MINIREVIEW

From Sirtuin Biology to Human Diseases: An Update*

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Originally rising to notoriety for their role in the regulation of aging, sirtuins are a family of NAD+-dependent enzymes that have been connected to a steadily growing set of biological processes. In addition to regulating aging, sirtuins play key roles in the maintenance of organismal metabolic homeostasis. These enzymes also have primarily protective functions in the development of many age-related diseases, including cancer, neurodegeneration, and cardiovascular disease. In this minireview, we provide an update on the known roles for each of the seven mammalian sirtuins in these areas.

Over three-quarters of a century ago, Clive McCay and colleagues first noted that rats kept on a calorie-restricted diet lived longer than those fed freely (1). Despite the length of time that has elapsed since this discovery, the molecular mechanism that drives this life span extension has remained elusive. Originally described as a silencing factor in yeast (silencing information regulator), the protein Sir2 came out on top in a screen for modulators of yeast life span (2). Moreover, Sir2 was required for the life span of yeast to be extended by calorie restriction (3). These discoveries launched a new field in biology: the study of Sir2 and its homologs in mammals, called sirtuins.

Mammals have seven sirtuins (SIRT1–7) that possess NAD+-dependent deacetylase, deacylase, and ADP-ribosyltransferase activities (4). Sirtuins are found in different subcellular locations, including the nucleus (SIRT1, SIRT6, and SIRT7), cytosol (SIRT2), and mitochondria (SIRT3–5), although in some studies, SIRT1 has been found to possess transferase activities (4). Sirtuins are found in different subcellular locations, including the nucleus (SIRT1, SIRT6, and SIRT7), cytosol (SIRT2), and mitochondria (SIRT3–5), although in some studies, SIRT1 has been found to possess transferase activities (4). Sirtuins have been shown to regulate life span in lower organisms, including yeast, nematodes, and fruit flies (5), although their role in worm and fly life span has recently been debated (6, 7). Most of these studies have described a key role for SIRT1 in regulating the metabolic response to calorie restriction (CR) (8), a dietary intervention that robustly extends life span across numerous species. However, whole-body overexpression of SIRT1 in mice does not affect life span (9). Nevertheless, SIRT1 does appear to promote healthy aging by protecting against several age-related pathologies (10).

The strongest link between mammalian sirtuins and the anti-aging effects of CR comes from SIRT3, which mediates the prevention of age-related hearing loss by CR (11). Hearing loss is a hallmark of mammalian aging and is characterized by a gradual loss of spiral ganglion neurons and sensory hair cells in the cochlea of the inner ear, which is triggered by oxidative damage in these cells (12). Remarkably, CR prevents hearing loss and oxidative damage in wild-type mice, whereas SIRT3-deficient mice are resistant to the effects of CR. In addition, SIRT3 is required for the CR-mediated reduction of oxidative damage in multiple tissues via regulation of the glutathione antioxidant system (11). Indeed, SIRT3 has been shown to directly modulate reactive oxygen species (ROS) by deacetylating manganese superoxide dismutase (13, 14). This evidence suggests a broader role for SIRT3 in regulating age-related pathologies that depend on cellular levels of ROS.

Evidence for a positive effect of sirtuins on longevity also comes from the recent discovery that SIRT6 overexpression extends life span in mice (15). Although early experiments using Sirt6 knockout mice suggested a role in aging (16), this is the first demonstration that a mammalian sirtuin positively regulates life span. Notably, the observed life span extension seems to be modest (the median life span increases between 10 and 15%) and gender-specific (affecting males only) for reasons that remain unclear. Despite reduced levels of insulin-like growth factor 1 (IGF-1) in serum, a phenotype previously associated with life span regulation, the “anti-aging” effect of SIRT6 could be explained by SIRT6 acting as a tumor suppressor (as described below) (17). These results provide encouraging evidence that mammalian sirtuins may in fact represent critical modulators of life span and age-related diseases.

Metabolism

Because sirtuin enzymatic activity is dependent upon the presence of NAD+*, sirtuin activity is directly linked to the metabolism, cancer biology, cardiovascular disease, inflammation, and brain pathology.

