefer *et al.* indicated the production of apolycopenal in a lycopene-producing *E. coli* strain expressing mouse BCO2 (Kiefer et al. 2001) By analogy with retinal (that can be further transformed to either retinol or retinoic acid), it has been suggested that apolycopenals could be metabolized to the corresponding acid or alcohol forms (i.e. apolycopenoic acid or apolycopanol). Hu *et al.* have been able to produce apo-10'-lycopenol and apo-10'-lycopenoic acid by incubating apo-10'-lycopenal with ferret liver homogenates, suggesting that the enzymatic equipment allowing such metabolisation is present in mammals (Hu et al. 2006). However, the *in vivo* relevance of apocarotenoic acids/apocarotenols remains questionable since so far, they have only been observed in *Bco1*^{-/-} mice fed with xanthophyll or beta-carotene rich diets (Amengual et al. 2013).

In humans, adipose tissue and liver are the main lycopene storage tissues, and contain about 60% and 30%, respectively, of the total lycopene body stores (Chung et al. 2009, Landrier, Marcotorchino,

and Tourniaire 2012, Moran, Erdman, and Clinton 2013). Furthermore, it has been observed that lycopene bioavailability and deposition in the liver of rodents is increased in the context of a high fat diet (Bernal et al. 2013, Martin-Pozuelo et al. 2015). In the liver, the uptake of lycopene is probably mediated via chylomicrons-remnant receptors, *i.e.* the LDL-receptor (LDLR), the LDL-receptor related protein 1 (LRP1), and the heparan sulfate proteoglycans (HSPGs) (Dallinga-Thie et al. 2010). In adipose tissue and adipocytes, the uptake of lycopene is mediated, at least in part, by CD36 (Moussa et al. 2011) and is not related to its physicochemical properties (Sy et al. 2012). Lycopene is then stored in the adipocyte lipid droplets and in membranes (Gouranton et al. 2008). It is generally assumed that lycopene in these tissues could mediate some biological effects. It is worth noting that these tissues are also key sites in the development of inflammatory processes in the context of the metabolic syndrome and more generally for cardiometabolic disorders.

In terms of biological function, lycopene is well known for its antioxidant properties (Palozza et al. 2010). It displays anti free radical properties mediated by eleven conjugated double bonds. It is essential in scavenging lipid peroxyl radicals, reactive oxygen species, and nitric oxide (Engelmann, Clinton, and Erdman 2011). In addition, several studies have shown that lycopene displays anti-inflammatory effects in several tissues and in several pathophysiological disorders, which are highly relevant in the context of cardiometabolic disorders. This is notably the case in adipocytes and adipose tissue (Gouranton, Thabuis, et al. 2011, Marcotorchino et al. 2012, Luvizotto Rde et al. 2013, Singh et al. 2016, Fenni et al. 2017), in the liver (Wang 2012, Ip et al. 2014), and in arterial wall cells (Armoza et al. 2013, Hung et al. 2008) .

Among others, these anti-inflammatory effects could be responsible for the numerous health effects attributed to lycopene (Wang 2012, Story et al. 2010) in the field of liver steatosis (Wang 2012), cardiovascular diseases (Muller et al. 2015, Thies et al. 2012), adiposity and obesity (Bonet et al. 2015, Landrier, Marcotorchino, and Tourniaire 2012). Indeed, inflammation appears as a major hallmark and is intimately related to all cardiometabolic disorders, including type-2 diabetes,

cardiovascular diseases and metabolic syndrome (Esser, Paquot, and Scheen 2015). It is noteworthy that obesity is a major driving force of inflammation and thus constitutes a major risk factor for the development of these disorders. Obesity is characterized by a chronic low-grade or metabolic inflammation, which mainly originates from adipose tissue enlargement (Gregor and Hotamisligil 2011). Pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF- α), interleukin (IL)-6, and IL-1 β , and chemokines, such as MCP1/CCL2 or RANTES/CCL5, are produced by adipose tissue (Tourniaire et al. 2013) and are widely acknowledged as important pathophysiological factors implicated in insulin resistance. In addition, these markers of inflammation also stimulate the production of acute phase proteins, such as C-reactive protein (CRP), serum amyloid A, and adhesion molecules, such as soluble intercellular adhesion molecule type 1 (sICAM1) or VCAM, in the liver, which are markers of increased CVD risk (Pearson et al. 2003, Ridker and Morrow 2003).

