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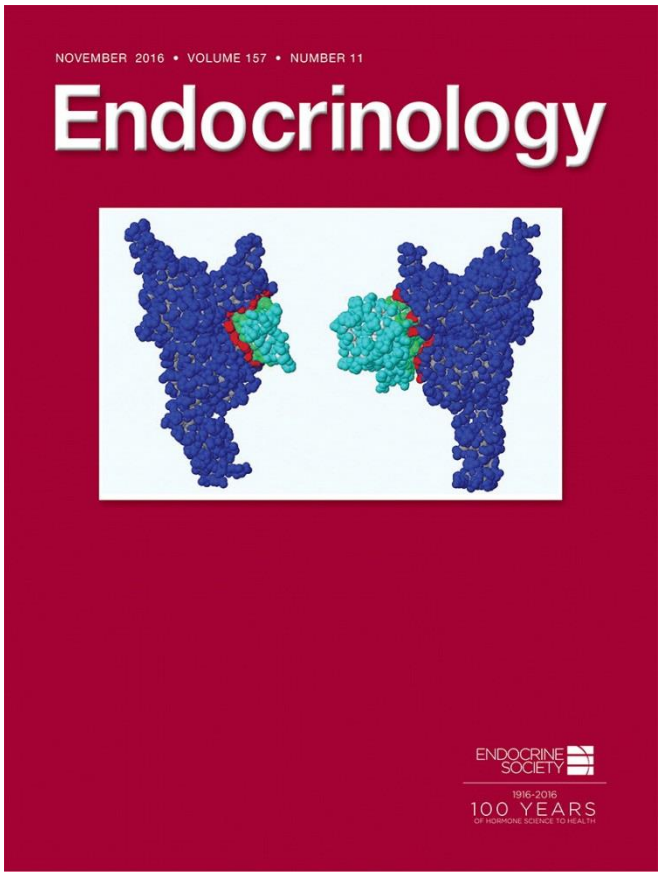
ENDOCRINOLOGIA
USA: Ricerca-Copertina per uno studio padovano

La prestigiosa rivista di endocrinologia sperimentale «Endocrinology», organo della società scientifica di endocrinologia americana *Endocrine Society*, ha dedicato la copertina del numero di novembre 2016 ad un recente studio del gruppo di ricercatori guidato dal Prof. **Carlo Foresta** dell'Università di Padova.

La ricerca che ha meritato la copertina della prestigiosa rivista ha evidenziato l'esistenza di un nuovo meccanismo attraverso il quale il più importante ormone testicolare, il testosterone, esercita i suoi effetti a livello cellulare.

Il gruppo del Prof. Foresta, coordinato dal Dott. **Luca De Toni**, ha individuato un nuovo meccanismo recettoriale che può essere implicato sia nella normale attività fisiologica dell'ormone testicolare, che nelle patologie testosterone-dipendenti quali l'infertilità maschile, la neoplasia prostatica e le malattie metaboliche.



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Segue abstract:

Osteocalcin and Sex Hormone Binding Globulin Compete on a Specific Binding Site of GPRC6A

Luca De Toni, Diego Guidolin, Vincenzo De Filippis, Simone Tescari, Giacomo Strapazzon, Maria Santa Rocca, Alberto Ferlin, Mario Plebani, and Carlo Foresta

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The undercarboxylated form of osteocalcin (ucOC) regulates male fertility and energy metabolism, acting through theGprotein-coupled receptor (GPRC)6A, thus forming anewpancreas-bone-testis axis. Recently, GPRC6A has also been suggested to mediate the nongenomic responses of free testosterone (T). However, these data did not consider the physiological scenario,wherecirculating T is mainly bound to sex hormone-binding globulin (SHBG) and only a small percentage circulates freely in the blood. Here, by the use of computational modelling, we document the existence of similar structural moieties between ucOC and SHBG that are predicted to bind to GPRC6A at docking analysis. This hypothesis of competition was assessed by binding experiments on human embryonic kidney-293 cells transfected with human *GPRC6A* gene. Unliganded SHBG specifically bound the membrane of human embryonic kidney-293 cells transfected with *GPRC6A* and was displaced by ucOC when coincubated at 100-fold molar excess. Furthermore, specific downstream Erk1/2 phosphorylation after stimulation of GPRC6A with ucOC was significantly blunted by 100-fold molar excess of unliganded SHBG. Intriguingly previous incubation with unliganded SHBG, followed by incubation with T, induced Erk1/2 phosphorylation in a dose-dependent manner. Neither binding nor stimulating activities were shown for SHBG saturated with T. Experiments on mutation constructs ofGPRC6Astrengthened the hypothesis of acommonbinding site ofucOCand SHBG. Given the role of GPRC6A on energy metabolism, these data agree with epidemiological association between SHBG levels and insulin sensitivity, suggest GPRC6A as a likely SHBG receptor, and add bases for the possible regulation of androgen activity in a nonsteroidal manner.

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