Aging

Following the first publication describing a role for yeast Sir2 in promoting longevity (2), many laboratories focused on elucidating whether sirtuins might play similar roles in other organisms. Sirtuins have been shown to regulate life span in lower organisms, including yeast, nematodes, and fruit flies (5), although their role in worm and fly life span has recently been debated (6, 7). Most of these studies have described a key role for SIRT1 in regulating the metabolic response to calorie restriction (CR) (8), a dietary intervention that robustly extends life span across numerous species. However, whole-body overexpression of SIRT1 in mice does not affect life span (9). Nevertheless, SIRT1 does appear to promote healthy aging by protecting against several age-related pathologies (10).

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Metabolism

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abolic state of the cell. Indeed, nearly every sirtuin has been shown to play a role in regulating metabolism and energy homeostasis, often in roles that help the cell adapt to periods of low-energy input (Fig. 1). Indeed, sirtuins are involved in multiple metabolic pathways, as described below.

**Lipid Metabolism**—Lipid catabolism is especially important during fasting. SIRT1 is induced in several tissues during CR (18) and responds to the organism’s need for energy by stimulating lipid breakdown through the transcription factor FoxO1, which directly induces expression of the rate-limiting lipolytic enzyme adipose triglyceride lipase (19). SIRT1 also inhibits cells’ ability to synthesize fat by deacetylating the lipogenic activator SREBP-1c, preventing this factor from binding the promoters of lipogenic genes (20, 21). Notably, when SIRT1 is absent from specific tissues, mice have significant defects in their ability to metabolize lipids normally, leading to fat accumulation (4), and even haploinsufficiency was shown to lead to increased weight gain on a high-fat diet (22).

Despite these seemingly clear results, further study has shown that the effects of SIRT1 may in fact be dose- or context-dependent. Although SIRT1-overexpressing mice were protected from hepatic steatosis when placed on a high-fat diet in one study (23), another study found the opposite result (24), attributing the outcome to SIRT1 inhibition of cAMP-responsive element-binding protein, a transcription factor that normally activates fatty acid metabolism and gluconeogenesis. Additionally, overexpression of SIRT1 in theforebrain of female mice led to increased fat mass and increased expression of adipogenic genes in white adipose tissue (25). Taken together, these studies suggest that whether SIRT1 promotes lipid catabolism or instead promotes adipogenesis may be tissue- and expression level-dependent.

The metabolic effects of SIRT3 appear thus far to be more straightforward (Fig. 1). SIRT3 is up-regulated by fasting in liver and brown adipose tissue and promotes mitochondrial oxidative metabolism via deacetylation of numerous metabolic enzymes (26), including long-chain acyl-CoA dehydrogenase, an enzyme involved in fatty acid catabolism (27, 28). The importance of this activity is demonstrated by an abnormal accumulation of fatty acid oxidation intermediates in Sirt3 knock-out mice. When fasted, these mice also show reduced ATP production and are intolerant to cold. Conversely, Sirt3 knock-out mice are unable to cope with a high-fat diet and gain more weight than their wild-type counterparts, developing hepatic steatosis and exhibiting signs of inflammation (29). Furthermore, wild-type animals on a high-fat diet have reduced hepatic SIRT3 activity and increased protein acetylation relative to those on a control diet (30), suggesting that a feedback mechanism may be involved in the interplay between SIRT3 activity and diet.

SIRT6 promotes fatty acid oxidation as well, interestingly through a mechanism involving another sirtuin. SIRT1 and the transcription factors FoxO3a and NRF1 form a complex on the Sirt6 promoter, leading to SIRT6 expression and promotion of fat oxidation in wild-type mice (31). Mice with a liver-specific deletion of Sirt6 develop a fatty liver, and primary hepatocytes from these mice show relatively low levels of fatty acid oxidation. By contrast, mice with transgenic overexpression of SIRT6 show down-regulation of genes associated with lipid storage and are somewhat protected against the accumulation of visceral fat when placed on a high-fat diet (32). These studies cast Sirt6 as an important promoter of fat utilization.