The overall objective of the present review is to summarize the knowledge related to the anti-inflammatory effects of lycopene, its metabolites, tomatoes, tomato products or extracts, from cell culture to human clinical studies that could beneficially impact prevalence of cardiometabolic disorders.

***In vitro* studies**

We have demonstrated the ability of lycopene to inhibit the expression of pro-inflammatory cytokines and chemokines *in vitro* in murine and human adipocytes (Gouranton, Thabuis, et al. 2011). These data were also reproduced *ex vivo* in adipose tissue explants from mice subjected to a high fat diet (characterized by low-grade inflammation), and confirmed by another group in human adipocytes (Warnke et al. 2016). The molecular mechanism was investigated and the involvement of NF- κ B was confirmed (Gouranton, Thabuis, et al. 2011). Similar results (*i.e.*, inhibition of cytokine and chemokine expression in various *in vitro* and *ex vivo* models) were obtained with apo-10'-lycopenoic acid, a metabolite of lycopene (Gouranton, Aydemir, et al. 2011). Finally, lycopene attenuated LPS-

mediated induction of TNF α in macrophages via NF- κ B and JNK, as well as macrophage migration *in vitro* (Marcotorchino et al. 2012). Consequently, lycopene decreased macrophage-induced cytokine, acute phase protein and chemokine mRNA levels in adipocytes. Similarly, tomato extract suppressed inflammation and pro-inflammatory cytokine production during interaction between adipocytes and macrophages (Kim et al. 2015).

In macrophages, lycopene (Zou et al. 2013, Hadad and Levy 2012, Feng, Ling, and Duan 2010) and tomato aqueous extracts (Schwager et al. 2016, Navarrete, Alarcon, and Palomo 2015) suppressed the pro-inflammatory response (including cytokines and interleukins such as TNF α , IL-1 β , IL-6...) in RAW264.7 cells incubated with LPS, probably via an inhibition of the NF- κ B pathway (Hadad and Levy 2012). In THP-1 cells, lycopene also prevented the activation of the pro-inflammatory cascade mediated by oxysterols via an inhibition of NF- κ B and an increase in PPAR γ expression. Lycopene synthetic metabolites apo-10'-lycopenoic acid and apo-14'-lycopenoic acid repressed NF- κ B activation induced by cigarette smoke extract in THP-1 macrophage cells (Catalano et al. 2013) and MMP9 expression (Palozza et al. 2012).

The effects of lycopene and tomato products have been studied in several vascular endothelial cell models, including HUVEC cells. In these cells, tomato oleoresin and purified lycopene significantly inhibited the TNF α -mediated expression of several adhesion molecules, including ICAM-1 and VCAM-1, via a decrease in NF- κ B signaling (decrease in I κ B protein concentration and p65 phosphorylation level) (Armoza et al. 2013, Hung et al. 2008). Tomato extracts also limited the gene expression of pro-inflammatory cytokines and chemokines (TNF α and IL-8) and induced the gene expression of anti-inflammatory cytokines, such as IL-10, after stimulation by TNF α , possibly by targeting NF- κ B signaling (Hazewindus et al. 2014, Di Tomo et al. 2012). This effect was associated with a limitation of monocyte migration. Similarly, tomato aqueous extracts blunted the production of a large range of interleukins and chemokines (Schwager et al. 2016). Interestingly, lycopene has also been depicted as able to attenuate the activation of cell signaling related to inflammation, such as ERK, p38 (Chen et

al. 2012), PI3K/AKT or NRF2 (Sung et al. 2015). Other pro-inflammatory stimuli have been tested regarding the ability of lycopene to blunt the pro-inflammatory responses to HMGB1 (high mobility group box 1; (Lee et al. 2012)) or LPS (Wang et al. 2013).

