perhaps in a more subtle form. We have deliberately used...

activation of NFκB through the

known atherothrombogenic factor. This suggests Rho/

Rho-kinase inhibition as a potential therapeutic strategy for

the prevention of atherogenesis [8].

The recent results from our ongoing studies in patients

with Barter’s and Gitelman’s syndrome (BS/GS) [9,10] provide

additional support as well as additional evidence for the

importance of Rho/Rho kinase signaling-CRP relationship

in atherothrombogenesis. Of direct relevance is our recent

demonstration in BS/GS patients that RhoA/Rho kinase

pathway is blunted as shown by the reduced gene and protein

expression and response to angiotensin II (Ang II) challenge

of Rho kinase and PAI-1 [11], and by the reduced gene and protein

expression of the upstream regulator of RhoA, p115RhoGEF [12]. BS/GS, caused by gene defects in specific

kidney transporters and ion channels, presents a puzzling

clinical picture characterized by hypokalaemia, sodium

depletion, activation of the renin–angiotensin–aldosterone

system (RAAS), with increased plasma levels of Ang II

and aldosterone, yet normo/hypotension, reduced peripheral

resistance, and hyporesponsiveness to pressor agents [9,10].

BS/GS has been considered a good human model to explore

the mechanisms responsible for maintenance/controlling

vascular tone and vascular remodeling [10,13]. In fact,

understanding why patients with BS/GS do not develop

hypertension and its complications such as cardiovascular

remodeling and atherogenesis in spite of high Ang II and

activation of RAAS, sheds considerable light on the cellular

basis of hypertension. In BS/GS specifically, the short-term

Ang II signaling pathway is blunted as documented by the

increased regulator of G-protein signaling-2 [14] reduced Gaq

gene and protein expression [15,16] and reduced related

downstream cellular events such as intracellular Ca2+ and IP3

release, and PKC activity [15,17,18]. The long-term signaling

pathway of Ang II, which modulates the cell redox state to

promote cardiovascular remodeling and atherosclerosis,

is also altered in BS/GS [19,20]. The reduced peripheral

resistance, vascular hyperactivity, and normohypotension

typical of BS/GS patients and their collection of biochemical

characteristics present, therefore, a mirror image of those

found in hypertension. The downregulation of Rho/Rho

kinase pathway noted in our recent studies occurred in the

context of the increased level of the endothelial subunit of NO

synthase (eNOS) mRNA [21] alongside elevated urinary NO

metabolites and cGMP levels [22], which parallels in humans

the upregulation of the NO system upon Rho kinase

inhibition recently shown in vitro in endothelial cells [7] and

in vivo in Dahl rats [23]. More importantly, we have very

recently found in BS/GS patients compared with normoten-

sive healthy subjects, unchanged CRP plasma level as well as

coreactants such as serum amyloid A, VCAM and

ICAM, and inflammatory process related cytokines such as

interleukin 6 and TNFα [24]. The BS/GS patients’

unchanged level of CPR [24] together with their down-

regulated Rho/Rho kinase pathway [11,12], reduced PAI-1

gene and protein expression [11] and unchanged plasma

level of the inflammatory cytokines interleukin 6 and

TNFα [24], whose expression is known to be dependent on

NFκB activity, also provide in a human model of altered

vascular tone regulation, confirmatory data in support of

those derived from in vitro studies [8]. In addition, our

findings in BS/GS could also shed some light on the molecular

mechanisms involved in CRP-induced gene expression.

One possible mechanism for the CRP-induced gene

expression is, in fact, the activation of NFκB through the

RhoA induced phosphorylation of the inhibitory subunit IκB

[25] and the activation of IκB kinase by Rho kinase [26].
Relevant to this mechanism, we have preliminary data that, instead, show in BS/GS patients compared with normotensive healthy subjects, an increased expression of IkB while NF-kB is unchanged, which is in keeping with a reduced activity of NF-kB (Caló LA and Pagnin E, personal observation).

In conclusion, the overall clinical, biochemical and molecular picture of BS/GS may contribute to an understanding of humans of the molecular mechanism of CRP/Rho/Rho kinase/NFκB relationship that determines the involvement of CRP in atherothrombogenesis demonstrated in vitro [8] and thus confirming the utility of Rho/Rho kinase inhibition for cardiovascular protection in humans.

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