Roles are beginning to be described for the other sirtuins in lipid metabolism and adipose biology. SIRT2 seems to fall in line with other family members described above: it inhibits adipocyte differentiation (33), possibly by deacetylating FoxO1 (34), and its transcription is suppressed in obese mice by hypoxia-inducible factor 1α (HIF-1α) (35). However, not all sirtuins act in the same direction: knocking down Sirt4 increases fatty acid oxidation, suggesting that this sirtuin opposes its mitochon-
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Glucose Metabolism—Most of the work done so far on how sirtuins regulate glucose metabolism has focused on SIRT1, which is known to modulate gluconeogenesis in liver mainly through its substrate peroxisome proliferator-activated receptor (PPAR)-γ coactivator 1α (4). Recently, other sirtuins have appeared on the stage as key regulators of glucose homeostasis. SIRT6 has come to the fore as an important regulator of glucose uptake and metabolism (Fig. 1). Sirt6 knock-out mice die early in life from a fatal hypoglycemia. These animals exhibit increased expression of the glucose transporter GLUT1, leading to increased glucose uptake in skeletal muscle and brown adipose tissue (37). Sirt6-deficient embryonic stem cells similarly show lower oxygen consumption and greater lactate production than controls. In part, this phenotype appears to be related to the ability of SIRT6 to lower expression of glycolytic genes, such as Pfk1 and Glut1, through deacetylation of histone H3K9. In this context, SIRT6 works as a co-repressor of HIF-1α, and the increased glucose uptake seen in Sirt6 knock-outs is reversed by treatment with a HIF-1α inhibitor (37). These results indicate that SIRT6 may function as a critical modulator of glucose homeostasis. Recently, SIRT2 has also been found to take part in glucose metabolism by promoting gluconeogenesis through deacetylation and stabilization of the rate-limiting enzyme phosphoenolpyruvate carboxykinase (38), adding this protein to the list of sirtuins that control glucose homeostasis.

Other Metabolic Processes—Sirtuins have important functions in additional metabolic pathways that promote adaptation to periods of low-energy input. For example, SIRT3 activates ketone body synthesis via HMGCS2 (39). It also up-regulates the electron transport chain via SDHA (40) and the urea cycle via ornithine transcarbamoylase (28). SIRT5 enhances the urea cycle through CPS1 (carbamoyl phosphate synthetase 1), the first step of the cycle. Indeed, Sirt5 knock-out mice show reduced basal CPS1 activity and lack the increase in activity normally seen with fasting (41). SIRT5 has been shown to deacetylate CPS1 (41), and a recent study indicates that SIRT5 may demalonylate and desuccinylate CPS1 as well (42). Suggestively, in the absence of SIRT5, the levels of succinylated of CPS1 were increased, indicating that SIRT5 may function as a bona fide deacylase. All together, these studies highlight that we are yet learning about the enzymatic functions of sirtuins, and future studies will surely investigate the mechanisms through which sirtuins might work together to coordinate metabolic responses.

Cancer

Tumorigenesis is a multistep process that involves the acquisition of several mutations leading to cell transformation and cancer initiation. Among the hallmarks of cancer cells, metabolic reprogramming is also an important regulator of tumor growth, allowing tumor cells to fulfill their energetic and anaerobic demands (43). In addition to their role in regulating metabolism, sirtuins are important in the regulation of genomic stability, making them excellent candidates to control tumorigenesis (Fig. 2).

A large amount of data generated over the last decade has involved SIRT1 in tumorigenesis by modulating cellular stress responses and DNA repair (44). However, the ability of SIRT1 to promote or suppress tumorigenesis seems to depend on the specific tumor type, cellular context, and signaling pathway affected. Several studies support a role for SIRT1 as a tumor suppressor. SIRT1 opposes Myc-dependent transformation by interacting with and deacetylating this proto-oncogene (45). Furthermore, overexpression of SIRT1 in vivo protects against metabolic syndrome-associated liver cancer by reducing DNA damage and inflammation. Importantly, a moderate increase of SIRT1 in these mice protects from spontaneous and aging-associated cancers (9). Moreover, recent work has demonstrated that SIRT1 interacts with HIF-1α and represses its activity, thereby inhibiting growth and angiogenesis of xenograft tumors (46). Finally, a recent study reported increased levels of acetylated H3K56, a substrate for SIRT1 and SIRT2, in human tumors (47). Although the influence of SIRT1 and SIRT2 in modulating this histone mark specifically in tumors has not been addressed, it is tempting to speculate that decreased levels or activity of these sirtuins could have an impact on tumorigenesis by increasing the levels of H3K56 acetylation. Notably, H3K56 acetylation has been shown to be a primary substrate for SIRT6, thereby raising the possibility that the modulation of this particular histone mark in tumors may depend on this chromatin deacetylase rather than SIRT1/2, as proposed.