Preclinical studies

Cardiovascular diseases

In the context of hyperhomocysteinemia, a risk factor for atherosclerosis, lycopene supplementation (10-20 mg/kg of body weight p.o. for 10 weeks) has been shown to reduce aortic lipid depots and decrease the level of numerous circulating inflammatory markers (serum VCAM1, MCP1, IL-8) (Liu et al. 2007).

In vivo myocardial ischemia/reperfusion (I/R) injury models are used to study the potential of compounds to limit damages associated with this event. Whereas several studies have been published regarding the benefits of lycopene treatment on I/R induced cardiac dysfunctions (Xu et al. 2015), only a few have documented the consequences on inflammatory aspects. It was shown in rats by Bansal *et al.* that oral administration of lycopene for 31 days (1 mg/kg), before inducing a surgical occlusion of the left anterior ascending coronary artery followed by a reperfusion, was able to diminish damages associated with I/R, as well as inflammatory cell infiltration in myocardial tissue (Bansal et al. 2006). He *et al.* have demonstrated that chronic lycopene intake (10 mg/kg body weight daily for 4 weeks) can protect against inflammation associated with post-myocardial infarction remodeling, as shown by diminished expression of Tnf and Il1b mRNAs and decreased NF- κ B activation in mice (He et al. 2015). Using an opposite approach, *i.e.* inducing cardiac remodeling first then administering lycopene (40 mg/kg body weight daily for 28 days), Wang *et al.* found that lycopene could partially maintain cardiac function and limit p38 activation pathway (Wang et al. 2014). This was in agreement with what was previously reported by another group using another model of myocardial infarction (induced by isoproterenol): lycopene intake also diminished the

infarction area size and inflammation assessed by measurement of circulating CRP level and tissular myeloperoxidase activity (Upaganlawar, Gandhi, and Balaraman 2010). In a recent study, Tong *et al.* showed that acute (intravenous) lycopene administration just after ischemia diminished the size of the infarct and that it was associated with a decrease in the activation of two inflammatory signaling pathways, JNK and p42/44 MAPK (Tong et al. 2016).

Obesity models / metabolic syndrome / non-alcoholic liver steatosis

Several groups have explored the anti-inflammatory effects of tomato extract and/or lycopene intake - mainly in rats - in the context of obesity. In these studies, obesity was induced using high fat diets, associated or not with administration of lycopene, and the consequences of lycopene intake on obesity onset was observed. Bahcecioglu and colleagues have used two doses of lycopene (2 and 4 mg/kg bw/d for 6 weeks) and reported beneficial effects of lycopene administration on insulin sensitivity, liver steatosis and inflammation in rats only at a dose of 2 mg/kg/d (Bahcecioglu et al. 2010). However, the highest dose led to fewer beneficial changes, suggesting that there might be an optimal dosage of lycopene in this context. A similar observation was made in a study involving mice fed with a high fat and high cholesterol (HF/HChol) diet supplemented with two doses of dried tomato peel (9% or 17%) for 12 weeks (Zidani et al. 2017).

Overall, all studies have highlighted the decrease in local and/or systemic inflammation following tomato product/lycopene consumption, except in the studies by the group of Periago (Bernal et al. 2013, Martin-Pozuelo et al. 2015). However, it should be noted that in these papers, the HF/HChol diet had no effect on circulating TNF α or IL-6 compared with control diet, neither did it induce signs of inflammation in the liver, as assessed histologically. Conversely, a similar study performed with lycopene (isolated from algae or tomato) supplementation of HF/HChol diet led to a reduced degree of liver steatosis and atherosclerotic depot in the aorta, as well as anti-inflammatory effects (decreased serum levels of ceruloplasmine, CRP, myeloperoxidase and decreased 15-lipoxygenase and cyclo-oxygenase activities in PBMCs) (Renju, Kurup, and Saritha Kumari 2014). Interestingly, the

lycopene from algae origin displayed more beneficial effects than the one isolated from tomato, suggesting that synergetic effects with other compounds present in these matrices play a role in this effect.

Others have used a model of diet-induced obesity (DIO) involving high fat diet plus sucrose, supplemented or not with lycopene, in rats. Under these conditions, it was observed that lycopene treatment improved insulin resistance related parameters (plasma insulin, glycemia) and could limit inflammation at the central level (decreased plasma concentrations of leptin, resistin and IL6 but not TNF α), in the adipose tissue (decreased mRNA expression of leptin, resistin, Mcp1 and Il6 but not Tnf) (Luvizotto Rde et al. 2013) and also in the brain (Yin et al. 2014). Pierine *et al.* investigated the effect of lycopene supplementation in rats already obese, and again the absence of effect on the circulating level of TNF α was observed, whereas a decreased production was found in the kidney (Pierine et al. 2014).

In a very extensive study, the anti-inflammatory effects of lycopene at a dose of 10 mg/kg of diet limited adiposity, prevented hyperinsulinemia and insulin-resistance during the development of DIO in mice. It was found that lycopene limited liver steatosis and inflammation (by decreasing IL6, TNF α , NF- κ B and TLR4) (Singh et al. 2016). Furthermore, it was found that some circulating inflammatory markers (TNF α , IL-1 β) were also diminished by lycopene administration, suggesting a generic anti-inflammatory effect. This study also indicated for the first time that lycopene could act on the gut microbiota, as reflected by caecal bacterial abundance and short chain fatty acid production. The limitation of bacteria and the preservation of gut and colon epithelial integrity associated with obesity and insulin-resistance, could participate in the overall anti-inflammatory properties of lycopene at the systemic level.

In agreement, we also recently showed that supplementation with lycopene or tomato powder (TP) for 12 weeks diminished the hepatic steatosis induced by high fat diet (Fenni et al. 2017), and reported an anti-inflammatory effect of lycopene or TP in the liver but also an impact on lipid metabolism. We also investigated the impact of lycopene and TP supplementation on adipose tissue

inflammatory status, and reported an overall down-regulation of genes encoding pro-inflammatory markers such as cytokines (Il6, Tnf α), adipokines (resistin, visfatin, leptin), acute phase proteins (Saa3, haptoglobin) and chemokines (Ccl5, Mcp1, Cxcl10), a down-regulation of genes encoding metalloproteinases (Mmp3 and Mmp9), and an up-regulation of genes encoding anti-inflammatory proteins such as Il-10 and Tgf- β . In addition, we confirmed at the protein level that some of these pro-inflammatory markers (IL-6, TNF α , MCP1, CCL5) were reduced compared to HFD conditions. We also observed that lycopene and TP strongly reduced the phosphorylation levels of p65 and I κ B *in vivo*, consistently with *in vitro* data, which suggests that the anti-inflammatory effect of lycopene and TP on adipose tissue results from their ability to inhibit NF- κ B signaling in adipose tissue. Despite this clear impact of lycopene or TP on the NF- κ B signaling pathway, we cannot exclude that this effect was strictly due to the reduced adiposity, which could result in a deactivation of this signaling pathway.