In contrast with the above observations, recently published data have added evidence for a tumor-promoting function of SIRT1. A new positive feedback loop involving N-Myc and SIRT1 has been described to promote tumorigenesis in a mouse model of neuroblastoma (48). N-Myc induces the expression of Sirt1, which in turn deacylates and stabilizes N-Myc, thereby promoting tumor growth. Furthermore, a complex between SIRT1 and estrogen receptor-α has been found to be essential to promote the expression of prosurvival genes and to inactivate tumor suppressor genes in breast cancer cells (49). Sirt1 expression also appears to be up-regulated in hepatocellular carcinomas, where it inhibits senescence and apoptosis and leads to tumor growth (50, 51). However, the precise molecular mechanism through which SIRT1 exerts this tumor-promoting function remains unclear.

As mentioned above, metabolic reprogramming is a key feature of cancer cells. Although differentiated cells under normal conditions obtain energy by oxidizing fuels such as glucose through mitochondrial oxidative phosphorylation, Warburg observed that rapidly proliferating cancer cells often up-regulate glycolysis, which we now understand allows cells to generate macromolecules needed for cellular proliferation. Recent studies reported that SIRT3 normally counteracts this metabolic switch by destabilizing HIF-1α through down-regulation of ROS (52, 53). Overexpressing SIRT3 also suppresses the Warburg effect in various cancer cell lines lacking SIRT3 (52, 53), suggesting that SIRT3 may be a tumor suppressor. Consistent with this role, Sirt3 expression is down-regulated in human breast cancers, and Sirt3 knock-out mice have a higher incidence of spontaneous mammary tumors (54). As noted above,
SIRT6 is a key regulator of glucose metabolism, and lack of this chromatin factor leads to a phenotype that is reminiscent of the Warburg effect (37). Indeed, SIRT6 has been recently described as a tumor suppressor that regulates cancer metabolism (106). Mechanistically, SIRT6 suppresses aerobic glycolysis and Myc-dependent ribosome biosynthesis, and lack of this sirtuin leads to robust metabolic reprogramming, sufficient to promote tumorigenesis. In line with this, Sirt6 expression is down-regulated in human pancreatic and colorectal cancers, and conditional deletion of Sirt6 promotes intestinal tumorigenesis in vivo (106). Consistent with a tumor-suppressive function, it has recently been shown that overexpression of SIRT6 induces apoptosis in cancer cell lines (55). However, the mechanism and physiological relevance of this observation remain as yet unexplored.

The roles of other sirtuins in cancer development have just started to emerge (Fig. 2). Because SIRT2 regulates normal mitotic progression by controlling the activity of the anaphase-promoting complex/cyclosome (56), SIRT2 was proposed to be a tumor suppressor by preventing chromosomal instability during mitosis. Indeed, Sirt2-deficient mice develop spontaneous and gender-specific tumors, with females primarily developing mammary tumors, whereas hepatocellular carcinomas arise in males (57). Finally, a recent study has demonstrated that SIRT7 functions as an H3K18 deacetylase, repressing transcription of multiple genes involved in anchorage-independent growth and contact inhibition (58). In this context, SIRT7 depletion markedly reduced tumorigenicity of cancer cells, suggesting that SIRT7 may play a critical role in maintaining oncogenic transformation.

Inflammation

Inflammation plays a central role in the pathogenesis of many diseases, including cancer, diabetes, and cardiac disease. Current research points to an anti-inflammatory role for sirtuins, especially SIRT1 and SIRT3. Several studies have shown SIRT1 to be protective against inflammation (e.g. Ref. 59), a function that may counteract the effects of inflammatory factors such as NF-κB (60) and TNF-α (61). SIRT1 is also important for preventing lung inflammation following exposure to airborne particulate matter (62). Furthermore, suppression of SIRT1 is seen during inflammation (63), but one study prevented these effects by pretreating mice with the SIRT1-activating compound resveratrol (64).