Since apo-10'-lycopenoids are proposed to be the major products of lycopene metabolism via BCO2, the effect of apo-10'-lycopenoic acid towards liver steatosis was investigated in the genetically obese mouse model Ob/Ob (Chung et al. 2012). It was found that apo-10'-lycopenoic acid supplementation diminished the severity of liver steatosis and that this result was mediated by SIRT1 which, among other functions, is able to inhibit NF- κ B inflammatory signaling (Schug and Li 2011). In a study comparing the potential of lycopene vs. apo-10'-lycopenoic acid to limit liver steatosis in DIO Bco2^{-/-} mice, Ip *et al.* identified that these two molecules had distinct modes of action, with apo-10' lycopenoic acid acting on SIRT1 activity and expression in the liver while lycopene was acting at the level of mesenteric fat through actions of PPAR α and PPAR γ (Ip et al. 2015). Another nuclear receptor that could mediate anti-inflammatory effects of lycopene and apo-10'-lycopenoic acid is RAR (retinoic acid receptor). We showed that apo-10'-lycopenoic acid was able to transactivate RAR, concomitantly to the prevention of the production of inflammatory markers in adipocytes (Gouranton, Aydemir, et al. 2011). Furthermore, Aydemir *et al.* have shown that lycopene administration to mice could lead to

the induction of RARE-mediated cell signaling and could even restore vitamin A deficiency (Aydemir et al. 2012).

Human studies

Cross-sectional and prospective studies

Adjusted circulating concentrations of lycopene as well as many other carotenoids were inversely associated with CRP concentrations in large studies, such as the National Health and Nutrition Examination Survey III (NHANES III) (Ford et al. 2003, Kritchevsky et al. 2000), and in other studies (Kim et al. 2010). High plasma lycopene concentration (reflected by the highest tertile) was associated with lower plasma CRP, IL-6 and MMP9 concentrations in a general population of 285 Swedish men and women before adjustment but these associations were lost after adjustments for age, sex, alcohol intake, BMI, systolic blood pressure and total cholesterol (Ryden et al. 2012). Similarly, lycopene status was inversely associated with IL-6 (Walston et al. 2006) and other markers of endothelial function, such as s-ICAM 1 (van Herpen-Broekmans et al. 2004). In the YALTA prospective study, the initial plasma level of lycopene was inversely associated with sICAM1 protein level 15 years later (Hozawa et al. 2007). Similarly, plasma lycopene concentration was inversely associated with plasma CRP and E-selectin concentrations in men and women of an Aboriginal population and the association remained significant after adjustment for classical confounding factors (Rowley et al. 2003). No relationship was found between plasma lycopene and plasma CRP concentrations in a population of middle-aged and older women (Wang et al. 2008).

Interventions studies

Lycopene supplementation

Short-term lycopene supplementation (1 week; 80 mg/day) in young healthy participants did not modify post-prandial inflammatory status (CRP, ICAM or VCAM) (Denniss et al. 2008). In obese

people, 4 weeks of lycopene supplementation (Lyc-O-Mato, 30 mg/day) did not modify plasma concentrations of inflammatory markers (TNF α , IL6, CRP) (Markovits, Ben Amotz, and Levy 2009). Similarly, no impact of 1-week lycopene supplementation (7 mg/day) was observed in patients with prehypertension (Petyaev et al. 2012) and no impact of 2 weeks supplementation (lyc-O-Mato 3 capsules /days; approx. 14.64 mg of lycopene/day) was observed on TNF α in a smoker (n=12) and non-smoker (n=15) population (Briviba et al. 2004). Seven mg per day of lycopene for 2 months also did not modify inflammatory markers in CVD patients and healthy volunteers (n=36 for each group) (Gajendragadkar et al. 2014). In a large study involving 224 healthy middle-aged volunteers supplemented for 12 weeks with lycopene capsules (10 mg/day) or tomato-rich diet, no modification of inflammatory markers was observed (Thies et al. 2012).