Other sirtuins may also negatively regulate inflammation. SIRT2, for instance, may down-regulate the immune response through deacetylation of the NF-κB subunit p65 at Lys-310 (65). Lys-310 is hyperacetylated in Sirt2 knock-out mouse embryonic fibroblasts following TNF-α stimulation, leading to an increase in the expression of NF-κB target genes. These results suggest that SIRT2 is a negative regulator of NF-κB gene expression and therefore potentially of inflammation as well. SIRT6 binds many of the same promoters in the mouse genome as NF-κB subunit RelA (66), and it deacetylates Lys-9 of histone H3, leading to RelA destabilization and cessation of gene expression (67). Like SIRT2, SIRT6 may also have an anti-in-
flamatory role through suppression of NF-κB target gene expression. However, Sirt6-deficient T cells exhibit reduced interferon-γ secretion upon activation (68), and SIRT6 also enhances TNF-α translation in dendritic cells (69), so the picture is not entirely clear. Finally, in one study, Sirt7 knock-out mice had elevated myocardial levels of several cytokines compared with controls, demonstrating that SIRT7 may help fight inflammation (70).

Cardiovascular Disease

Cardiovascular disease is one of the leading causes of death worldwide and involves the deterioration of heart and blood vessel function. Remarkably, early studies demonstrated that CR protects from cardiovascular disease by improving both endothelial and heart function (71). Given the role of sirtuins in mediating, at least in part, some of the effects of CR, multiple studies have explored their function in cardiovascular disease. Most of this work described the role of SIRT1 in endothelial function, vessel inflammation, vascularization, and cholesterol metabolism and has been reviewed previously (72). Here, we summarize recent findings regarding the role of sirtuins in cardiac function.

SIRT1, SIRT7, and, more recently, SIRT3 and SIRT6 have been described as key regulators of cardiac hypertrophy, one of the main causes leading to heart failure. Early studies demonstrated that SIRT1 and SIRT7 play a protective role against cardiac hypertrophy by deacetylating and modulating p53 activity (70, 73, 74). Recently, the protective role of SIRT1 has been extended to its ability to regulate fatty acid oxidation (75). A normal healthy heart utilizes both fatty acids and glucose simultaneously to obtain energy. However, cardiac hypertrophy is accompanied by a metabolic shift similar to the Warburg effect that favors glycolysis and impairs fatty acid oxidation (76). In a phenylephrine-induced cardiac hypertrophy model, SIRT1 prevented the development of cardiac hypertrophy by promoting fatty acid oxidation (75). Mechanistically, SIRT1 binds to PPARγ, favoring the deacetylation of PPARγ coactivator 1α and preventing the down-regulation of fatty acid oxidation genes (75). In line with a protective role for SIRT1 in cardiovascular disease, it also protects mice from hyperglycemia-induced endothelial dysfunction by inhibiting the expression of p66Shc (77). Mice deficient in p66Shc have increased resistance to oxidative stress and improved endothelial function and are protected against vascular and cardiac diseases (78). In contrast with these observations, transgenic mice overexpressing SIRT1 develop larger atherosclerotic lesions compared with control animals (24). A similar phenotype was observed in a different line of SIRT1 transgenic mice, where SIRT1 overexpression reduced cardiac function and was associated with impaired mitochondria (80). Furthermore, a recent study using Sirt1-deficient mice also demonstrated a detrimental role for SIRT1 in cardiac function (81). In response to a hypertrophic stimulus, Sirt1-deficient mice failed to develop cardiac hypertrophy, a phenotype associated with impaired Akt signaling. Moreover, hearts of mice overexpressing SIRT1 exhibited increased phosphorylation and deacetylation of Akt and developed cardiac hypertrophy under basal conditions (81). These conflicting results for SIRT1 may be influenced by differences in expression levels in the different mouse models (82), suggesting that a beneficial effect of SIRT1 in the context of cardiac function, like the topic areas covered above, may be confined to a window of optimal activity.