On the opposite, it was reported that 12 week of a lycopene-rich diet (224-350 mg lycopene/week) in overweight middle-aged individuals (n=54) led to a reduction in SAA concentration in the HDL₃ fraction while 12 weeks of lycopene supplementation (70 mg/week) in the same study group led to a reduction in SAA concentration in both plasma and HDL₃ fraction (McEneny et al. 2013). Lycopene supplementation (7 mg or 15 mg /day for 8 weeks) also reduced CRP, ICAM and VCAM plasma concentrations in healthy men (n=126) (Kim et al. 2011). In 26 healthy volunteers, Lyco-O-Mato (5.7 mg of lycopene) for 26 days reduced TNF α production from whole blood after a LPS challenge *in vitro* (Riso et al. 2006).

Tomato supplementation

In type-2 diabetes patients (n=15), tomato juice supplementation for 4 weeks (300 ml/day) did not improve CRP, ICAM or VCAM plasma concentrations compared to placebo (Upritchard, Sutherland, and Mann 2000). It has been established that a tomato-rich diet (300 g/day for 1 month) had no impact on plasma concentrations of E-selectin, ICAM and CRP in 103 healthy volunteers (Blum et al. 2007). Tomato juice consumption for 2 weeks in healthy volunteers (daily dose of lycopene: 20.6 mg) reduced plasma CRP concentration (Jacob et al. 2008). Interestingly, in healthy overweight

volunteers, a combination of dietary anti-inflammatory molecules, including tomato extract, resulted in an increase in plasma adiponectin concentration, that displays anti-inflammatory activity, whereas no other modification was observed (Bakker et al. 2010). This result suggests that this anti-inflammatory mix could have a beneficial impact on adipose tissue inflammatory status as reflected by adiponectin (Ruhl and Landrier 2015). Consumption of tomato product blunted the post-prandial induction of plasma IL-6 in healthy women and men (n=25) (Burton-Freeman et al. 2012). Plasma concentration of lycopene, related to the consumption of a diet rich in fruits and vegetables, was inversely associated with a decrease in the LPS-mediated production of IL-6 in PMBC of overweight women (Yeon, Kim, and Sung 2012). An intake of 330 ml/day of tomato juice for 20 days also significantly reduced plasma concentrations of IL-8 and TNF α in overweight participants while only IL-6 was diminished in obese participants (Ghavipour et al. 2012). A similar reduction in plasma concentrations of plasma IL-6 and TNF α was observed in patients with metabolic syndrome who consumed tomato juice 4 times a week for a period of 2 months (Tsitsimpikou et al. 2014). A reduction in CRP concentrations was also observed in women with heart failure but not in men following consumption of a vegetable juice (340 ml/d?) for 30 days (Biddle et al. 2014). In women (n=30), tomato juice consumption (280 ml/day containing 32.5 mg of lycopene) for 8 weeks reduced MCP1 and increased adiponectin (Li et al. 2015), but no control group was used in this study. A similar reduction in MCP1 was observed in healthy people (n=12) consuming a vegetable soup constituted mainly of tomato (500 ml/day for 14 days) (Sanchez-Moreno et al. 2006). The postprandial impact of a tomato-rich diet (3 types: raw tomatoes, tomato sauce or tomato sauce with olive oil) was evaluated in healthy volunteers (n=40): such regimens led to a reduction in MCP1 and to an increase in IL-10 for the 3 diets, and an increase in IL18 for tomato sauce. IL6 and VCAM were reduced with tomato sauce plus olive oil (Valderas-Martinez et al. 2016). A similar postprandial impact of carotenoid-rich tomato extract has been depicted in 146 healthy normal weight individuals regarding the level of oxidized LDL (Deplanque, Muscente-Paque, and Chappuis 2016). A recent

meta-analysis reported a significant decrease in IL-6 (standardized mean difference -0.25; $p = 0.03$) following tomato supplementation (Cheng et al. 2017).

Negative results associated with tomato juice supplementation (330 ml/day for 2 weeks in 22 healthy men) were reported in only one study where an increase in TNF α production was observed compared to wash-out periods (Watzl et al. 2003). The origin of this contrasted results is presently unknown.

Conclusion and perspectives

Based on the reported studies, the anti-inflammatory effect of lycopene and /or tomato products is rather clear, at least *in vitro* and preclinical studies. Indeed, in several cell models related to cardiometabolic health, lycopene or tomato products exert a strong and reproducible inhibition on the expression and secretion of cytokines and interleukins, as well as an impact on several signaling pathways that could participate to the overall effect including NF- κ B. Preclinical studies also strongly support these data. In most cases, an improvement of the inflammatory status has been reported *in vivo*, in key tissues (mainly in the liver and in adipose tissue) and in some cases at the systemic level. All data generated in the context of obesity and its comorbidities suggest that lycopene, and in some cases tomato products, have a beneficial impact on inflammation in key organs and are also associated with clear improvement in metabolic disorders.

Interestingly, this anti-inflammatory effect of lycopene and/or tomato product has been confirmed in some clinical studies at the systemic level. If the effect of isolated lycopene on inflammatory status is still not clear, it is noteworthy that most studies have been realized in healthy people with no inflammation disorders. When tomato supplements are administered to volunteers with an elevated inflammatory status (overweight/obesity or during post-prandial inflammation), it becomes clearer that such a nutritional approach may have beneficial effects on the control of inflammation. In line with this, it is important to specify that lycopene is classically associated with the health benefits of tomato consumption (Canene-Adams et al. 2005). However, these data show that the overlap between lycopene supplementation and tomato product consumption is not perfect regarding their health effects (Burton-Freeman and Sesso 2014).

Several important questions remain unsolved yet. It is presently not clear if the *all-trans* or *cis* isomers of lycopene display similar activities regarding their anti-inflammatory effect. It is also not clear if lycopene or its metabolites are responsible for the reported effects. Indeed, the activity of lycopene metabolites towards inflammation has been barely investigated so far.. It is also noteworthy that in the case of tomato product consumption, it cannot be excluded that the reported

effects are only due to lycopene and not to other molecules present, or even to the association of lycopene with other molecules. All these questions require further investigations *in vitro* and in preclinical models.

Regarding clinical studies, it is important to specify that the anti-inflammatory effects of lycopene and /or tomato products have been evaluated only on plasma. Thus, it will be of particular interest to confirm some of these data in tissue biopsies (notably from adipose tissue) to evaluate the contribution of lycopene or tomato products on tissue inflammation at a local level.

Finally, if the NF- κ B signaling pathway is highly suspected to be deactivated by lycopene or its metabolites, the precise molecular mechanism leading to this anti-inflammatory effect is presently not elucidated. Several mechanisms could be involved, such as an effect of the expression of phosphatases involved in the dephosphorylation of NF- κ B proteins, physical interaction with NF- κ B signaling proteins or effect on the production of lipid mediators such as resolvins. The fact that lycopene or its metabolites transactivated RAR (Aydemir et al. 2012, Gouranton, Aydemir, et al. 2011) also suggests that this nuclear receptor could be involved in lycopene-dependent anti-inflammatory effect since we recently reported that *all-trans* retinoic acid blunted the inflammation process in adipocytes (Karkeni et al. 2016) via an induction of PGC1 α , which reduces NF- κ B activation and transcriptional control of inflammation (Eisele et al. 2013). The transactivation of other nuclear receptors such as PPAR γ by lycopene or its metabolites (Ip et al. 2015) could also be responsible for the anti-inflammatory effect as previously reported (Szeles, Torocsik, and Nagy 2007).

In conclusion, the impact of lycopene and tomato products on the control of inflammation associated with cardiometabolic disorders is presently well established *in vitro* and in preclinical studies. Further investigations are mandatory to demonstrate the interest of such nutritional approach in clinical studies. If confirmed, this kind of supplementation could constitute a new strategy to limit or prevent inflammation and its associated consequences.

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