Due to its mitochondrial localization and ability to regulate cellular ROS levels, SIRT3 has also emerged as a critical regulator of cardiac function (83). Sirt3-deficient mice develop cardiac hypertrophy, whereas transgenic animals overexpressing SIRT3 in the heart are protected against agonist-mediated cardiac hypertrophy (84). At the molecular level, SIRT3 deacetylates and activates LKB1, thereby activating AMP-activated kinase, which suppresses Akt phosphorylation (85). Moreover, SIRT3-dependent deacetylation of FoxO3a leads to its nuclear localization and enhanced expression of antioxidant genes, such as manganese superoxide dismutase, reducing cellular ROS levels (84). Importantly, both Akt activation and increased ROS levels play a crucial role in the development of cardiac hypertrophy (86, 87). Thus, by regulating these two pathways, SIRT3 exerts a key antihypertrophic function in cardiomyocytes.

SIRT6 is also involved in cardiac hypertrophy and myocardial infarction. In models of cardiac hypertrophy, Sirt6 expression is up-regulated, yet its deacetylase activity is reduced (88). Increased activity of SIRT6 protects cardiomyocytes from a hypertrophic response in vitro by suppressing NF-κB activation (88). Furthermore, increased NAD synthesis protects cardiomyocytes from hypertrophy, possibly through SIRT6 activation (89). In line with this, a recent study reported that Sirt6 acts as a negative regulator of cardiac hypertrophy by repressing IGF/Akt signaling (90). However, in contrast with these results, inhibition of nicotinamide phosphoribosyltransferase, an enzyme involved in NAD synthesis, reduces myocardial infarction by inhibiting neutrophil infiltration and ROS production within the infarcted hearts (91). Interestingly, the same protective phenotype was observed when Sirt6 expression was silenced, implying that although SIRT6 may protect against cardiac hypertrophy, lower SIRT6 levels may be beneficial in the context of myocardial infarction.

Brain

Important roles have been elucidated for SIRT1 and SIRT2 in the brain. SIRT1 in particular has shown itself to be beneficial in multiple models of neuropathology. Alzheimer disease is characterized by the accumulation of the β-amyloid peptide and the aggregation of tau protein (92). In a mouse model of Alzheimer disease, brain-specific knock-out of Sirt1 increased levels of β-amyloid plaque formation, whereas overexpression of SIRT1 decreased the plaque levels (93). SIRT1 may contribute to this effect because it activates transcription of the ADAM10 gene, which encodes α-secretase, an enzyme whose activity helps the brain avoid plaque formation. SIRT1 also deacetylates and destabilizes tau protein, thereby suppressing its aggregation (94). Likewise, in a mouse model of α-synuclein pathology, which drives conditions such as Parkinson disease (95), SIRT1 played a protective role by preventing protein aggregation (96). One possible mechanism is that SIRT1 deacetylates HSF1 to increase levels of HSP70, a chaperone that could prevent aggregation by helping with protein folding. SIRT1 overexpression
improved motor function in a mouse model of Huntington disease (97), whereas brain-specific knock-out of Sirt1 worsened disease-related pathology (98). Sirt1 knock-out mice also have defective short- and long-term memory despite seemingly normal gross brain anatomy, an effect possibly due to a decrease in hippocampal synaptic plasticity (99).

By contrast, models of neuropathology show protective effects when Sirt2 is knocked down, where inhibition of SIRT2 lowered toxicity in a striatal neuron model of Huntington disease (100). Thus, although SIRT1 is protective against brain pathology, SIRT2 may have opposing effects.

SIRT1 and SIRT2 are also important for differentiation and migration of certain types of brain cells. In primary neurons, SIRT1 promotes neurite outgrowth and increases cell survival, and it also decreases mTOR signaling (101). Other studies have found that SIRT2 both promotes (102) and inhibits (103) oligodendrocyte differentiation. SIRT2 also promotes myelin formation in Schwann cells by deacetylating Par-3, a regulator of cell polarity (104).

Little is known about the activity of the remaining sirtuins in the brain. SIRT3 was important for neuron viability in a primary cell model that used NMDA to deplete NAD and induce excitotoxic injury (105). Mice with a neuron-specific deletion of Sirt6 did not die of hypoglycemia like full-body knock-outs (79). Rather, they initially exhibited growth retardation, with lower levels of pituitary growth hormone and IGF-1, ultimately lowered toxicity in a striatal neuron model of Huntington disease (98).


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